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A Pilot and Feasibility Study to Evaluate the Effectiveness of Tofacitinib Add-On Therapy to Remdesivir in Severely Ill COVID-19 Patients

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ABSTRACT

Aim: *This placebo-controlled and randomized pilot study aimed to assess the feasibility and impact of tofacitinib/remdesivir combination therapy compared to remdesivir alone on clinical and laboratory findings of severely ill COVID-19 patients for future large-scale studies.*

Method: *Fifty patients were included in this study. They were randomly allocated into two groups of 25 subjects each. Patients in the treatment group received a five-day course of tofacitinib (10 mg twice daily) in addition to a five-day course of remdesivir, whereas the control group received a 10-day course of remdesivir with a placebo.*

Results: *There was no significant difference in rates of need for intubation (oxygen saturation level), intensive care unit (ICU) admission, death and length of hospitalization between the two groups (P>0.05). Nevertheless, the PRIEST severity score was significantly reduced in the treatment group compared to the control group (P=0.03, effect size [95% CI]: -0.616 [0.0233–1.1723]). Moreover, the mean level of C-reactive protein after 10 days was significantly decreased in the treatment group but increased in the control group (P=0.006).*

Conclusion: *Tofacitinib adopted in this pilot study modulate the inflammation and reduce the PRIEST score in severe COVID-19 patients. So, it is feasible and could be applied in future larger-scale trials to precisely determine its effects on coronavirus infections.*

Keywords: COVID-19, tofacitinib, remdesivir, oxygen saturation, mortality, C-reactive protein.

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INTRODUCTION

The recent global pandemic of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to many problems for people and healthcare centers. Efficient treatment for COVID-19 patients has become a global medical challenge. SARS-CoV-2 infection has an unpredictable clinical course due to its complex pathophysiology, which can quickly progress to severe and even fatal consequences (1-3).

To date, various medical treatments against COVID-19 infection have been identified. These include antiviral medications such as remdesivir, molnupiravir and nirmatrelvir-ritonavir as well as immunomodulatory therapies such as corticosteroids (e.g., dexamethasone), IL-6 inhibitors (e.g., tocilizumab) and JAK inhibitors (e.g., baricitinib). However, there remains a strong desire to find more efficient therapeutic options without significant side effects on patients; nevertheless, there is still a strong desire to find more efficient therapeutic options without any side effects on patients (4, 5). In this regard, many clinical trials have investigated the specific and safe treatments for COVID-19 so far, including remdesivir, favipiravir, lopinavir/ritonavir, umifenovir, ribavirin, chloroquine and hydroxychloroquine, corticosteroids, various antibiotics (6), convalescent plasma, immune modulators (7), interleukin inhibitors, tocilizumab, baricitinib and anticoagulants (8, 9). Although some of these treatments have shown good effects on the recovery of patients, there is still insufficient evidence regarding their decisive effect against COVID-19. Moreover, several reports about some adverse effects associated with these treatments have limited their clinical use (10, 11). Combination therapy with the intravenous antiviral drug remdesivir (RDV) and immunomodulators produced better outcomes than treatment with RDV or immunomodulator alone in severe diseases. However, there is little information about the effect of combination therapy with oral antiviral drugs and immunomodulators in mild-to-moderate and severe COVID-19 cases (12).

Tofacitinib is an oral Janus kinase (JAK1, JAK2 and JAK3) inhibitor that blocks intracellular transport pathways and this in turn leads to suppress the production of common γ-chain cytokines (*i.e.*, IL-2, IL-4, IL-15 and IL-21) (13). Also, tofacitinib ameliorates the function of interleukin-6 and interferons, and reduces the release of cytokines from T helper cell type 1 & 17, which are involved in the pathogenesis of severe acute respiratory syndrome (SARS) (14, 15). Recent studies reported that tofacitinib can lead to lower mortality risk in COVID-19 patients(16, 17).

The present randomized, placebo-controlled, parallel-arm pilot study has tried to evaluate the feasibility and impact of tofacitinib/remdesivir combination therapy compared to remdesivir alone on SARS-CoV-2-related symptoms and clinical outcomes for the future large-scale studies. This pilot trial assessed the acceptability and feasibility of tofacitinib, estimating its effect size and preliminary effect in severely ill COVID-19 patients for the future definitive and large-scale trials. ❑

MATERIALS AND METHODS

Study design

This randomized, placebo-controlled, parallel-arm pilot study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, with the ethical code IR.AJUMS.REC.1400.415 (approval date: October 9, 2021), and it was registered in the Iranian Registry of Clinical Trials (IRCT) with the following identifier IRCT ID: IRCT20200426047212N2 (registration date: November 11, 2021). Eligible patients who referred to the emergency department of Razi hospital in Khuzestan province of Iran were enrolled in our study. This pilot study included a 10-day treatment period and a four-week follow-up period. The local institutional ethics committee of the study center oversaw the proceedings and documentation. This study was conducted from November 2021 to March 2022.

Patients

Participants to the present study comprised patients aged 18 to 70 years who had the specified symptoms of severe COVID-19, including cough, shortness of breath, fever and blood oxygen saturation (SpO_2) ≤ 93% (2), positive results of SARS-CoV-2 RT-PCR test, CT (computed tomography) scan score > 4 quantified by the total severity score (TSS) (18) and conscious willing-

ness. Patients with acute underlying diseases, pregnant and lactating women as well as individuals with hypersensitivity to tofacitinib/remdesivir were excluded from the study.

Randomization, blinding and allocation concealment

All patients were randomly assigned into the intervention and control groups using a six-item randomized block method in an equal allocation ratio (1:1). "Block randomization" (https://www.sealedenvelope.com/power/binary-superiority/) was used to maintain the double-blinding in which the statistician designed the block size of 6 and two treatment arms without knowing patients' information. Neither the participant nor the main investigator and observer was aware of the treatment allocation. Allocation concealment was done by assigning unique codes using statistical software allocation. Nurses administered the drugs to patients. Eventually, a statistician categorized the patients based on the unique codes in order to perform statistical analysis.

Treatment allocation

Eligible patients in the treatment group received tofacitinib at a dose of 10 mg twice daily (for five days) in addition to a five-day course of remdesivir (an IV loading dose of 200 mg on day 1, followed by daily maintenance doses of 100 mg for other days). Patients in the control group received a 10-day course of remdesivir with a placebo. To ensure the similarity between tofacitinib and placebo, the latter was produced by the same drug company and the study drugs were placed in similar envelopes.

Before beginning the pilot study, nasopharyngeal smears, serum and blood samples were collected from all patients for laboratory tests. Physician-researchers and nurses followed up the patients to collect their clinical and paraclinical data, evaluate drug safety and monitor vital signs and possible adverse events.

Outcomes

Oxygen saturation status and respiratory function were the main outcomes of the present study. The secondary outcomes included the length of hospitalization and/or stay in the intensive care unit (ICU), ICU admission rate, 30-day mortality rate, changes in the laboratory manifestations and probable side effects.

The PRIEST score is a tool for assessment of 30-day probability of adverse outcome in acutely ill patients with suspected COVID-19 who were attending the emergency department. In this pilot study, PRIEST COVID-19 clinical severity score was assessed based on the criteria reported by Goodacre *et al* (19).

Sample size

Considering the binary outcomes, assuming alpha = 0.05 and power =0.8 (β= 0.20), effect size=0.36 and proportion of cases exposed with adverse outcomes and/or good prognosis in each parallel group based on the previous similar study (16), sample size was calculated by the following formula for both parallel groups: $N= ([(Z_{\alpha/2}+Z_{\beta})^2 (p_1q_1+p_2q_2)])/x^2 \approx 22$. So, at least eligible sample size for each group was 22 cases.

Statistical analysis

Statistical analysis has been performed using SPSS software version 26 (SPSS Inc., Chicago, Ill., USA). Categorical and continuous variables presented as frequency or percentages and the mean±SD (standard deviation), respectively. Chi-square and/or Fisher exact test were used to estimate the significant values. The differences between continuous variables were analyzed by the independent sample t-test and/or Mann-Whitney U test based on the normality nature of data. Effect size with corresponding 95% confidence intervals (CI) was estimated for all significant measures. A P-value <0.05 was considered as statistically significant. ❑

RESULTS

Fifty confirmed severe COVID-19 patients out of 62 cases who were assessed for eligibility were assigned to this clinical trial, and randomly allocated into two groups. Twelve cases were excluded from the study due to failure to meet the inclusion criteria and/or refusal to participate. Eventually, 25 cases from the treatment group and 25 cases from the control group were completely followed-up and analyzed (Figure 1).

The attrition rate and rate of randomized eligible patients were calculated to be 0% and 90.9%, respectively.

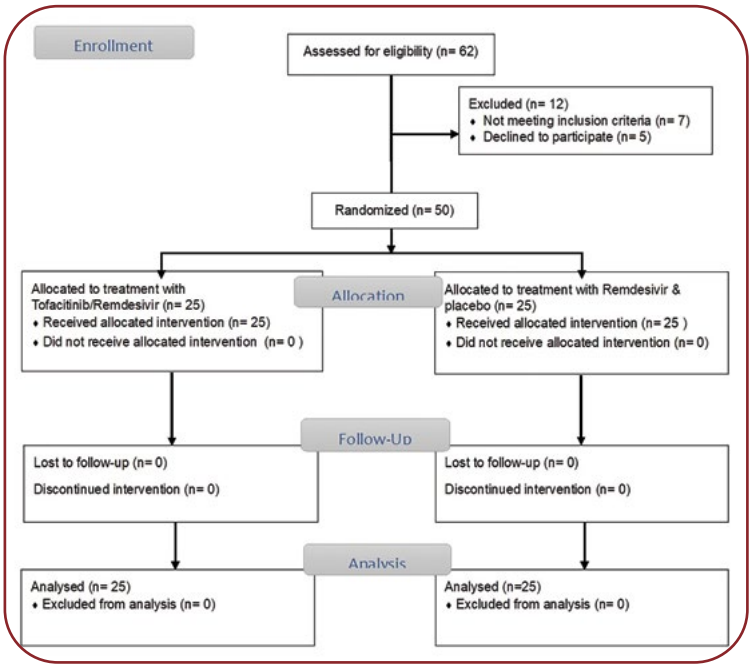

FIGURE 1. Patient CONSORT flow diagram

TABLE 1. Demographics and admission day clinical characteristics between the two study groups of COVID-19 patients

Admission day variables and symptoms	Treatment group (n=25)	Control group (n=25)	P value
Age (years)	59.88 ±13.45	58.6±11.46	0.72
Gender, n (%)			
Male	10 (0.4)	14 (0.56)	0.39
Female	15 (0.6)	11 (0.44)	
Nasal cannulas	3 (0.12)	3 (0.12)	1
Face masks	6 (0.24)	10 (0.4)	0.36
Oxygenation with reservoir bag	14 (0.56)	10 (0.4)	0.39
Non-invasive ventilation	1 (0.04)	0	>0.99
Supplemental oxygen therapy	24 (0.96)	23 (0.92)	>0.99
Diabetes mellitus	8 (0.32)	8 (0.32)	1
Ischemic heart disease	7 (0.28)	9 (0.36)	0.76
HTN	9 (0.36)	12 (0.48)	0.62
CKD	1 (0.04)	0	>0.99
ESRD	0	0	_
Obesity	0	1 (0.04)	>0.99
RA	2 (0.08)	1 (0.04)	>0.99
Other (cancer, chemotherapy history, etc)	6 (0.24)	5 (0.2)	>0.99
Reactive airway disease	2 (0.08)	0	0.49
Ventilator	13 (0.52)	11 (0.44)	0.81
Cough	16 (0.64)	14 (0.56)	0.82
Chest pain	2 (0.08)	2 (0.08)	1
Headache	6 (0.24)	2 (0.08)	0.26
Weakness	20 (0.8)	10 (0.4)	0.04
Myalgia	10 (0.4)	5 (0.2)	0.26
Chills	10 (0.4)	11 (0.44)	>0.99
Sore throat	7 (0.28)	3 (0.12)	0.32
Diarrhea	1 (0.04)	2 (0.08)	>0.99
Vomiting	3 (0.12)	3 (0.12)	1
Nausea	4 (0.16)	5 (0.2)	>0.99
Dyspnea	14 (0.56)	16 (0.64)	0.82
Anorexia	7 (0.28)	4 (0.16)	0.52
Fever	10 (0.4)	14 (0.56)	0.48
Sputum	0	0	_
Duration of symptoms before admission (days)	7.64±2.27	7.48±3.35	0.84

HTN: hypertension; CKD: chronic kidney disease; ESRD: end-stage renal disease; RA: rheumatoid arthritis.

Clinical and paraclinical parameters	Groups	Admission day	Day 10	Mean difference	*P*-value[2]
WBC [10^3/uL]	Treatment	9.84±3.72	11.71±4.79	1.87	0.01
	Control	12.38±6.33	15.11±10.24	2.72	0.01
	p-value[1]	0.09	0.15		0.035
Neutrophils, %	Treatment	80.79±11.09	80.96±12.88	0.17	0.92
	Control	84.17±9.14	84.34±10.13	0.16	0.93
	p-value[1]	0.24	0.31		0.94
Lymphocytes, %	Treatment	13.33±9.82	12.67±12.06	-0.65	0.66
	Control	10.66±8.69	10.84±9.20	0.18	0.89
	p-value[1]	0.31	0.3		0.5
Hemoglobin (g/dL)	Treatment	12.5±1.41	12.5±1.29	-0.004	0.98
	Control	11.2±1.74	11.57±2.01	0.36	0.29
	p-value[1]	0.006	0.09		0.95
Platelet (cells/µL)	Treatment	257.48±102.05	260.4±87.11	2.92	0.89
	Control	289.68±135.82	293.56±117.82	3.8	0.85
	p-value[1]	0.34	0.18		0.81
INR	Treatment	1.17±0.25	1.14 ±0.19	-0.028	0.65
	Control	1.16±0.19	1.18±0.35	0.032	0.52
	p-value[1]	0.85	0.47		0.44
PT (s)	Treatment	13.52±1.73	13.36±1.63	-0.16	0.65
	Control	12.88±1.26	13.04±2.03	0.16	0.65
	p-value[1]	0.14	0.96		0.52
PTT (s)	Treatment	35.84±13.85	37.92±17.53	2.08	0.65
	Control	35.24±8.15	37.84±17.1	2.6	0.5
	p-value[1]	0.85	0.76		0.93
CRP (mg/L)	Treatment	42.04±30.38	22.4±30.92	-19.64	0.006
	Control	47.42±51.19	51.67±47.89	4.24	0.69
	p-value [1]	0.65	0.03		0.06
LDH (IU/L)	Treatment	630.24±241.05	634.48±229.67	4.24	0.92
	Control	779.36±439.2	785.12±487.93	5.76	0.94
	p-value[1]	0.14	0.06		0.98
BUN (mg/dL)	Treatment	19.88±6.5	19.52±7.30	-0.36	0.69
	Control	23.96±15.39	24.56±10.77	0.6	0.81
	p-value[1]	0.23	0.26		0.72
Creatinine (mg/dL)	Treatment	1.136±0.27	1.09±0.23	-0.04	0.45
	Control	1.09±0.42	1.2±0.34	0.1	0.14
	p-value[1]	0.66	0.3		0.1
Total bilirubin (mg/dL)	Treatment	1.12±0.24	1.03±0.23	-0.08	0.23
	Control	0.89±0.38	0.94±0.26	0.04	0.58
	p-value[1]	0.01	0.68		0.22
Direct bilirubin (mg/dL)	Treatment	0.27±0.089	0.24±0.07	-0.03	0.16
	Control	0.21±0.047	0.22±0.06	0.008	0.64
	p-value[1]	0.008	0.19		0.16
AST (U/L)	Treatment	43.68±18.5	40.36±17.02	-3.32	0.41
	Control	42.32±25.37	37.12±19.82	-5.2	0.3
	p-value[1]	0.83	0.28		0.77
ALT (U/L)	Treatment	39.44±20.79	45.28±22.05	5.84	0.09
	Control	36.96±39.88	33.6±27.13	-3.36	0.71
	p-value [1]	0.78	0.74		0.34
ALP (U/L)	Treatment	228±84.62	238.32±77.81	10.32	0.51
	Control	201.28±107.47	242.72±130.47	41.44	0.03
	p-value[1]	0.33	0.42		0.2
Neutrophil-to-lymphocyte ratio	Treatment	30±67.61	13.81±19.48	-16.19	0.22
	Control	36.55±100.17	15.52±15.16	-21.03	0.24
	p-value[1]	0.78	0.6		0.82

[1]Intergroup comparison
[2]Intragroup comparisons

TABLE 2. Comparison of the laboratory parameters before and after treatments between the two study groups of COVID-19 patients

Patients' baseline characteristics

As shown in Table 1, there was no significant difference in mean age and gender distribution between the two groups (P >0.05). Also, the rate of underlying diseases was not significantly different between the two groups (P >0.05). Patients' admission day clinical characteristics, including usage rates of nasal cannula, face mask, oxygenation with reservoir bag, non-invasive ventilation and supplemental oxygen therapy were assessed, and no significant differences were found between the two groups (P >0.05). Furthermore, we observed no significant difference in the incidence rates of admission day clinical symptoms

Clinical variables	Treatment group	Control group	P-value[1]	Effect size (95% CI)
Pre-treatment PRIEST score	7.96 ±2.3	6.36±2.14	0.01	
Post-treatment PRIEST score	6.24±4.146	6.68±4.44	0.71	
P-value[2]	0.02	0.61		
Mean difference	-1.72	0.32	0.03	-0.616 (0.0233–1.1723)
Length of hospitalization	7.8±4.01	10.36±6.07	0.08	–
Length of stay in ICU	3.52±4.11	7.32±11.28	0.1	–
Need for intubation, n %	6 (0.24%)	7 (0.28%)	>0.99	–
ICU admission, n %	15 (0.6%)	13 (0.52%)	0.77	–
Death rate, n %	6 (0.24%)	7 (0.28%)	>0.99	–

[1]Intergroup comparison
[2]Intragroup comparisons

TABLE 3. Comparison of the clinical outcomes between the two study groups of COVID-19 patients

between the two groups (P >0.05), except for weakness, which was more frequent in the treatment group (P=0.04).

Treatment effect on the clinical and laboratory outcomes

In both groups, only the levels of white blood cells (WBC) and C-reactive protein (CRP) were significantly changed after a 10-day treatment period. The increase in the mean WBC level in the control group was significantly higher than the treatment group (P=0.035). Also, the mean CRP level after 10 days was increased in the control group but significantly decreased in the treatment group (P=0.006). The mean alkaline phosphatase (ALP) level was also significantly increased in the control group (P=0.03), whereas its change in the treatment group was not notable after 10 days (P=0.51). The changes in other laboratory markers were not significant in each group and/or between the two groups (P >0.05) (Table 2).

The PRIEST COVID-19 severity score was significantly reduced in the treatment group compared to the control group (P=0.03, effect size [95% CI]: -0.616 [0.0233–1.1723]). Nevertheless, we found no significant difference in rates of need for intubation, ICU admission, death rate and length of hospitalization and/or stay in ICU between the two groups (P >0.05) (Table 3). ❑

DISCUSSION

Cytokine storm syndrome induces a poor prognosis in COVID-19 patients (2) and tofacitinib is one of the inhibitors of cell signaling pathways related to cytokine storms (13). Recent studies have reported conflicting results regarding the effectiveness of tofacitinib on COVID-19 patients. Most of the recent clinical trials found no strong clinical evidence regarding the clinical effectiveness of tofacitinib compared with standard care alone or placebo (20). However, Maslennikov *et al*'s retrospective study reported that tofacitinib was able to reduce the risk of ICU admission and mortality in COVID-19 patients without any side effects (21).

In the present randomized pilot trial, we investigated the acceptability and feasibility of tofacitinib added to remdesivir (as routine COVID-19 medication) on COVID-19-related symptoms and outcomes as well as its effect size for future large-scale trials. Control medications included remdesivir and placebo. In our study, 50 patients with COVID-19 out of 62 eligible patients were randomly divided into two groups. The basic characteristics of the two groups were completely balanced and there was no significant difference in age, gender distribution and extent of underlying diseases.

Analysis of treatment effect on clinical and laboratory outcomes showed some significant findings. The average increase in the number of white blood cells (WBC) in the control group was significantly higher than the treatment group. In addition, the mean level of CRP significantly decreased in the treatment group but increased in the control group.

The overall satisfaction of patients in both groups towards tofacitinib was very high, with 0% attrition rate, particularly compared with other similar trials (16, 17). Also, the high rate of randomized eligible patients (90.9 %) implies that the screening population appears to have a high propensity to participate in tofacitinib-related trials.

Considering that no side effects related to tofacitinib were found, it can be used for patients with coronavirus infections in future large-scale studies. Furthermore, all patients had a positive

impression and expectations towards tofacitinib as add-on therapy, implying that blinding and application of placebo in patients had been successfully performed. All clinical personnel and researchers involved in this pilot study followed international ethical and "Good Clinical Practice" standards to protect patients and collect quality data. Moreover, successful blinding of both investigator and outcome assessor was useful in achieving objective and unbiased measurements.

The findings of the present pilot trial showed that the PRIEST COVID-19 severity score in patients who underwent the treatment with tofacitinib has been significantly reduced compared to those who received remdesivir plus placebo. However, there was no significant difference in rates of need for intubation, ICU admission, death rate and length of hospitalization between the treatment and control groups. Our pilot trial showed that tofacitinib may probably be an acceptable first-line add-on therapy for relieving the severe coronavirus infections. PRIEST score is a useful tool to identify patients at the highest risk of adverse outcomes (19). So, treatments that reduce PRIEST score can be useful for better management of hospitalized COVID-19 patients.

Despite the results of previous studies regarding the favorable effects of tofacitinib in increasing the oxygen saturation and reducing the respiratory failure (20, 16), the present study did not find any evidence supporting the effect of tofacitinib in reducing the need for intubation in patients. Such contradictory results may be due to the difference in the nature of various studies and/or use of different standard drugs. In the present study, remdesivir was used as a standard drug instead of glucocorticoids. Hence, judgment about the effectiveness of these standard drugs in combination with the target drug requires further comparative studies.

In confirmation with some recent studies (16, 20, 21), our results showed a significant reduction in CRP levels in COVID-19 patients who received tofacitinib. In addition to CRP, several other laboratory markers were also investigated in the present pilot study, which did not significantly change after 10-day treatment with tofacitinib plus remdesivir versus remdesivir alone. C-reactive protein is one the main inflammatory markers releasing in response to interleukin-6, which plays a role in the development of cytokine syndrome. Previous studies have also demonstrated that the CRP level was associated with the severity of COVID-19 (22, 23). Based on our findings, tofacitinib may probably be an acceptable treatment for ameliorating severe inflammation. Crowding and patient boarding in emergency departments are risk factors associated with low patient satisfaction and high mortality rate (24). In this regard, reducing the severity of infection in critically ill patients can lead to earlier discharge or shorter hospitalization and facilitate the management of emergency care.

Tofacitinib was the first JAK inhibitor (mostly JAK3) to be used clinically for the treatment of inflammatory bowel disease and rheumatoid arthritis (25). Baricitinib and ruxolitinib are other JAK inhibitor drugs with greater affinity for JAK1. Based on Kalil *et al*'s randomized, double-blind, placebo-controlled trial, combination therapy with barcitinib and remdesivir showed superior effects to remdesivir alone in accelerating clinical improvement among COVID-19 patients (26). However, COVID-19 mortality rate was not significantly reduced by baricitinib and/or ruxolitinib (26, 27).

The strengths of the present study are double-blindness and randomization. However, allocating only critically ill patients to treatment in this trial minimized the possible impact of the difference in infection severity on treatment-related results. Also, the single-center nature of this feasibility study limited the generalizability of results to other populations of different races and ethnicities and/or situations. ❑

CONCLUSION

Our findings demonstrate that tofacitinib adopted in this pilot study for severely ill COVID-19 patients may effectively modulate the inflammatory process and reduce the PRIEST COVID-19 clinical severity score. So, tofacitinib is a feasible treatment option, which could be used in future larger-scale trials to precisely determine the effects of this medication on coronavirus infections, particularly given that the attrition rate was 0% and the double blinding of both patients and researchers was successful. Any drug that effectively reduce the severity of diseases can also help to limit the number of inpatient days, decrease the risk of hospital-associated co-infections and adverse effects of medication, improve the quality of treatment

and decrease the costs for patients and healthcare systems. Anyway, future multicenter clinical trials and prospective studies with larger sample size should be considered to investigate the effectiveness of tofacitinib on infectious diseases and its mechanism of action based on FDA and WHO standards before its widespread clinical use. ❑

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and the 2008 Helsinki Declaration and its later amendments or comparable ethical standards. Also, the current study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, with the following ethical code: IR.AJUMS.REC.1400.415.

Informed consent: The decision to participate in this study was completely voluntary for all patients. At the end of the study, all participants had free access to their laboratory and clinical results.

Conflicts of interest: none declared.

Financial support: none declared.

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Availability of supporting data: Data supporting the findings of this study are available from the corresponding author on request.

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