

Preliminary Efficacy of Tocilizumab Treatment in The Patients With COVID-19.

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Research

Keywords: COVID-19, Tocilizumab, preliminary efficacy, safety

Posted Date: January 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-147574/v1>

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Abstract

Background: Interleukin-6 (IL-6) was considered to be with the severity and mortality in COVID-19 patients, which implies a potential therapeutic target for treatment. We aimed to evaluate the safety and initial efficacy of Tocilizumab treatment for COVID-19 patients.

Methods: In the retrospective study, sixty-one patients with COVID-19 with the mean age of 69 were enrolled from Feb 27 to Mar 14, 2020 in Wuhan Huoshenshan Hospital. Twenty-nine of them received one dose (400 mg) of add-on Tocilizumab treatment as the treated group and remaining 32 cases served as control group. The clinical manifestations and laboratory examinations were compared between the two groups.

Results: The average duration of symptoms to admission was 28.2 days. Compared with the cases in control group, the treated cases exhibited a significant increase of serum IL-6 on the seventh day since Tocilizumab injection, however, there were no differences in whole blood white cell count, circulating lymphocyte count, serum C-reactive protein, and respiratory parameters or other clinical manifestations between the treated and control groups. There were no adverse events associated with Tocilizumab treatment in the treated COVID-19 patients.

Conclusions: In the elder moderate and severe patients with COVID-19, one dose of Tocilizumab treatment was safe but no clinical benefit was observed on the seventh day in this study.

Trial registration: Chinese Clinical Trail Registry, ChiCTR2000033705. Registered June 10, 2020 - Retrospectively registered, <http://www.chictr.org.cn/showprojen.aspx?proj=54989>.

Background

Global cases of confirmed COVID-19 have exceeded 83 million with 1,831,703 deaths by 5 January 2021(1). The ongoing antiviral and immune modulation therapeutic regimens mainly include hydroxychloroquine, chloroquine, Favipiravir, Remdesivir, and convalescent plasma, mesenchymal stem cell therapy as well. However, most of them are lack of evidence from randomized control clinical trials to recommend some specific and efficient therapeutic approaches. The pathogenesis of COVID-19 is not fully understood, the direct and indirect injuries induced by acute SARS-CoV2 infection influence the outcome of COVID-19. In particular, the indirect over-activated immune-mediated inflammatory injury was usually manifested by overactivation of peripheral T cells. Simultaneously, recent studies showed that interstitial mononuclear inflammatory infiltrates in lungs were both found in the patients(2). Cytokine storm syndrome (CRS) often leads to the development of acute respiratory distress syndrome (ARDS), or multiple organ dysfunction syndromes (MODS)(3). That clinical biomarkers such as interleukin-6 (IL-6), C-reactive protein, and ferritin, were also considered to be with the severity and mortality in COVID-19 patients(4, 5), which implies a potential therapeutic target for treatment of COVID-19. Tocilizumab, being a recombinant humanized monoclonal antibody directed against the interleukin-6 receptor (IL-6R), was previously issued to use in treatment of rheumatoid arthritis by American FDA in 2010(6). In the epidemic

of COVID-19, Tocilizumab was recommended to treat COVID-19 patients with increased IL-6 levels to block cytokine storm(7). We hypothesize that the Tocilizumab as an additional immunotherapy may be associated with improved clinical outcome in the COVID-19 patients with elevated IL-6 levels. Due to the difficulty of performing prospective randomized controlled studies in such epidemic condition, we reported the findings in this retrospective study to analyze the efficacy and safety of Tocilizumab in the patients with COVID-19.

Methods

Study patients

Sixty-one patients (40 males, 21 females) with COVID-19 were enrolled from Feb 27 to Mar 14, 2020 in Wuhan Huoshenshan Hospital, Hubei, China. Diagnostic criteria are based on the guideline of China's National Health Commission(7). Clinical classification of moderate cases means the COVID-19 patients showing fever and respiratory symptoms with radiological findings of pneumonia(7). Adult cases meeting any of the following criteria while patient was breathing ambient air at rest were diagnosed as severe type: (1) Dyspnea and respiratory frequency ≥ 30 breaths/ min; (2) Percutaneous oxygen saturation $\leq 93\%$; (3) Arterial partial pressure of oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2) ≤ 300 mmHg(7). Cases requiring mechanical ventilation, shock, with other organ failure that required ICU care were excluded(7). This study was approved by the Ethics Committee of Wuhan Huoshenshan Hospital (Approval number: HSSLL033). Twenty-nine patients with COVID-19 treated with Tocilizumab in addition to conventional treatment. 32 cases were enrolled in control group. Inclusion criteria included: (1) Diagnosed as COVID-19 (clinical classification of moderate or severe cases); (2) age > 18 years old; (3) IL-6 level > 7 pg/mL. Exclusion criteria: (1) Pregnant or lactating women; (2) Alanine transaminase (ALT)/ Aspartate transaminase (AST) > five times ULN, neutrophil < $0.5 \times 10^9/\text{l}$, platelet < $50 \times 10^9/\text{l}$; (3) Diagnosis of rheumatism immunity, malignant tumor, and other related diseases; (4) Long-term oral administration of anti-rejection drugs or immunomodulatory drugs; (5) Allergic reaction to Tocilizumab or any auxiliary materials; (6) Active hepatitis, tuberculosis; (7) Patients received organ transplantation; (8) Mental disorders.

Treatment protocol

In this retrospective study, all patients received a routine treatment protocol according to the guideline published by the China's National Health Commission(7), including antiviral drugs, symptom relievers, and oxygen therapy. Tocilizumab (Roche Pharma (Schweiz) Ltd, B2084B21) was solved in 100ml normal saline. Only one dose of 400 mg was given through an intravenous drip with infusion time more than one hour(7). The following outcomes were compared between groups: whole blood white cell count (WBC), lymphocyte count, level of IL-6 and C-reactive protein (CRP), peripheral oxygen saturations, body temperature, respiratory rate, respiratory support strategies, and length of hospital stay (Figure 1).

Statistical analysis

All data, are expressed as mean (\pm SD). Chi-square test or Fisher's exact test were used for categorical variables, Student's t test or repeated-measures one-way analysis of variance (ANOVA) with Tukey's post hoc test were used for continuous variables where appropriate. A two tailed p value of $p < 0.05$ was considered significant. GraphPad Prism Version 8.4.0 (GraphPad Software Inc., San Diego, CA, USA) was used for all analyses.

Results

Demographic characteristics

The 61 patients had a mean (\pm SD) age of 69 (\pm 13.1) years, ranged from 19 to 93 years and there were 40 (65.6%) men. Mean duration (\pm SD) of symptoms to admission was 28.2 (\pm 13.3) days (29.4 \pm 13.7 days in the control group, 27.0 \pm 13.0 days in the treated group). 51 (83.6%) patients with the course of the disease over two weeks. 34 patients (55.7%) met moderate type criteria, and 27 (44.3%) met severe type criteria according to the "New Coronavirus Pneumonia Diagnosis and Treatment Plan (Seven Edition)". 36 patients (59.0%) had at least a chronic co-existing illness. 29 patients (47.5%) received one dose of Tocilizumab as treatment group and the others were assigned to the control group. After admission, all patients needed an oxygen therapy, including nasal cannula in 35 patients (57.4%), mask oxygen in 15 patients (24.6%), high-flow nasal oxygen therapy in 11 patients (18.0%), and no patient received noninvasive ventilation or invasive ventilation. The baseline data of enrolled patients were showed in table 1. A significant difference was not found between the cases of two groups.

Adverse events

No adverse drug reaction related to Tocilizumab was reported. All patients survived in this study. There was no difference in the days of hospitalization between groups (Table 2). Patients given Tocilizumab had higher blood IL-6 levels at seventh day (Figure 2). Between Tocilizumab treated patients with serum IL-6 levels above and below 100 pg/ml at seventh day, the length of hospital stays showed no differences (26 \pm 13.2 vs. 26 \pm 10.7, $p > 0.05$, shown as mean \pm SD days). Until last follow up (April 10, 2020), one Tocilizumab treated patient was still in hospital.

No difference of clinical presentations between treated and control groups

On the median day seven, the changes of clinical manifestations and laboratory examinations between the two groups were compared. All patients return to normal temperature (< 37.3 °C, axillary temperature), mean respiratory rate (RR) and oxyhemoglobin saturation by pulse oximetry (SpO₂) were also in a normal range. Respiration support was de-escalated, including nasal cannula in 53 patients (86.9%), mask oxygen in 2 patients (3.3%), high-flow nasal oxygen therapy in 6 patients (9.8%). There was no difference of body temperature, RR, SpO₂, or the way of oxygen therapy between the two groups (Table 2).

IL-6 expression levels were analyzed in all patients on day one defined as the first day of detectable increasement of IL-6 with the mean \pm SD of 32.6 \pm 43.9 pg/ml in control group and 29.4 \pm 46.1 pg/ml in

the treatment group (Figure 1A). After 7 days, mean IL-6 expression levels were significantly upregulated in the treatment group as compared with control group ($p < 0.01$, Figure 2A). White blood cell count showed a decrease in both groups as compared with the level on day one ($p < 0.05$). But there was no difference between the two groups at the same time point (Figure 2B). Compared with the level on day one, CRP levels on day seven were decreased in both groups. No difference was found between the two groups at the same time point (Figure 2C). There was no difference in lymphocyte count between groups at any time (Figure 2D).

Imaging features were similar in the two groups

Varying degrees of consolidations or mixed ground-glass opacities were presented by chest computerized tomography (CT, uCT760, United Imaging Com.) in most patients (Figure 3). Differences of percentage of infection were calculated by a modified 3-D convolutional neural network-based method, the values less than 1.0% were not included for the observational error. Imaging features were followed up until April 10. 17 patients in the control group and 18 patients in the Tocilizumab treatment group were performed at least two CT scans for comparison. The mean time interval between inspections was 17.7 days (17.5 ± 8.8 days in the control group, 17.9 ± 11.3 days in the Tocilizumab treatment group, shown as mean \pm SD). Different levels of lesions absorption were reported in 11 patients of Tocilizumab treatment group (61.1%) and 10 patients in the control group (58.8%). There were no differences between groups at any time (Figure 4).

Discussion

Inflammatory cytokines are elevated COVID-19 patients, and related to the severity and prognosis of the disease(8, 9). Histological examination also shown mononuclear inflammatory lymphocytes were infiltrated in lungs(8), suggesting an inflammatory factor or a CRS have occurred. Severe or life-threatening CRS is a medical emergency requiring treatments includes fluids resuscitation and corticosteroids in some patients, which may cause further deterioration of lung function and aggravation of infection(10). Several cytokines including IL-6 are participated in the pathological process of CRS, and immunosuppression using Tocilizumab, an anti-IL-6R antibody, can reverse the syndrome(11, 12). Previous study indicated that an elevated level of IL-6 was associated with a high case fatality of COVID-19 patients(13). And circulating IL-6 levels were closely linked to the severity of COVID-19 infection in a recent meta-analysis(5). Therefore, in theory, interfering of IL-6R with Tocilizumab might be a potentially therapeutic for COVID-19.

Tocilizumab was used to treat rheumatoid arthritis (6). The latest guideline issued by Chinese National Health Commission recommended Tocilizumab for treatment of COVID-19 patients with increased IL-6 levels (7). Serum IL-6 level were analyzed in 1,086 patients in Wuhan Huoshenshan Hospital by Mar 13, the positive rate was 14.83% (> 7 pg/mL), and 29 patients treated with Tocilizumab were enrolled in this study.

Tocilizumab binds both soluble and membrane-bound IL-6R and inhibits IL-6 mediated signaling through these receptors without increasing half-life of IL-6(10). Clearance of single-dose Tocilizumab was slow, with a half-life more than 6 days in both rats and monkeys(14). In human, after the third dose of 8 mg/kg, its maximum half-life nearly 240 h. So, it can be administered biweekly or monthly(15). In our study, one dose 400 mg Tocilizumab was associated with a rebound IL-6 upregulation on the median day seven. Which is reasonable as that Tocilizumab has a long elimination half-life time, the block of IL-6R would stimulate more IL-6 expression(16).

Unfortunately, No clinical benefit of Tocilizumab in treatment of 29 patients with moderate or severe COVID-19 in this retrospective study. One explanation is that the illness of patients included in this study is relatively mild. By 7 January 2021, there were 87,331 confirmed cases and 4,634 deaths have been reported in China, the mortality was nearly 5.3%(17), and according to a new report, the mortality of critical cases reached 60.5%(18). While all the patients survive during the entire observation period in our study. The recommendation of Tocilizumab was mentioned in the latest guideline published in Mar 4(7). Before that, IL-6 was not routine tested and the clinicians were more willing to try additional Tocilizumab treatment in relatively mild patients in order to avoid any uncertain factors in critical cases.

In the pathogenesis of SARS-CoV and MERS-CoV, cytokine genes of IL-6 can be markedly high(19, 20). One research also found elevated plasma levels of cytokines including IL-6 in patients with COVID-19(21). In our study, the baseline CRP levels were less than 100 mg/L in both groups, indicating the inflammatory reaction may not be serious in these patients. Which could minimize the clinical benefits of Tocilizumab treatment. However, the elevation of IL-6 was not observed in a recent study(9). Indicating a second and probably a more important possibility, that IL-6 may not play a key role in the pathogenesis of COVID-19, even in the cases with obvious inflammatory response.

Many reasons could explain our frustrating results, including small sample size, differences in baseline levels, lack of IL-6 data, and failure to include critically ill patients. We acknowledge these shortcomings and expect further well-designed RCT trails looking at timing of treatment intervention and type of aged patients to draw a more rigorous conclusion. Meanwhile, COVID-19 patients may experience life-threatening CRS which may cause severe damage to various systems. It is wise to provide effective organ support and carefully prevent complications, instead of expecting unproved miracles.

Conclusions

In summary, in the elder moderate and severe COVID-19 patients, one dose Tocilizumab treatment was safe but no clinical benefit was demonstrated on the seventh day in this study.

Abbreviations

ALT: alanine transaminase; ARDS: acute respiratory distress syndrome; AST: aspartate transaminase; CRP: C-reactive protein; CRS: cytokine storm syndrome; FiO₂: fraction of inspired oxygen; IL-6: Interleukin-

6; IL-6R: interleukin-6 receptor; MODS: multiple organ dysfunction syndromes; PaO₂: arterial partial pressure of oxygen; RR: respiratory rate; SpO₂: pulse oximetry; WBC: whole blood white cell count.

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Committee of Wuhan Huoshenshan Hospital (Approval number: HSSLL033). All written consents from patients were waived due to the retrospective nature of the current study.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: This work was supported by the Natural Science Foundation of Shaanxi Province of China (grant number 2019JM-465) and Subject Boosting Program of Air Force Military Medical University (XJZT18ML63).

Authors' contributions: Yu Chen gathered the data, conducted the statistical analyses and drafted the manuscript and figures. Xijing Zhang, and Yu Chen conceived the concept of the study and supervised data collection. The authors critically reviewed and validated the final version of the manuscript.

Acknowledgements: Not applicable.

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Tables

Table 1 Demographic Characteristics of enrolled Patients

Characteristic	Treatment group (N=29)	Control group (N=32)	p value
Age (mean ± SD, years)	68.5 ± 11.3	69.4 ± 15.8	0.8
Male/Female	22/7	18/14	0.11
Existing illness	17	19	>0.99
AD	0	1	
Anemia	1	1	
CHD	9	7	
CKD	1	1	
CLD	1	1	
COPD	0	4	
Diabetes	8	10	
Hypertension	11	8	
State of illness			0.31
mild or moderate	14	20	
Severe	15	12	
Temperature (mean ± SD, °C)	36.7 ± 0.4	36.5 ± 0.3	0.06
RR (mean ± SD, bpm)	20.1 ± 2.2	20.0 ± 1.4	0.83
SpO₂ (mean ± SD, %)	96.1 ± 2.6	96.3 ± 2.6	0.79
Oxygen therapy			0.98
Nasal cannula (<3L/min)	17	18	
Mask oxygen	7	8	
High-flow oxygen	5	6	
Noninvasive ventilation	0	0	
Invasive ventilation	0	0	
Duration of symptoms to admission (mean ± SD, days)	27.0 ± 13.0	29.4 ± 14.0	0.48
Hospitalization (Mean ± SD, days)	6.3 ± 7.0	3.5 ± 6.2	0.1

AD, Alzheimer disease; CHD, coronary heart disease; CKD, chronic kidney disease; Chronic Liver Disease, CLD; COPD, chronic obstructive pulmonary disease. RR, respiration rate.

Table 2 Comparison of parameters between treated and control group at the seventh day of Tocilizumab treatment

Characteristics	Treatment group (N=29)	Control group (N=32)	<i>p</i> value
Temperature (Mean ± SD, °C)	36.5 ± 0.2	36.5 ± 0.2	0.53
RR (Mean ± SD, bpm)	19.0 ± 1.6	19.2 ± 1.4	0.63
SpO₂ (Mean ± SD, %)	97.8 ± 1.3	97.9 ± 0.9	0.78
Oxygen therapy			0.99
Nasal cannula (<3L/min)	25	28	
Mask oxygen	1	1	
High-flow oxygen	3	3	
Length of hospital stay (Mean ± SD, days)	22.1 ± 9.5	26 ± 11.3	0.15
Death	0	0	

Figures

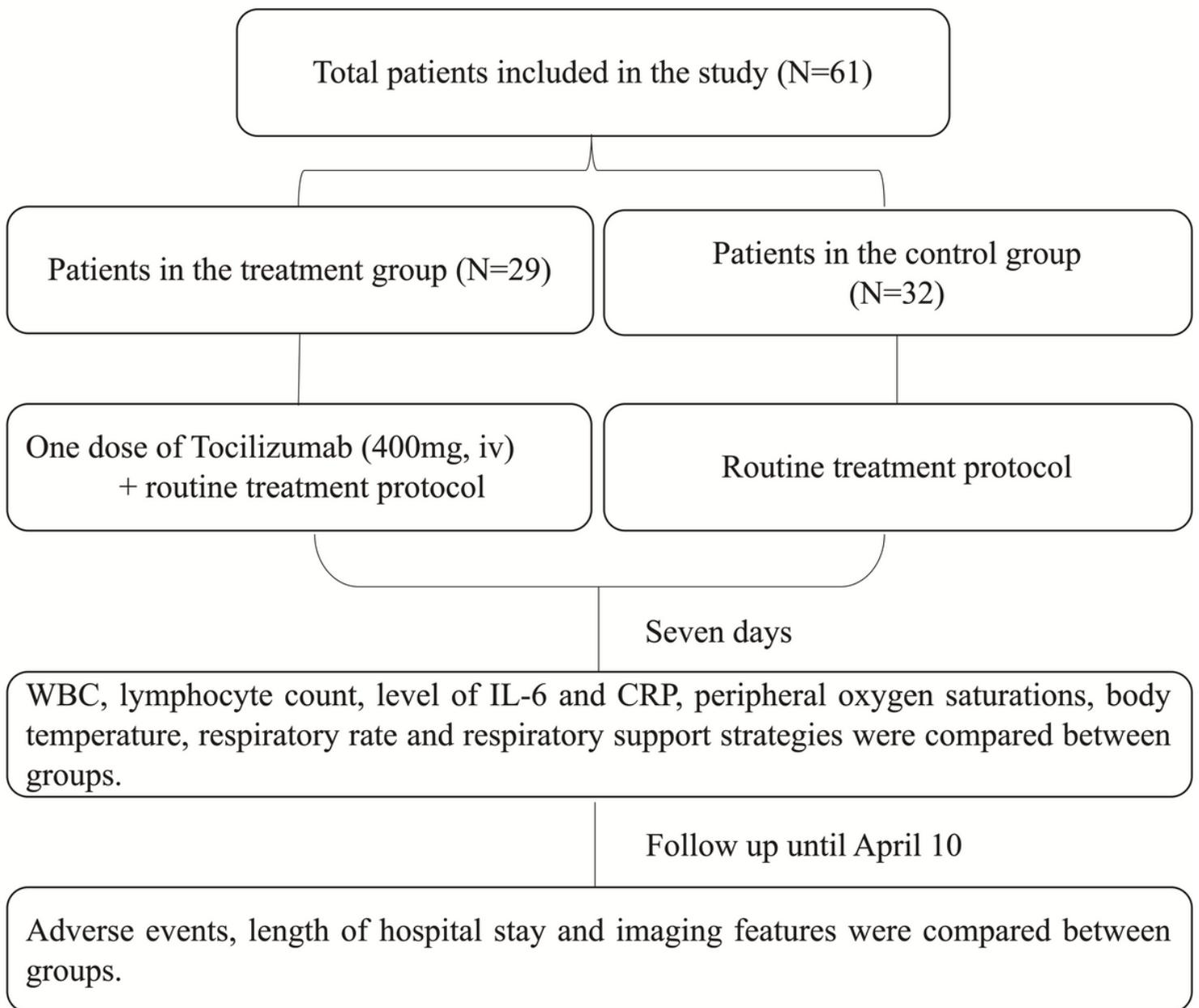


Figure 1

Flow chart.

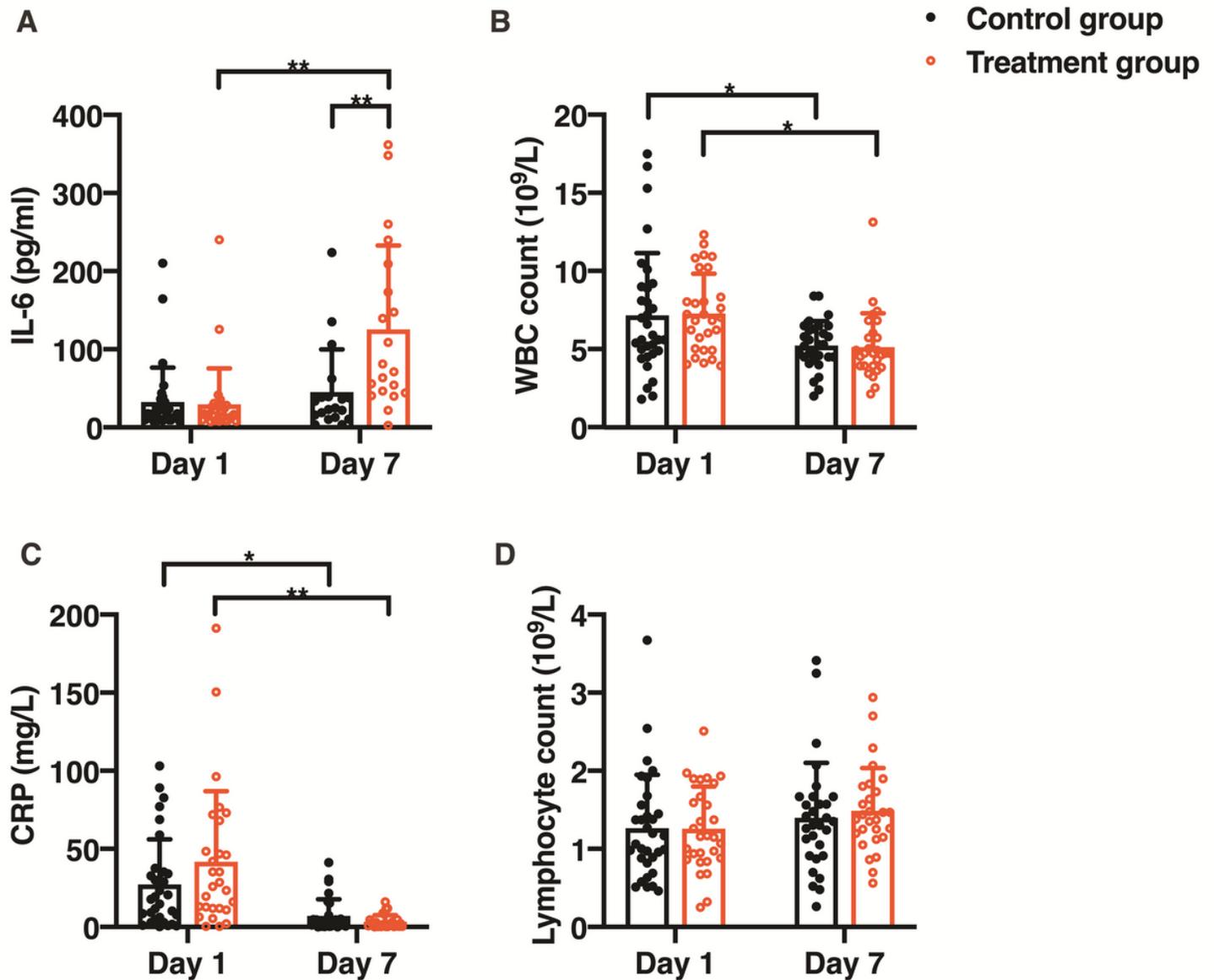
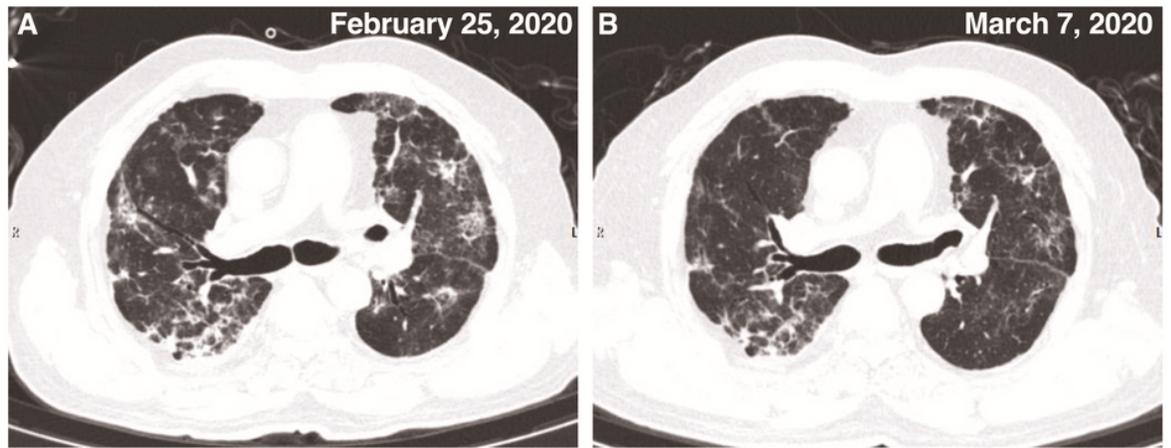


Figure 2

The Values of IL-6, CRP, WBC and lymphocyte count between groups. Day 1, the time of first detectable IL-6 elevation. * $p < 0.05$, ** $p < 0.01$. A: after 7 days, mean \pm SD IL-6 expression levels were upregulated in the treatment group as compared with control group (125.5 ± 107.3 pg/ml vs. 45.1 ± 54.9 pg/ml). B: white blood cell count showed a decrease in both groups as compared with the level on day 1 ($5.2 \pm 1.5 \times 10^9/L$ vs. $7.2 \pm 3.9 \times 10^9/L$ in control group ($5.1 \pm 2.1 \times 10^9/L$ vs. $7.3 \pm 2.5 \times 10^9/L$ in treatment group). There was no difference between the two groups at the same time point. C: compared with the level on day 1, CRP levels on day seven were decreased in both groups. (7.0 ± 10.7 mg/L vs. 27.3 ± 28.8 mg/L in control group. 3.4 ± 4.3 mg/L vs. 41.8 ± 45.1 mg/L in treatment group) and no difference was found between the two groups at the same time point. D: There was no difference in lymphocyte count between groups at any time.

A 75-year-old male patient in the control group.



An 81-year-old male patient in the treatment group.



Figure 3

Chest CT imaging images. The CT image (A) of a 75-year-old male patient in the control group was performed at February 27, patchy and punctate ground-glass opacities and consolidations could be observed. CT scan was performed again at March 7, the density of patchy and punctate consolidation decreased (B). The CT image of an 81-year-old male patient in the treatment group (C) was performed at February 25, consolidation in the subpleural area could be found. CT scan was performed again at March 7, the density and range of consolidation decreased (D).

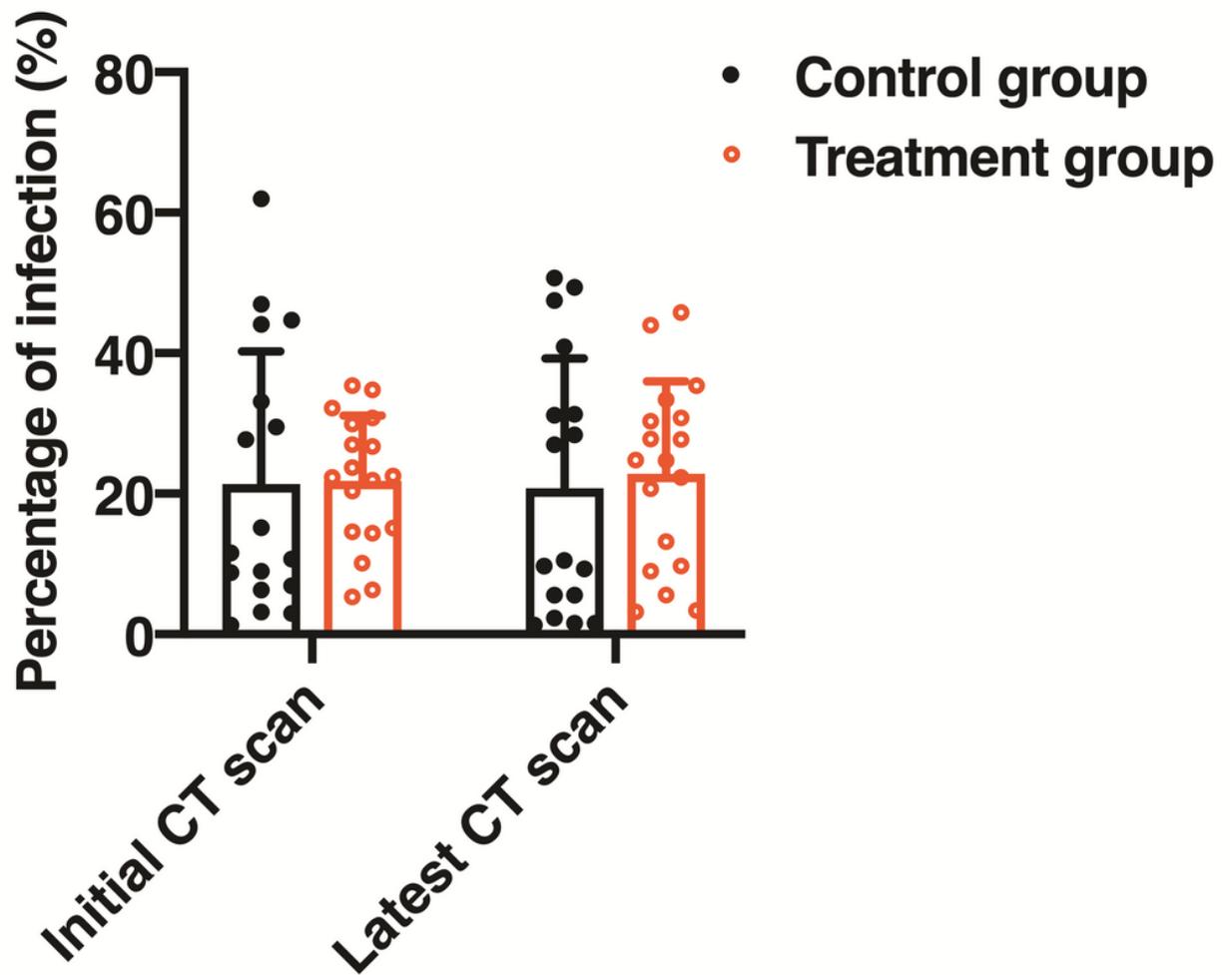


Figure 4

The Values of percentage of infection calculated by an AI method from CT reports between groups. Mean time interval between inspections (initial CT scan and latest CT scan) was 17.7 days (17.5 ± 8.8 days in the control group, and 17.9 ± 11.3 days in the Tocilizumab treatment group, shown as mean \pm SD). The mean \pm SD infection percentage of initial CT scan and latest CT scan was $21.3 \pm 18.8\%$ and $20.7 \pm 18.4\%$ respectively in the control group, and $21.8\% \pm 9.3\%$ and $22.8\% \pm 13.2\%$ in the treatment group. There were no differences between groups at any time.