Received: 22 March 2020 | Accepted: 26 March 2020
DOI: 10.1002/jmv.25801

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Tocilizumab treatment in COVID-19: A single center experience

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Abstract

Tocilizumab (TCZ), a monoclonal antibody against interleukin-6 (IL-6), emerged as an alternative treatment for COVID-19 patients with a risk of cytokine storms recently. In the present study, we aimed to discuss the treatment response of TCZ therapy in COVID-19 infected patients. The demographic, treatment, laboratory parameters of C-reactive protein (CRP) and IL-6 before and after TCZ therapy and clinical outcome in the 15 COVID-19 patients were retrospectively assessed. Totally 15 patients with COVID-19 were included in this study. Two of them were moderately ill, six were seriously ill and seven were critically ill. The TCZ was used in combination with methylprednisolone in eight patients. Five patients received the TCZ administration twice or more. Although TCZ treatment ameliorated the increased CRP in all patients rapidly, for the four critically ill patients who received an only single dose of TCZ, three of them (No. 1, 2, and 3) still dead and the CRP level in the rest one patient (No. 7) failed to return to normal range with a clinical outcome of disease aggravation. Serum IL-6 level tended to further spiked firstly and then decreased after TCZ therapy in 10 patients. A persistent and dramatic increase of IL-6 was observed in these four patients who failed treatment. TCZ appears to be an effective treatment option in COVID-19 patients with a risk of cytokine storms. And for these critically ill patients with elevated IL-6, the repeated dose of the TCZ is recommended.

KEYWORDS
COVID-19, cytokine storms, interleukin-6, SARS-CoV-2, Tocilizumab

1 | INTRODUCTION

In December 2019, A novel coronavirus disease (COVID-19), caused by infection with SARS-CoV-2, has rapidly spread across continents. The first report of pathological characteristics of the patient who died from severe infection with SARS-CoV-2 showed that an increased concentration of highly proinflammatory cytokines.[1] Actually, the cytokine storms mediated by overproduction of proinflammatory cytokines have been observed in a large population of critically ill patients infected with COVID-19.[2,3] Patients suffered from cytokine storms progress to cardiovascular collapse, multiple organ dysfunction, and death rapidly. Therefore, early identification, treatment, and prevention of the cytokine storms are of crucial importance for the patients.

IL-6 is a cytokine that plays an important role in inflammatory reaction and immune response.[4] The most recent clinical experiences in China suggested that IL-6 is one of the most important cytokines involved in COVID-19-induced cytokine storms. For this reason, TCZ, a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R), is recommended in seriously ill patients with elevated IL-6 by the *Diagnosis and Treatment of Pneumonia Infected by Novel Coronavirus* issued by the *National Health Commission of China* in the latest 7th version. However, there are limited real-life data about the effect of TCZ on the inflammatory activity in COVID-19 patients.

In this retrospective observational study, we aimed to present treatment responses of TCZ in the COVID-19 patients and to some extent, provide guidance for clinical use.

2 | METHODS

2.1 | Study design and participants

The patients infected with COVID-19, who were treated with TCZ from January 27 to 5 March 2020 at Zhongfaxincheng campus of Tongji Hospital in Wuhan, China, were recruited in this retrospective study. All patients were anonymous. The study was approved by the ethical committee of Huazhong University of Science and Technology.

2.2 | Procedures

The data of demographics, comorbidities, treatments, laboratory results, and clinical outcomes of the patients were obtained from the medical records. Based on *Diagnosis and Treatment of Pneumonia Infected by Novel Coronavirus* issued by the *National Health Commission of China*, the COVID-19 was classified into four types: mildly ill, moderately ill, seriously ill and critically ill.[5] The serum levels of CRP and IL-6 were observed before and after TCZ administration. CRP, an acute-phase reactant reflecting the inflammatory activity, was defined as elevated when it was higher than 5.0 mg/L.[2] The level of IL-6 was defined as elevated when it was higher than 7.0 pg/mL.[2] The patients whose laboratory data of CRP or IL-6 is complete deficiency before or after TCZ administration were considered as study dropouts. The most recent CRP or IL-6 values before TCZ administration was selected as the value of before TCZ therapy and the changes of the value after TCZ administration was observed for a week. The clinical outcome of the patients was evaluated within 1 week after TCZ therapy.

2.3 | Statistical analysis

Statistical analysis was done with SPSS, version 23.0. Data are presented as median (min-max) or as the number and percentage, as appropriate. The Wilcoxon signed-rank test used to compare parameters whenever appropriate. A *P*-value of less than .05 was considered statistically significant.

3 | RESULTS

Fifteen patients (12 males and 3 females) with COVID-19 were included in this study. The characteristics of patients, the use of TCZ and other anti-inflammatory drugs are summarized in Table 1. The median age (min-max) of the patients was 73 (62-80) years. Two (13.3%) patients were moderately ill, six (40.0%) patients were seriously ill, and seven (46.7%) patients were critically ill. Ten (66.7%) patients had one or more co-morbidities, including cadiocerebrovascular diseases and endocrine system diseases. Eight (53.3%) patients received TCZ in combination with MP. Five (33.3%) patients received TCZ administration twice or more. The dose of TCZ used in patients was the range from 80 to 600 mg per time.

The laboratory findings of the 15 patients before, and in the first week after TCZ treatment are summarized in Table 2. The CRP levels were far above the normal range in all patients before the start of TCZ therapy, and were rapidly ameliorated after the TCZ treatment. The value of CRP at the first time it was detected after TCZ therapy was significantly decreased compared with before TCZ therapy, which dropped from 126.9 (10.7-257.9) to 11.2 (0.02-113.7) mg/L ($P < .01$). Although TCZ has benefits in relieving inflammatory activity, for the four critically ill patients who received only single dose of TCZ therapy, three of them (No. 1, 2, and 3) were still dead and the CRP level in the rest one patient (No. 7) failed to return to normal range (nearly 20 times higher than normal) during the week-long session. In the other 11 patients, CRP levels were in or near the normal range within 1 week.

Elevated IL-6 is the indication for TCZ use in COVID-19. The levels of IL-6 before TCZ administration ranged from 16.4 to 627.1 pg/mL (2 times to nearly 90 times higher than normal). After starting TCZ therapy, serum IL-6 level in 10 (66.7%) patients tended to spike shortly in first and then decreased. One patient (No. 13) demonstrated a persistent decrease of IL-6 after TCZ administration combined with MP. The clinical classification of these patients is mainly moderately ill and seriously ill patients. But in these four critically ill patients who failed the treatment (No. 1, 2, 3, and 7), a persistent and dramatic increase of IL-6 was observed. Except for patients No. 1, 2, 3, and 7, patient No. 15 also had a clinical outcome of aggravation.

4 | DISCUSSION

In this study, we evaluated the effect of TCZ therapy in COVID-19 patients in real life. Our findings supported the effectiveness of TCZ in the prevention or treatment of cytokine storms induced by COVID-19. In most patients, acute phase reactant levels were decreased and the patients were getting to a stable condition reflected by a later gradual decrease of IL-6 after TCZ administration.

Corticosteroids such as MP are the conventional agents used to fight cytokine storms. However, in the treatment of corticosteroids, a high dose and a long-time period were often required and follow with subsequent risk of side effects. In an attempt to provide a corticosteroid-sparing effect, TCZ was recommended in COVID-19 patients to prevent or treat cytokine storms. The rationale for the use of the anti-IL-6 receptor antibody TCZ in COVID-19 patients is based on our understanding of the role of IL-6 in this disease and the experience with this drug in the treatment of cytokine release syndrome caused by chimeric antigen receptors redirect T cells.[6]

TABLE 1 The characteristics of COVID-19 patients treated with TCZ

Case No.	Age	Sex	Clinical classification	Co-morbidity	Therapy							
					Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	73	M	Critically ill	Hypertension	TCZ 480 mg MP 40 mg	MP 40 mg	MP 40 mg	MP 40 mg	...	...	...	...
2	62	M	Critically ill	None	TCZ 600 mg MP 40 mg	MP 40 mg bid	MP 40 mg bid	MP 40 mg bid	...	...	...	...
3	62	M	Critically ill	Hypertension	TCZ 320 mg MP 80 mg bid	MP 80 mg bid	MP 80 mg bid	MP 80 mg bid	MP 80 mg bid	MP 80 mg bid	...	...
4	74	M	Critically ill	Hypertension Stroke history	TCZ 480 mg	...	...	TCZ 480 mg	...	...	...	...
5	72	M	Critically ill	Hypertension	TCZ 100 mg	TCZ 240 mg	...	...	...	...	...	...
6	73	M	Critically ill	None	TCZ 80 mg	TCZ 160 mg	TCZ 80 mg	...	...	...	...	...
7	65	M	Critically ill	Hypertension Stroke history	TCZ 480 mg MP 40 mg	MP 40 mg bid	MP 80 mg bid	MP 80 mg bid	MP 80 mg bid	MP 80 mg bid	...	...
8	66	F	Seriously ill	Stroke history	TCZ 480 mg MP 80 mg	MP 80 mg	MP 80 mg	MP 80 mg	...	...	...	...
9	73	M	Seriously ill	Hypertension Diabetes	TCZ 480 mg	...	TCZ 480 mg	...	...	...	...	...
10	77	M	Seriously ill	Hypertension Diabetes	TCZ 400 mg	...	...	...	...	...	...	...
11	65	F	Seriously ill	Hypertension Diabetes	TCZ 400 mg MP 40 mg	MP 40 mg bid	MP 40 mg bid	MP 40 mg bid	MP 40 mg	MP 40 mg	MP 40 mg	...
12	77	M	Seriously ill	Hypertension Diabetes	TCZ 400 mg	...	...	...	...	...	...	...
13	75	M	Moderately ill	None	TCZ 480 mg MP 40 mg	MP 40 mg bid	MP 40 mg bid	MP 40 mg bid	MP 40 mg bid	...	...	...
14	77	M	Moderately ill	None	TCZ 80 mg	TCZ 160 mg	TCZ 80 mg	...	...	...	...	...
15	80	F	Seriously ill	None	TCZ 240 mg MP 40 mg	MP 40 mg bid	MP 40 mg bid	MP 40 mg bid	...	...	MP 20 mg	MP 20 mg

Abbreviations: bid, twice a day; F, female; M, male; MP, methylprednisolone; TCZ, tocilizumab.

TABLE 2 The laboratory findings of COVID-19 patients at before and after TCZ treatment

		After TCZ therapy							
Case No.	Before TCZ therapy	Day1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Clinical outcomes
CRP, mg/L									
1	199.9	113.7	76.7	50.7	…	51.8	…	Death	Death
2	257.9	53.1	…	…	19.9	12.8	Death	…	Death
3	175.8	92.7	21.7	15.9	…	17.9	Death	…	Death
4	177.6	38.0	…	…	2.8	…	…	…	Clinical stabilization
5	32.2	…	…	…	2.8	…	…	1.1	Clinical stabilization
6	253.1	…	…	…	…	…	…	5.0	Clinical stabilization
7	126.9	74.7	40.6	20.6	11.1	51.9	147.6	93.5	Disease aggravation
8	96.1	…	29.0	9.2	…	5.7	…	…	Clinical stabilization
9	91.0	…	…	…	11.2	…	…	3.4	Clinical stabilization
10	10.7	<0.02	…	…	…	…	0.5	…	Clinical stabilization
11	97.7	…	…	…	…	…	…	1.3	Clinical stabilization
12	26.3	…	…	…	…	…	…	0.5	Clinical improvement
13	91.2	…	…	…	…	…	2.5	…	Clinical stabilization
14	160.2	…	…	…	10.7	…	…	2.1	Clinical stabilization
15	180.6	…	31.5	11.8	8.0	…	…	6.3	Disease aggravation
IL-6, pg/mL									
1	16.4	71.0	…	…	…	5000.0	5000.0	death	Death
2	32.7	…	232.9	…	1602.0	2230.0	death	…	Death
3	73.6	419.5	960.2	…	…	5000.0	death	…	Death
4	392.0	935.5	…	…	396.8	…	…	…	Clinical stabilization
5	24.4	…	204.3	…	172.4	…	…	172.0	Clinical stabilization
6	31.9	…	483.8	…	269.4	…	…	…	Clinical stabilization
7	46.8	55.5	73.7	70.1	483.0	557.0	3225.0	3628.0	Disease aggravation
8	72.7	…	208.8	133.1	…	…	…	…	Clinical stabilization
9	76.7	…	197.9	…	129.4	…	…	119.1	Clinical stabilization
10	46.5	59.3	…	…	…	…	45.7	…	Clinical stabilization
11	21.4	…	429.9	…	…	…	…	197.0	Clinical stabilization
12	19.7	…	…	125.0	…	…	…	108.8	Clinical improvement
13	71.1	12.4	…	…	…	…	66.6	…	Clinical stabilization
14	627.1	905.6	…	416.2	243.9	…	…	249.0	Clinical stabilization
15	112.8	247.4	688.2	828.1	1707.0	…	1087.0	704.7	Disease aggravation

Abbreviations: CRP, C-reactive protein; IL-6; interleukin-6; TCZ, tocilizumab.

The present study suggested that a single dose of TCZ seems to fail to improve the disease activity in critically ill patients although it was used in combination with glucocorticoid. However, repeated doses (even repeated with a lower dose) of TCZ might improve the condition of critically ill patients. Therefore, in addition to the safety advantage, a repeated dose of TCZ is more likely to be effective than glucocorticoid in the treatment of COVID-19. Moreover, single dose of TCZ might be expected to benefit these seriously ill patients with about 10 times elevated IL-6. And the moderately ill patient with an extremely higher level of IL-6, almost 90 times of normal, could also benefit from repetitive TCZ therapy. Nevertheless, it seems that repeat the dose at a frequency of daily, every other day, or every 3 days with a totally two to three doses would be sensible in these critically ill patients or patients with an extremely higher level of IL-6. Considering the long half-life time of TCZ and the saturate properties of receptor binding, the dose of TCZ could be reduced when repeated use.

IL-6 can be used to evaluate the severity of the infection and predict the prognosis.[7] Dynamic observation of IL-6 levels is also helpful in understanding the progression of COVID-19 and the response to treatment. IL-6 level tends to further spiked and then decreased in most patients after starting TCZ therapy. Actually, IL-6 is mainly eliminated via IL-6R-mediated clearance.[8] Binding of TCZ to IL-6R inhibits receptor-mediated clearance of IL-6, leading to its accumulation in serum. This is the likely explanation for the spiked IL-6 levels in TCZ-treated COVID-19 patients in this study. And a later gradual decrease of IL-6 might partly benefit from the inhibition of inflammatory activity by TCZ that resulting in stabilization or improvement of clinical outcome. Given the application of TCZ combined with PM in patient 13, we propose that PM might account for the persistent decrease of IL-6 in this patient since stopping PM administration trend to lead an increase of IL-6. It is the other possible risk factors, not an

inflammatory activity, which may attribute to the aggravation of the patient No. 15.

Our result should be evaluated with caution although we reported a good response in patients with TCZ. The number of cases reported is still small and using laboratory parameters to define the disease activity is still challenging. Furthermore, the treatment duration observed in our study may not be sufficient to make a final conclusion. Therefore, observation with a sufficient number of COVID-19 patients is still needed to document the effectiveness of TCZ.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

JL and DL were responsible for the design of the study and revised the final manuscript. PL and YL contributed to the acquisition, analysis and interpretation of data. PL is responsible for summarizing all data and wrote the draft. All data were checked by LQ and XL.

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How to cite this article: 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;92:814–818. https://doi.org/10.1002/jmv.25801