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Tocilizumab combined with favipiravir in the treatment of COVID-19: A multicenter trial in a small sample size

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ABSTRACT

Background: Since December 2019, COVID-19 has spread to almost every corner of the world. In theory, tocilizumab and favipiravir are considered to be reliable drugs for the treatment of COVID-19 with elevated IL-6. We aimed to assess the efficacy and safety of tocilizumab combined with favipiravir in patients with COVID-19.
Methods: This was a multicenter trial in adults with COVID-19. Patients were randomly assigned (3:1:1) to a 14-day combination of favipiravir combined with tocilizumab (combination group), favipiravir, and tocilizumab. The primary outcome was the cumulative lung lesion remission rate (lung CT examination indicated absorption of lung inflammation).
Results: Between Feb 2 and March 15, 2020, 26 patients were recruited; 14 were randomly assigned to the combination group, 7 were assigned to the favipiravir group and 5 were assigned to the tocilizumab group. The cumulative lung lesion remission rate at day 14 was significantly higher in combination group as compared with favipiravir group ($P = 0.019$, HR 2.66 95 % CI [1.08–6.53]). And there was also a significant difference between tocilizumab and favipivavir ($P = 0.034$, HR 3.16, 95 % CI 0.62–16.10). In addition, there was no significant difference between the combination group and the tocilizumab group ($P = 0.575$, HR 1.28 95 %CI 0.39–4.23). Furthermore, combined therapy can also significantly relieve clinical symptoms and help blood routine to return to normal. No serious adverse events were reported.
Conclusion: Tocilizumab combined with or without favipiravir can effectively improve the pulmonary inflammation of COVID-19 patients and inhibit the deterioration of the disease.

1. Introduction

At the end of 2019, several unexplained viral pneumonia appeared in Wuhan China, and then quickly swept the world [1]. As of May 28, 2020, more than 5.7 million people have been infected and more than 350000 people have died around the world [2]. Although most people infected with SARS-CoV-2 are self-limited, it still causes serious loss of life and property all over the world [3].

Recently, numerous studies [4–6] have shown that cytokine release syndrome (CRS) was an important cause of death of COVID-19 patients, in which IL-6 played an important role. Herold et al. [7] found that IL-6 levels can predict respiratory failure in patients with COVID-19 (including 40 patients). The increase of IL-6 was closely related to the need for mechanical ventilation ($p < 0.001$). In addition, the highest

Abbreviations: CRS, cytokine release syndrome; IL-6, interleukin-6.

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IL-6 level of the patients could well predict the occurrence of respiratory failure ($p < 0.001$, AUC = 0.98). Patients with IL-6 levels ≥ 80 pg/mL had a 92 % risk of respiratory failure, 22 times higher than patients with lower IL-6 levels. Liu et al. [8] also showed that the increase of IL-6 level was positively correlated with the severity of COVID-19. The IL-6 was significantly decreased and the pulmonary imaging evaluation was improved in 25 cases. At the same time, the IL-6 level of 3 patients further increased and the disease worsened.

Tocilizumab was a recombinant humanized monoclonal antibody against human interleukin 6 (IL-6) receptor [9]. Mainly used for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis. In addition, a number of reports have been successfully applied to the treatment of CRS [10,11]. Zhou et al. [12] research suggested that overactivated immune response caused by pathogenic GM-CSF + Th1 cells and inflammatory CD14+CD16+ monocytes may lead to pulmonary immunopathology, even death after SARS-CoV-2 infection. Then, their team conducted a retrospective clinical trial involving 21 patients. After the treatment of tocilizumab, the symptoms such as fever and cough were significantly improved within a few days. After 5 days of treatment, 75.0 % (15/20) of the patients had reduced oxygen intake and 1 patient did not need oxygen therapy. CT scan revealed shadow absorption of lung lesions in 19 cases (90.5 %). The percentage of peripheral blood lymphocytes gradually returned to normal [13]. Favipiravir was a new broad-spectrum antiviral drug that targeted RNA-dependent RNA polymerase (RdRp), and was approved for the treatment of influenza [14]. On February 13, 2020, favipiravir tablets were approved by Chinese FDA (batch number: 2020L00005) for COVID-19′s clinical trial. Cytological studies showed that favipiravir could effectively inhibit the infection of Vero E6 cells (ATCC-1586) induced by SARS-CoV-2 [15]. A subsequent clinical trial of 80 patients showed that the virus clearance time in the favipiravir group was shorter than that in the control group (Lopinavir-Ritonavir) (4[2.5–9] vs. 11 [8–13] $P < 0.001$) [16].

As early as February this year, our team put forward the hypothesis of using tocilizumab and antiviral drugs to treat severe COVID-19, and analyzed the possible mechanism in detail [4]. Subsequently, we designed this clinical trial to verify this hypothesis. Here, we report the results of a multicenter, randomized controlled trial of favipiravir combined with tocilizumab in patients with COVID-19.

2. Methods

2.1. Study design and patients

In this multicenter trial, we recruited patients with COVID-19 from 4 hospitals China. According to the proportion of 1:1:3, patients were randomly divided into favipiravir monotherapy group, tocilizumab monotherapy group and favipiravir + tocilizumab combination group. The study protocol has been approved by the ethics committee of each participating site. The trial was done in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization–Good Clinical Practice guidelines. The complete protocol for the clinical trial has been registered at Chinese clinical trial (ChiCTR2000030894 and NCT04310228).

We recruited 31 patients with COVID-19 between February 2nd and March 15th, 2020. All included patients should meet the following criteria: Laboratory-confirmed cases according to Chinese guidelines of COVID-19 [17]; ②Male or female more than 18 years old; ③Increased interleukin-6 ④Sign the informed consent. Key exclusion criteria included: Allergic to favipiravir or tocilizumab; ②Pregnant or lactating woman; ③ALT or AST > 5 times of upper limit of normal; Patients with active hepatitis, tuberculosis, and definite bacterial or fungal infections;⑤Other conditions judged by the investigators.

2.2. Procedures

The use of favipiravir was 1600 mg, twice a day on the first day, and 600 mg, twice a day from the second day to the seventh day, orally. After seven days of treatment with favipiravir, the researchers decide whether to continue to take favipiravir according to the specific conditions of the subjects. Tocilizumab was used according to the recommendation for the treatment of rheumatoid arthritis [9]. That was, the first dose was 4−8 mg/kg (recommended 400 mg) and added to 100 mL 0.9 % normal saline (intravenous infusion time should be more than 1 h). For patients with fever, if there was still fever within 24 h after the first used, it should be used once more (the dose was the same as before).

When entering and leaving the group, all patients were examined for blood routine, blood biochemistry, IL-6, SARS-CoV-2 RNA (throat swab or sputum), pulmonary CT examination and so on. In addition, we also detected the changes of T lymphocyte subsets by flow cytometry before and after entering the group. All patients were clinically classified according to the severity of the disease (based on the Chinese COVID-19 guidelines [seventh edition], Table S1). What's more, physicians were allowed to use any necessary treatment and laboratory test with their standard of care.

2.3. Outcomes

The primary outcome was the cumulative lung lesion remission rate (lung CT examination indicated absorption of lung inflammation). Secondary outcomes were the improvement of clinical symptoms (cough, diarrhea, dyspnea, fever, myalgia) before and after treatment; the changes of blood routine test and IL-6; changes of oxygen therapy. In addition, we also analyzed the peripheral blood T lymphocyte subsets (count and proportion) before and after treatment. Safety endpoints were the frequencies of adverse events in each group.

2.4. Statistical analysis

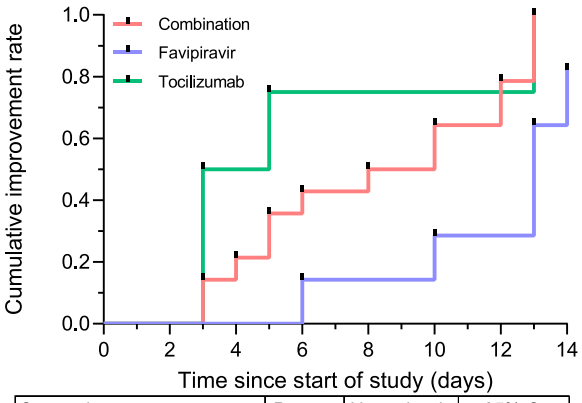
Statistical analysis was conducted with R (version 3.6.2) and GraphPad Prism 8 (GraphPad, San Diego, CA, USA). Quantitative variables were expressed as the median and range. Categorical variables were demonstrated with number and percentage. The student *t* test or Kruskal-Wallis analysis were used to compare continuous variables, and Chi-square or Fisher's exact tests were used to categorical variables. Cumulative improvement rate of lung CT imaging between favipiravir group and combination group curves were analyzed by log-rank (Mantel-Cox) test. $P < 0.05$ was considered to be statistically significant.

3. Result

3.1. Patients and baseline analysis

Between February 2nd and March 15th, 2020, 31 patients were screened, of whom 26 were eligible (Fig. 1). Among the 26 patients, 7 patients in the favipiravir group, 5 patients in the tocilizumab group and 14 patients in the combination group (favipiravir combined with tocilizumab). The median age of patients was 73.5 years (ranging 34–89 years; over the age of 70 accounted for 65.4 % [17/26]). There was no statistical difference in age among the three groups($P = 0.817$). What's more, the male-to-female ratio was balanced, 53.8 % (14/26) were men (Table 1). In terms of blood routine, 80.8 % of the patients' WBC were in the normal range (reference values were shown in Table S2). The median WBC of Combination group, Favipiravir group and Tocilizumab group was 5.6, 7.6 and 7.0*10^9/L, respectively. The proportion of neutrophil in 80 % of patients was in the normal range. The percentage of lymphocytes decreased in 42.3 % (11/26) patients, including 3 patients in combination group, 3 patients in favipiravir group and 4 patients in tocilizumab group.

The proportion of patients with underlying diseases was as high as



Comparison	P value	Hazard ratio	95% CI
Favipiravir vs. Combination	0.019	2.66	1.08 to 6.53
Favipiravir vs. Tocilizumab	0.034	3.16	0.62 to 16.10
Tocilizumab vs. Combination	0.575	1.28	0.39 to 4.23

Fig. 1. The cumulative lung lesion remission rate at day 14.

73.1 % (19/26), of which hypertension was the most common (42.3 %). The most common clinical symptoms were cough and fever. 71.4 % and 57.1 % of the patients in the combination group had cough and fever. According to Chinese COVID-19 guidelines [seventh edition], more than half of the patients (53.8 %, 14/26) were severe or critical type, while 42.8 % (6/14) of the patients in the combination group were severe or critical type. In addition, the rates in the favipiravir group and tocilizumab group were 71.4 % (5/7) and 60.0 % (3/5), respectively.

3.2. Primary outcome

The Kaplan-Meier survival curves were presented in Fig. 1. The cumulative lung lesion remission rate at day 14 was significantly higher in combination group as compared with favipiravir group (HR 2.66 95 % CI [1.08–6.53], P = 0.019). Although there was a significant difference between favipivavir and tocilizumab (P = 0.034), the 95 % confidence interval contains 1(HR 3.16, 95 % CI 0.62–16.10), and the results were interpreted carefully. In addition, there was no significant difference between the combination group and the tocilizumab group (P = 0.575, HR 1.28 95 %CI 0.39–4.23).

3.3. Secondary outcomes

The mortality or the incidence of invasive mechanical ventilation in favipiravir group (28.5 % [2/7]) was higher than that in combination group (0% [0/14]) or tocilizumab group (0% [0/5]) (Fig. 2). There were no more deaths or patients requiring mechanical ventilation during hospitalization. After 2 months of follow-up, all patients were discharged from hospital (except death cases), and no special discomfort was complained.

The clinical symptoms of combination group were significantly relieved after treatment, and only a few people had mild cough. There were significant differences in fever, cough and dyspnea (P = 0.002, 0.041, 0.023, respectively). The fever symptoms were also significantly relieved in the favipiravir group (P = 0.029), and there was no significant difference in other symptoms. Similarly, in the tocilizumab group, the symptoms were basically relieved after treatment, but there was no statistical difference (Fig. 3).

There were also different changes in blood routine test after treatment. In the combination group, the proportion of neutrophil decreased significantly (mean value before and after treatment was 63.5 % and 56.7 % respectively, P = 0.002, Fig. 4B), and the proportion of lymphocytes increased significantly (mean value before and after treatment was 25.3 % and 31.2 % respectively, P = 0.043, Fig. 4D). There were also statistical differences in the proportion of neutrophil and lymphocytes in the tocilizumab group (neutrophil percentage [before 69.8 % vs. after 55.5 % P = 0.032; lymphocyte percentage [before 19.2 % vs. after 30.3 %, P = 0.019). The neutrophil count decreased and the lymphocyte count increased in each group, but there was no statistical difference (Fig. 4A and C). There was no significant difference in favipiravir group. It is worth noting that after the treatment of tocilizumab, IL-6 increased significantly (Fig. 4F) in both the combination group (median value [before 10.5 pg/mL vs. after 61.6 pg/mL], P = 0.005)

Table 1
Baseline demographics and Clinical data of the study population.

	Combination	Favipiravir	Tocilizumab
Sex female (%)	8 (57.1 %)	2 (28.6 %)	2 (40.0 %)
BMI (kg/m^2)	24.8 (17.6–37.8)	21.1 (20–28)	21.5 (20.8–26.4)
Age (year)	75 (34–81)	70 (45–89)	71 (48–77)
Blood routine test			
WBC (10^9/L)	5.6 (2.8–8.3)	7.6 (2.8–17)	7.0 (4.7–8.7)
Erythrocyte (10^12/L)	3.6 (2.7–4.8)	3.2 (2.4–4.7)	3.1 (2.9–4.2)
Neutrophil (10^9/L)	3.6 (1.2–5.3)	5.7 (2.3–16.7)	4.8 (3.2–5.1)
Lymphocyte (10^9/L)	1.2 (0.9–2.3)	0.8 (0.2–2.7)	1.2 (0.6–2.4)
Hemoglobin (g/L)	112 (83–144)	100.5 (87–132)	88 (83–137)
Neutrophil (%)	63.6 (44.1–71.3)	80.4 (56.1–98.1)	71.5 (59.1–76.2)
Lymphocyte (%)	22.9 (17.8–39.8)	14.9 (1.2–30.5)	17.8 (12.9–28.1)
IL-6 (pg/mL)	10.2 (7.4–71.9)	19.8 (9–222.5)	27.5 (9.0–78.7)
Blood biochemical test			
Albumin (U/L)	36.4 (30–45.8)	39.4 (32.8–43.2)	37.8 (28.2–40.3)
Tbil (μmol/L)	8.6 (3.2–27.7)	9.9 (3.8–28)	10.3 (7.1–15.6)
ALT (U/L)	22 (8–67)	21 (11–46)	37 (8–156)
AST (U/L)	21 (13–42)	20.5 (12–48)	22 (14–130)
LDH (U/L)	180 (140–328)	201 (134–255)	207.5 (190–225)
CK (U/L)	59 (14–190.2)	35.4 (25.6–129)	34.8 (24.7–44.8)
CK-MB (U/L)	11.4 (4–20.5)	10.7 (10–11.4)	12.7 (11.2–14.2)
ALP (U/L)	71 (42–94)	68.5 (35–153)	71 (58–100)
GGT (U/L)	21 (10–95)	26 (9–44)	53 (37–89)
Glucose (mmol/L)	5.5 (3.2–23.1)	6.2 (4.5–10.5)	5.2 (4.9–6.0)
BUN(μmol/L)	4.6 (3.2–7.6)	6.2 (3.5–18.2)	6.4 (1.9–6.9)
Cr(μmol/L)	63 (45–91.2)	65.4 (44–74)	64 (54–103)
Uric acid (μmol/L)	316 (149–432)	229.5 (123–429)	190 (157–686)
Triglyceride (mmol/L)	1.6 (1.1–11.3)	1.5 (0.3–2.2)	2.4 (1.7–2.7)
Total cholesterol (mmol/L)	4.2 (2.9–5.4)	4.2 (1.5–5.0)	4.5 (3.0–5.8)
Blood coagulation function			
PT (s)	12.6 (10.4–15.2)	13.9 (11.1–16.8)	13.6 (12.2–14.2)
APTT (s)	34.6 (24.2–46.2)	40.6 (28.6–43)	34.6 (32.5–41.8)
TT (s)	16.2 (14.4–19.1)	17.6 (15–23.7)	15 (14.3–15.8)
FIB (g/L)	3.3 (1.9–4.7)	3.6 (0.8–7.8)	3.8 (3.1–4.4)
INR	1 (0.9–1.2)	1.1 (1–1.4)	1.1 (0.9–1.3)
Concomitant disease			
HBP	6 (42.9 %)	3 (42.9 %)	2 (40.0 %)
Diabetes	1 (7.1 %)	1 (14.3 %)	1 (20.0 %)
Coronary artery disease	2 (14.3 %)	1 (14.3 %)	3 (60.0 %)
Smoking	5 (35.7 %)	4 (57.1 %)	3 (60.0 %)
Drinking	3 (21.4 %)	1 (14.3 %)	2 (40.0 %)
Clinical symptoms			
Cough	10 (71.4 %)	3 (42.9 %)	4 (80.0 %)
Diarrhoea	2 (14.3 %)	0 (0%)	1 (20.0 %)
Dyspnea	5 (35.7 %)	2 (28.6 %)	2 (40.0 %)
Fever	8 (57.1 %)	6 (85.7 %)	3 (60.0 %)
Muscle soreness	1 (7.1 %)	2 (28.6 %)	1 (20.0 %)
Clinical classification			
Mild type	0 (0%)	0 (0%)	0 (0.0 %)
Common type	8 (57.1 %)	2 (28.6 %)	2 (40.0 %)
Severe type	5 (35.7 %)	5 (71.4 %)	3 (60.0 %)
Critical type	1 (7.1 %)	0 (0%)	0 (0.0 %)

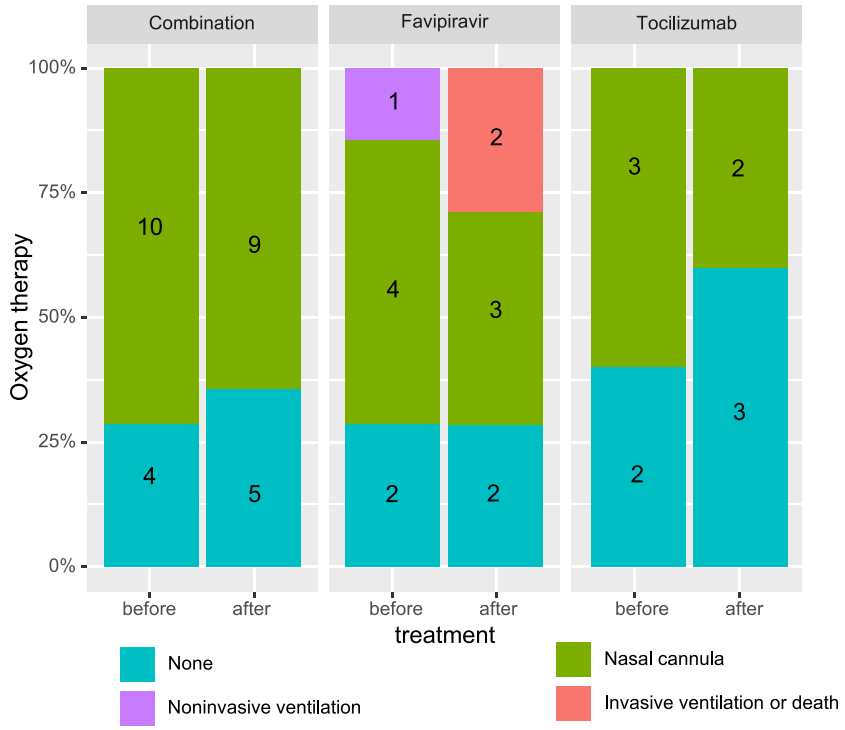


Fig. 2. Different oxygen therapy in three groups of patients before and after treatment.

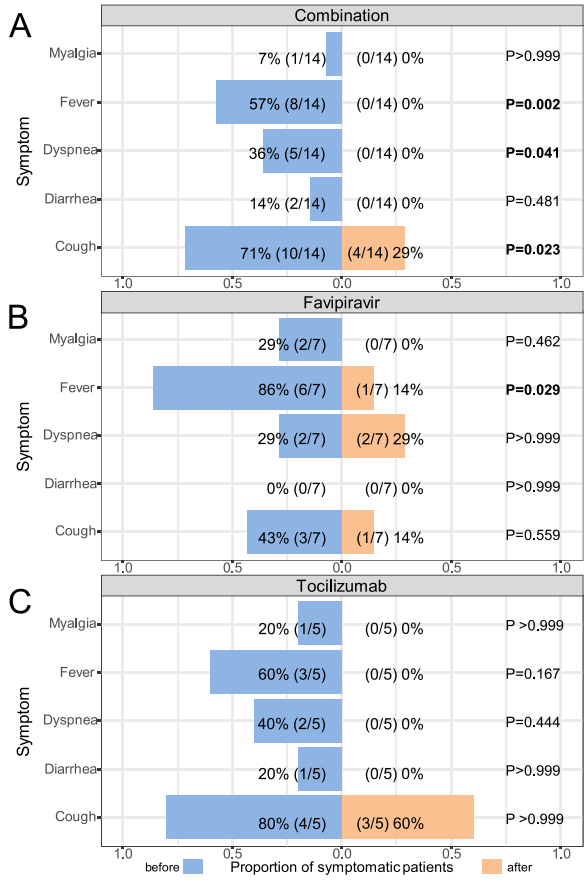


Fig. 3. Improvement of symptoms before and after treatment. (A) combination group (B) Favipiravir group (C) Tocilizumab group.

and tocilizumab group(median value [before 27.5 pg/mL vs. after 61.8 pg/mL], P = 0.190).

Fig. 5 showed the changes of lymphocyte subsets in the combined group before and after treatment. The proportion of CD4 + T cells decreased significantly (median value before 45 % vs. after 38 %, P = 0.033) and the proportion of CD8 + T cells increased significantly (median value before 21 % vs. after 25 %, P = 0.035). There was no significant difference between the decrease of CD4 + T cell count and the increase of CD8 + T cell count (P = 0.120 and P = 0.270, respectively). Although the proportion and count of CD3 + T cells increased to some extent, there was no statistical difference (P = 0.570 and P = 0.690, respectively). There was no significant difference in lymphocyte subsets between favipiravir group and tocilizumab group (Figs. S2 and S3).

3.4. Safety

Nine adverse reactions were reported in the combined treatment group, and two adverse reactions were reported in the favipiravir group and the tocilizumab group respectively (Table S3). The most common adverse events were elevated transaminase, especially after treatment with tocilizumab. It was worth noting that the need to monitor transaminase before and after treatment has been clearly mentioned in the instructions of tocilizumab. Diarrhea and hyperuricemia also occur. There were no serious adverse reactions, and all patients' adverse reactions were relieved a few days.

4. Discussion

In this multicenter trial in patients with COVID-19, we showed that a combination of an antiviral drug (favipiravir) and an IL-6 receptor blocker (tocilizumab) can significantly improve pulmonary inflammation and reduce mortality. Furthermore, combined therapy can also significantly relieve clinical symptoms and help blood routine to return to normal. The side-effects were generally mild and self-limiting.

An unexpected result was that the level of IL-6 not only did not decrease, but further increased after the administration of tocilizumab.

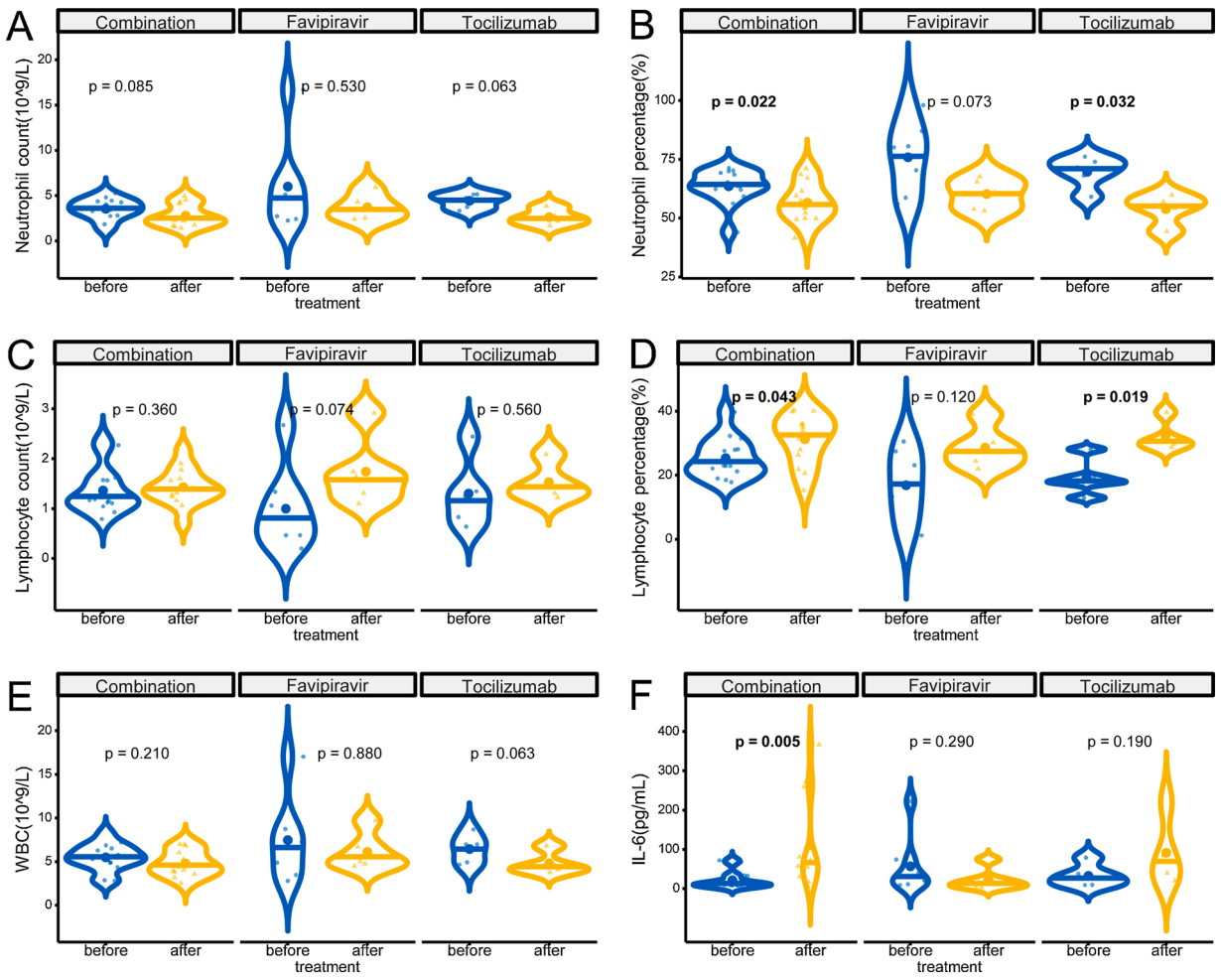


Fig. 4. Changes of blood routine test and IL-6 in peripheral blood before and after treatment. (A) Neutrophil count (B) Neutrophil percentage (C) Lymphocyte count (D) Lymphocyte percentage (E) White blood cell count (F) IL-6 concentration in peripheral blood. Blue and yellow are before and after treatment, respectively. The horizontal line represents the median and the large dot represents the mean value.

We knew that IL-6 played an important role in cytokine release syndrome, and several studies [7,8] have shown that the level of IL-6 could be used to predict the prognosis of COVID-19 patients. Did this mean that the application of tocilizumab not only had no advantages, but also has disadvantages? The answer was, of course, no. Both the results of our clinical trials and the results of Xu et al. [13] retrospective study supported that the use of tocilizumab were beneficial to COVID-19 's patients.

This could be explained by a theory called the "bathtub model" (Fig. 6). IL-6 in human body could be produced by mononuclear macrophages, Th2 cells, vascular endothelial cells, fibroblasts and other cells [18,19]. There were two main ways of eliminating IL-6, one was IL-6 direct degradation of IL-6 protein, the other was IL-6 receptor-mediated eliminating. IL-6-mediated immune injury was mainly through the excessive activation of the immune system after binding with IL-6R, resulting in the damage of target organs. The possible mechanism has been analyzed in detail in our previous research [4].

Under normal circumstances, the IL-6 produced by the human body and the IL-6 eliminated by the above pathway were dynamically balanced, and the peripheral blood IL-6 was always maintained at the level of 0–7 pg/ml (Fig. 6A). When infection occurred (COVID-19), IL-6 was synthesized rapidly. Due to the increase in synthesis and no change in the rate of elimination, there was an accumulation of IL-6 in human body (Fig. 6B). These increased IL-6 combined with IL-6R to mediate the transduction of Jak/Stat-related signaling pathways, resulting in lung injury [20]. After the treatment of tocilizumab (in the early stage, Fig. 6C), tocilizumab binds to IL-6R, while the production of IL-6 in vivo did not decrease rapidly. This was similar to there was no reduction in the amount of water entering, and one of the outlets was blocked, resulting in a further increase in IL-6. At this point, we tested the level of IL-6 in peripheral blood must be at a very high level. However, due to the combination of IL-6R and tocilizumab, the immune damage of the body was not serious. In the later stage of the treatment of tocilizumab (Fig. 6D), the level of IL-6 synthesized gradually decreased, and the IL-6 returned to the normal level.

This "bathtub theory" has been proven in the treatment of a variety of diseases with tocilizumab. In the study of tocilizumab in the treatment of rheumatoid arthritis, it was found that after treatment with 4 mg / kg, the average IL-6 level reached the peak at the second week after administration, and then decreased gradually [21–24]. Similarly, Nishimoto et al. [25] studied the treatment of rheumatoid arthritis and Castleman disease with tocilizumab. The serum IL-6 level increased gradually after treatment, reached the highest level on the 14th day, and tended to be stable on the 42nd day. In addition, the expression of IL-6 mRNA in peripheral blood cells did not increase significantly after administration of gradually. During the treatment of cytokine storm caused by CAR-T, there was also a transient increase and then decrease in serum IL-6 levels, which generally began to decrease after about a week of using [26].

Unfortunately, due to the particularity of COVID-19 and the time of this clinical trial, we only collected the level of IL-6 after 14 days of treatment and found that IL-6 was indeed significantly increased. We did

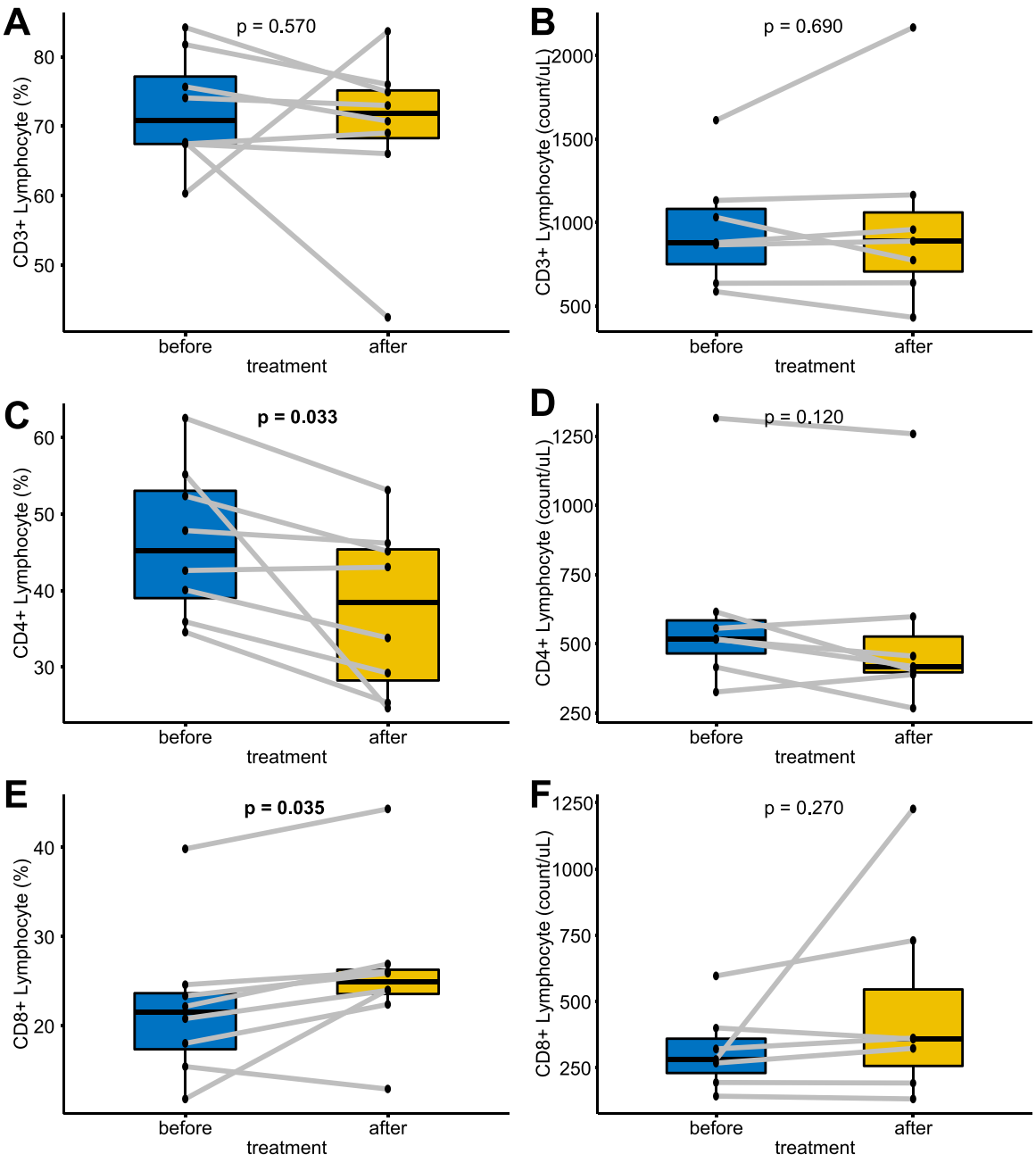


Fig. 5. Changes of peripheral blood lymphocyte subsets in combination group before and after treatment. (A) CD3+ Lymphocyte percentage (B) CD3+ Lymphocyte count (C) CD4+ Lymphocyte percentage (D) CD4+ Lymphocyte count (E) CD8+ Lymphocyte percentage (F) CD8+ Lymphocyte count.

not witness a continuous decrease of IL-6 in the follow-up. We planned to use the experimental animal model to further verify the correctness of the "bathtub theory" in COVID-19.

There is still some controversy about the IL-6 receptor (IL-6R) blockers in COVID-19. A study by Ramiro et al. [27] involving 172 people (86 in the treatment group and 86 in the control group) showed that, compared with the control group, glucocorticoids with tocilizumab can significantly improve the condition of oxygen therapy (HR: 1.8; [95 % CI 1.2–2.7]), reduce mortality (HR: 0.35; [95 % CI 0.19 to 0.65]) and decrease the likelihood to evolve to mechanical ventilation due to respiratory deterioration(HR: 0.29; [95 % CI 0.14 to 0.65]). Another study involving 154 patients (78 received tocilizumab) showed that tocilizumab significantly reduced mortality (HR: 0.55; [95 % CI 0.33, 0.90]) and improved clinical symptoms (OR: 0.58; [95 % CI 0.36, 0.94)]), but increased superinfections (54 % vs. 26 %; $p < 0.001$), mainly *Staphylococcus aureus* [28]. However, a study of IL-6R blockers (sarilumab) has come to the opposite conclusion [29]. A total of 56 people was included (28 in the sarilumab group and 28 in the control group). Compared with the control group, there was no significant difference in the 28-day clinical improvement rate between the sarilumab group and the control group (61 % vs. 64 %; $P > 0.05$). However, the median time of clinical improvement in the patients with mild lung consolidation (consolidation <17 %) and sarilumab was shorter than that in the control group (10 days vs. 24 days; $p = 0.01$).

Our study had several limitations. First of all, this was the first randomized controlled trial of tocilizumab in the treatment of COVID-19, but due to the small number of cases, the robustness of the results still needed to be verified by large-scale clinical trials. Secondly, due to population limitations, there was a lack of comparison of different dose gradients (the dose of tocilizumab was the dose of reference for rheumatoid arthritis). This may cause insufficient or excessive drug doses, thus affecting the clinical efficacy. Finally, the safety and efficacy of

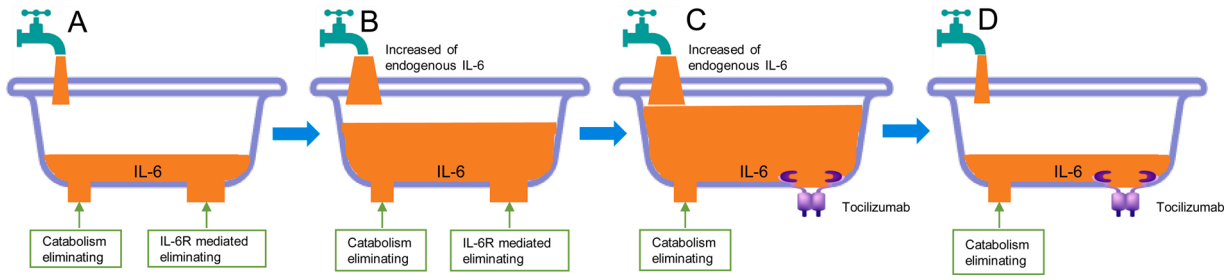


Fig. 6. Bathtub theory: the possible mechanism of the increase of IL-6 level after the treatment of tocilizumab. (A) Under the normal condition, the generation and clearance of IL-6 were in dynamic balance. (B) When infection occurred, the production of IL-6 increased sharply, but the clearance rate did not change much, so the level of IL-6 in peripheral blood increased. (C) In the early stage of the treatment of tocilizumab, the clearance of IL-6 decreased (because of tocilizumab bound to IL-6R), which led to the further increase of IL-6 in peripheral blood. IL-6 peaked at about 14 days. (D) Because the immune damage was initiated by the combination of IL-6 and IL-6R, and the combination of tocilizumab blocked their binding, the inflammatory response of the body was relieved. The production of IL-6 decreased and the concentration of IL-6 in peripheral blood decreased gradually until it returned to the normal level.

favipiravir (as an anti-SARS-CoV-2 drug) in the treatment of COVID-19 needed to be further verified.

5. Conclusion

In summary, tocilizumab combined with or without favipiravir can effectively improve the pulmonary inflammation of COVID-19 patients and inhibit the deterioration of the disease. Therefore, tocilizumab brings good news to COVID-19 patients with increased IL-6. As the sample size of this study is small, the conclusion of this study still needs to be further verified by clinical trials with large samples.

Ethical approval and consent to participate

This study has been approved by the Ethics Committee of Peking University First Hospital (2020-032) and has been registered in Chinese clinical trial registry (ChiCTR2000030096 and NCT04310228). All patients signed the informed consent form.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Guarantor of the article

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Authors' contributions

Hong Zhao, Qi Zhu and Chi Zhang drafted the manuscript; Ming Wei, Yuhong Qin, Guilin Chen, Ke Wang, and Junhua Yu participated in the collection and arrangement of clinical cases; Chi Zhang and Jiawen Li participated in the creation of figures and tables; Zhao Wu, and Chi Zhang participated in the proofreading of this paper; Xianxiang Chen and Guiqiang Wang provided the overall principle and direction of the study. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors report no declarations of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.biopha.2020.110825.

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