Tofacitinib versus standard of care treatment in patients with COVID-19: a multicenter non-randomized controlled study

Sergey Moiseev[1], Nikolay Bulanov[1], Anastasiia Zykova[2], Michail Brovko[1], Pavel Novikov[1], Larisa Akulkina[1], Natalia Chichkova[1], Natalia Trushenko[1], Maria Lukina[1], Yuriy Sorokin[1], Ekaterina Tao[1], Ekaterina Filatova[1], Aram Kitbalyan[1], Pavel Potapov[1], Lubov Ermolova[1], Olga Suvorova[1], Augusto Vaglio[3], Andreas Kronbichler[4], Sergey Avdeev[1], and Victor Fomin[1]

[1]Sechenov First Moscow State Medical University
[2]Lomonosov Moscow State University
[3]University of Firenze
[4]University of Cambridge

July 6, 2021

Abstract

This non-randomized controlled study aimed to assess the efficacy of tofacitinib in reducing the risk of invasive mechanical ventilation or death in patients with COVID-19. Patients with COVID-19 associated with reduced oxygen saturation, increased C-reactive protein ([?]50 mg/L), and/or persisting fever were recruited. Tofacitinib was administered in addition to standard of care therapy. Study outcomes were evaluated separately in the groups of patients with oxygen saturation at rest [?]93% and >93%. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox regression analysis adjusted for inverse propensity score weighting. Overall, 384 patients with COVID-19 (212 males; median age 60 years) were included in our study and were treated with tofactinib (n=131) or standard of care alone (n=253). The percentages of patients who started mechanical ventilation or died during hospitalization in the tofacitinib and control groups were 12.5% (9/72) vs. 14.1% (26/185) among patients who required respiratory support (HR 0.92, 95% CI 0.33-2.56), and 1.7% (1/59) vs. 4.4% (3/68) in those with normal oxygen saturation (HR 0.83; 95 CI 0.07-9.44). Tofacitinib did not reduce the risk of invasive mechanical ventilation or death in patients with COVID-19, although the analysis of these outcomes favored tofacitinib.

Title Page

Tofacitinib versus standard of care treatment in patients with COVID-19: a multicenter non-randomized controlled study

Sergey Moiseev,[1] Nikolay Bulanov,[1]Anastasiia Zykova,[2] Michail Brovko,[1]Pavel Novikov,[1] Larisa Akulkina,[1]Natalya Chichkova,[3] Natalya Trushenko,[4] Maria Lukina,[5] Yuriy Sorokin,[1] Ekaterina Tao,[1] Ekaterina Filatova,[1] Aram Kitbalyan,[1,2] Pavel Potapov,[1,2] Lubov Ermolova,[1] Olga Suvorova,[4] Augusto Vaglio,[6] Andreas Kronbichler,[7] Sergey Avdeev,[4] Victor Fomin[3]

Sergey Moiseev, MD, professor, Head, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

Nikolay Bulanov, MD, associate professor, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

Anastasiia Zykova, MD, assistant professor, Department of Internal Medicine, Lomonosov Moscow State University, Moscow, Russia

Mikhail Brovko, MD, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

Pavel Novikov, MD, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

Larisa Akulkina, MD, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

Natalya Chichkova, MD, professor, Vinogradov Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

Natalya Trushenko, MD, assistant professor, Clinic of Pulmonology, Sechenov First Moscow State Medical University, Moscow, Russia

Ekaterina Tao, MD, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

Maria Lukina, MD, assistant professor, Department of Clinical Pharmacology and Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

Yuriy Sorokin, MD, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

Ekaterina Filatova, MD, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

Aram Kitbalyan, MD, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Department of Internal Medicine, Lomonosov Moscow State University, Moscow, Russia

Pavel Potapov, MD, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Department of Internal Medicine, Lomonosov Moscow State University, Moscow, Russia

Lubov Ermolova, MD, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia,

Olga Suvorova, researcher, Clinic of Pulmonology, Sechenov First Moscow State Medical University

Augusto Vaglio, MD, professor, Department of Biomedical Experimental and Clinical Sciences "Mario Serio", University of Firenze, and Nephrology Unit, Meyer Children's Hospital, Firenze, Italy

Andreas Kronbichler, MD PhD, Department of Medicine, University of Cambridge, Cambridge, United Kingdom

Sergey Avdeev, MD, professor, Head, Clinic of Pulmonology, Sechenov First Moscow State Medical University, Moscow, Russia

Victor Fomin, MD, professor, Vinogradov Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

Correspondence to: Sergey Moiseev, Rossolimo, 11/5, Moscow 119435, Russia. avt420034@yahoo.com. https://orcid.org/0000-0002-7232-4640

Tofacitinib versus standard of care treatment in patients with COVID-19: a multicenter non-randomized controlled study

Sergey Moiseev,[1] Nikolay Bulanov,[1]Anastasiia Zykova,[2] Michail Brovko,[1]Pavel Novikov,[1] Larisa Akulkina,[1]Natalya Chichkova,[3] Natalya Trushenko,[4] Maria Lukina,[5] Yuriy Sorokin,[1] Ekaterina Tao,[1] Eka-

terina Filatova,[1] Aram Kitbalyan,[1,2] Pavel Potapov,[1,2] Lubov Ermolova,[1] Olga Suvorova,[4] Augusto Vaglio,[6] Andreas Kronbichler,[7] Sergey Avdeev,[4] Victor Fomin[3]

1Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia,

2Department of Internal Medicine, Lomonosov Moscow State University, Moscow, Russia,

3Vinogradov Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia,

4Clinic of Pulmonology, Sechenov First Moscow State Medical University, Moscow, Russia,

5Department of Clinical Pharmacology and Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

6Department of Biomedical Experimental and Clinical Sciences "Mario Serio", University of Firenze, and Nephrology Unit, Meyer Children's Hospital, Firenze, Italy,

7Department of Medicine, University of Cambridge, Cambridge, United Kingdom

Running title: Tofacitinib for COVID-19 pneumonia

Abstract

This non-randomized controlled study aimed to assess the efficacy of tofacitinib in reducing the risk of invasive mechanical ventilation or death in patients with Coronavirus Disease 2019 (COVID-19). Patients with COVID-19 associated with reduced oxygen saturation, increased C-reactive protein ([?]50 mg/L), and/or persisting fever were recruited. Tofacitinib was administered in addition to standard of care therapy. Study outcomes were evaluated separately in the groups of patients with oxygen saturation at rest [?]93% and >93%. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox regression analysis adjusted for inverse propensity score weighting. Overall, 384 patients with COVID-19 (212 males; median age 60 years) were included in our study and were treated with tofacitinib (n=131) or standard of care alone (n=253). The percentages of patients who started mechanical ventilation or died during hospitalization in the tofacitinib and control groups were 12.5% (9/72) vs. 14.1% (26/185) among patients who required respiratory support (HR 0.92, 95% CI 0.33-2.56), and 1.7% (1/59) vs. 4.4% (3/68) in those with normal oxygen saturation (HR 0.83; 95% CI 0.07-9.44). Tofacitinib did not reduce the risk of invasive mechanical ventilation or death in patients with COVID-19, although the analysis of these outcomes favored tofacitinib.

Key words. COVID-19, JAK-inhibitors, tofacitinib.

INTRODUCTION

The pathogenesis of severe Coronavirus Disease 2019 (COVID-19) involves an excessive host inflammatory response to severe acute respiratory syndrome (SARS)-CoV-2 virus that is characterised by a marked increase in systemic cytokines and inflammatory biomarkers. These changes resemble cytokine storm that is observed during macrophage activation syndrome or after chimeric antigen receptor T (CAR-T)-cell therapy [1, 2]. Given the lack of antiviral substances with efficacy against SARS-CoV-2 infection, which are capable of preventing the associated hyper-inflammatory immune response, glucocorticoids and various anti-cytokine agents (interleukin-6 inhibitors in particular) were widely used for the treatment of moderate to severe COVID-19 in real life practice and were investigated in multiple observational and randomised clinical trials [3]. In the RECOVERY study, the administration of dexamethasone, a glucocorticoid with broad anti-inflammatory activity, resulted in lower 28-day mortality among hospitalised patients with COVID-19 who were receiving either invasive mechanical ventilation or supplemental oxygen therapy alone [4]. Conflicting evidence exists about the role of tocilizumab, an interleukin (IL)-6 receptor inhibitor, on mortality rates in severe COVID-19 [5-7]. Nevertheless, the U.S. Food and Drug Administration (FDA) issued an emergency use authorisation for the use of tocilizumab in patients receiving glucocorticoids and requiring supplemental oxygen, non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation.

Inhibition of Janus kinases (JAK), a family of cytoplasmic tyrosine kinases that participate in the intracellular signalling downstream the receptors of multiple cytokines, including IL-2, IL-6, IL-10, interferon-γ, and granulocyte–macrophage colony-stimulating factor, has been proposed as a potential therapeutic strategy for severe SARS-CoV-2 infection [8]. Moreover, the JAK 1/2 inhibitor baricitinib was postulated to exert direct anti-viral effects preventing SARS-CoV-2 cellular entry [9]. In a double blind, randomised, placebo-controlled trial, baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among hospitalised adults with COVID-19 [10]. The survival rate and the time-to-death analyses favoured this combination, particularly among those requiring high-flow nasal oxygen or non-invasive ventilation. The differences between the two groups, however, did not reach statistical significance, although the odds of progression to death or invasive ventilation were 31% lower in the combination than in the control group.

Tofacitinib is an orally administered, non-selective JAK-inhibitor that is approved for treatment of various inflammatory diseases. The recently published, randomised placebo-controlled trial from Brazil, treatment with tofacitinib led to a lower risk of death or respiratory failure through day 28 than placebo among patients hospitalised with COVID-19 pneumonia [11].

The objective of this study (TOFA-COV-2) was to assess the efficacy of tofacitinib in reducing the risk of invasive mechanical ventilation or death in patients with moderately severe COVID-19.

METHODS

Study design and participants

TOFA-COV-2 is a multicentre non-randomized controlled study that was conducted in the three clinics of the Sechenov University (Moscow, Russia) in patients with moderately severe COVID-19. The study population consisted of adults ([?]18 years) with COVID-19, who were admitted to the university clinics between April 17 and August 1, 2020. A diagnosis of COVID-19 was confirmed by polymerase chain reaction (PCR) and/or chest computed tomography (CT) (4 or 5 on CO-RADS scale) [12]. The extent of bilateral lung involvement (0-24%, 25-49%, 50-74%, [?]75%) was evaluated in the five lung zones according to the anatomical structure of lung: left upper lobe, left lower lobe, right upper lobe, right middle lobe and right lower lobe.

In order to be included in this study, patients had to have COVID-19 involving at least 25% of lung tissue in combination with an oxygen saturation at rest [?]93% on ambient air, increased C-reactive protein (CRP; [?]50 mg/L), and/or fever ([?]38.0°C) that persisted for at least two days despite treatment with nonsteroidal anti-inflammatory drugs or paracetamol. Exclusion criteria for the administration of tofacitinib were coexistent infection, requirement for invasive mechanical ventilation, estimated glomerular filtration rate (eGFR) calculated using CKD-EPI formula [?]30 ml/min/1.73 m^2, elevated ALT and/or AST levels more than 3 times the upper limit of normal, chronic use of glucocorticoids or immunosuppressive agents, or administration of IL-6 inhibitors and/or high-dose glucocorticoids ([?]250 mg prednisone equivalent intravenously) for the treatment of COVID-19. Comparators were selected randomly from the same population using the above criteria.

The study was approved by the Ethical Committee of the Sechenov University. All patients provided written, informed consent for the off-label use of experimental medications, including tofacitinib, according to the provisional recommendations issued by the Russian Ministry of Health during the outbreak of COVID-19. The protocol of the study was registered at clinicaltrials.gov (NCT04750317).

Treatment

Tofacitinib was administered at a dose 10 mg twice daily on day 1, followed by 5 mg twice daily on day 2-5. The dosage was reduced to 5 mg once daily in patients with eGFR less than 60 ml/min/1.73 m^2. The dosage and duration of treatment were chosen based on the approved dosage of tofacitinib for rheumatoid arthritis. We felt that more intensive immunosuppression, that is, the administration of tofacitinib at a higher dose or for a longer course would be unnecessary and could be hazardous for patients with an active viral infection.

Certain side effects of tofacitinib, including infections due to bacterial or viral pathogens, lymphopenia and venous thromboembolic events are particularly relevant for hospitalised patients with COVID-19 [13].

All patients received standard of care treatment from the time of hospital admission according to the Russian COVID-19 guidelines. Standard of care treatment was administered at the physician's discretion and included oxygen supply if needed (target oxygen saturation at least 93%), hydroxychloroquine (400 mg twice on day 1, followed by 200 mg twice per day on days 2–5), azithromycin, lopinavir-ritonavir (400/100 mg twice daily), and low molecular weight heparin according to bodyweight and kidney function. Intravenous administration of dexamethasone was also permitted at a dose not exceeding 16 mg daily.

Outcomes

The primary outcome of the study was a composite of all-cause death or invasive mechanical ventilation, whereas the secondary outcomes were in hospital all-cause mortality and the requirement for invasive mechanical ventilation. The mortality rates in patients with COVID-19 depend largely on the need to start oxygen supply and the level of respiratory support [14]. Therefore, patients were divided into two groups according to oxygen saturation and the requirement for oxygen supply at enrolment, that is, with oxygen saturation at rest [?]93% (group 1) and >93% (group 2). The study outcomes were evaluated separately in the two groups. Primary and secondary end-points, if met, were determined prospectively for treated patients and retrospectively by chart review for control patients.

Statistical analysis

Normality of data was checked using the Shapiro-Wilk test. Demographic and baseline clinical characteristics, including comorbidities and blood parameters, were expressed as median (IQR) for continuous variables and as numbers (%) for categorical variables. Continuous variables were compared between tofacitinib and controls using the Mann-Whitney U-test test for two groups and the Kruskal Wallis test for three groups. Categorical variables across groups were compared by the Fisher's exact test or Pearson's χ^2 test.

All participants were followed up from the date of enrolment into the study until discharge or death. We conducted a survival analysis and compared the time to invasive mechanical ventilation or death between the treatment groups using unweighted Kaplan-Meier curves and univariable and multivariable Cox regression analysis with baseline fixed covariates. The effect of treatment was evaluated using an unadjusted and adjusted hazard ratio (HR) with 95% confidence interval (CI). The baseline model was adjusted for inverse propensity score weighting. Cox regression model validity was checked by evaluation of the proportional hazard assumption using Schoenfeld residuals.

We considered a two-sided p value test of less than 0.05 to be statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 22 (IBM Corporation, USA).

RESULTS

Overall, 384 patients with moderately severe COVID-19 were included in our study. There were 212 males (55.2%), and the median age was 60 years (IQR 48–70). All patients were Caucasians. Median duration of hospital stay until death or discharge was 16 days (IQR 14-20). 131 patients (34.1%) received tofacitinib in addition to standard of care, and 253 patients (65.9%) were treated with standard of care alone. Baseline clinical and demographic characteristics of patients with low and normal oxygen saturation who received tofacitinib or standard of care alone are presented in Tables 1 and 2.

Patients with reduced oxygen saturation. At enrolment, oxygen saturation at rest on ambient air was 93% or lower in 257 patients (group 1), of whom 72 received tofacitinib on top of standard of care treatment. Patients in the tofacitinib and control groups were well-matched by age, gender, body mass index, comorbidities, oxygen saturation, and various laboratory parameters, including white blood cells, neutrophils, lymphocytes, serum lactate dehydrogenase and eGFR. Median CRP levels were high in both groups. Patients who were treated with tofacitinib had less extensive ground-glass opacification on CT compared to controls, although almost all patients maintained target oxygen saturation using nasal oxygen and did not require high-flow

oxygen or non-invasive ventilation. Baseline differences in both groups were observed. In particular, two-times more patients received glucocorticoids in the tofacitinib group than in the control group (43.7% and 21.1%, respectively; p=0.001).

Overall, the primary composite end-point of death or mechanical ventilation was reached in 9 (12.5%) of 72 patients who were treated with tofacitinib and 26 (14.1%) of 185 patients who received standard of care treatment alone (HR 0.92, 95% CI 0.33-2.56). Invasive mechanical ventilation was initiated in 5 (6.9%) patients in the tofacitinib group versus 24 (13.0%) patients in the control group (HR 0.46; 95 CI 0.11-1.99), whereas 8 (11.1%) versus 21 (11.4%) patients in the two groups, respectively, died in the hospital (HR 1.25; 95 CI 0.44-3.54).

Unweighted Kaplan-Meier estimates showed no beneficial effect of treatment with tofacitinib compared with standard of care only (Fig. 1). Also, we found no differences between groups for the mortality end-point or requirement for invasive mechanical ventilation. In Cox regression analysis, addition of tofacitinib to standard of care did not result in a reduced risk of either primary or secondary outcomes (Table 3).

Patients with normal oxygen saturation. At baseline, oxygen saturation at rest was normal (94% or higher) in 127 patients. 59 of them were treated with tofacitinib in addition to standard of care, and 68 patients received only standard of care treatment. Various parameters, including age, gender, body mass index, comorbidities, oxygen saturation, white blood cells, neutrophils, and lymphocytes counts, serum creatinine level, were well balanced across groups. Like in group 1, patients in the tofacitinib group had less extensive ground-glass opacification on CT and a lower median CRP level compared to the control group. The proportions of patients who received treatment with glucocorticoids and low-molecular weight heparins in the tofacitinib group were significantly higher than in the control group.

The primary composite end-point of death or invasive mechanical ventilation was met in 1 (1.7%) of 59 patients who received tofacitinib plus standard of care treatment and 3 (4.4%) of 68 patients who were treated with standard of care alone (HR 0.83; 95 CI 0.07-9.44). No patient in the tofacitinib group required invasive mechanical ventilation, whereas 3 (4.4%) controls were intubated during hospital stay (p=0.25). One patient (1.7%) in the tofacitinib group deceased compared to 3 (4.4%) patients in the control group (HR 1.10; 95 CI 0.10-12.46).

Kaplan-Meier analysis showed no beneficial effect of tofacitinib added to standard of care treatment compared with standard of care alone (Fig. 2). The mortality rates and requirement for invasive mechanical ventilation also did not differ between the two groups. In Cox regression analysis, addition of tofacitinib to standard of care treatment was not associated with a reduced risk of either composite primary or secondary end-points compared with standard of care treatment (Table 3).

Patients treated with glucocorticoids. In total, 118 patients from the study population were treated with intravenous dexamethasone (supplemental table S1). Among 70 patients with reduced oxygen saturation, the primary end point of death or mechanical ventilation occurred in 4 (12.9%) of 31 patients in the tofacitinib group and 11 (28.2%) of 39 patients in the control group. Mechanical ventilation was required in 1 (3.2%) and 10 (25.6%) patients, respectively, whereas 4 (12.9%) patients treated with tofacitinib and glucocorticoids and 9 (23.1%) patients who received glucocorticoids alone died. All the differences in the end points rates between the two groups did not reach statistical significance in the univariate Cox analysis. Among 48 patients with normal oxygen saturation, the composite end point was met in 1 (3.0%) of 31 patients who were treated with tofacitinib in addition to glucocorticoids and in 2 (13.3%) of 15 patients who received glucocorticoids alone. The differences in the primary and secondary end point rates between the two groups were insignificant in the univariate Cox analysis.

Safety. Adverse events were reported in 34 (26.0%) of 131 patients treated with tofacitinib (Table 4). Treatment with tofacitinib was discontinued in 7 (5.3%) patients due to rapid respiratory deterioration (n=2) or serious adverse events (n=5) that included ST-elevation myocardial infarction (n=1), bacterial sepsis (n=2), jugular vein thrombosis (n=1), and bacterial colitis (n=1).

DISCUSSION

In our study, tofacitinib in addition to standard of care therapy did not reduce the composite end-point of invasive mechanical ventilation or death among hospitalised patients with moderately severe COVID-19. Most patients had signs of systemic inflammation, that is, persisting fever and/or elevated CRP. The primary end-point was not met both in patients requiring oxygen supply at the time of tofacitinib initiation and those with normal oxygen saturation. In multivariate Cox regression analysis adjusted for inverse propensity score weighting, the addition of tofacitinib to the standard of care therapy improved outcomes neither in hypoxic patients nor in those receiving no supplemental oxygen.

In both groups, analysis of the composite end-point rates non-significantly favoured tofacitinib. The percentages of patients who started mechanical ventilation or died during hospitalisation in the tofacitinib and control groups were 12.5% vs. 14.1%, respectively, among patients who required respiratory support, and 1.7% vs. 4.4%, respectively, in those with normal oxygen saturation. These differences could be related to the use of glucocorticoids that was two- to three-fold higher in the tofacitinib groups. The RECOVERY trial showed the efficacy of dexamethasone in reducing mortality only among hospitalised patients with more severe COVID-19 [4]. However, a favourable effect of glucocorticoids on the course of COVID-19 might also be present in cases with signs of excessive inflammatory response, even in the absence of hypoxia at the time of hospitalisation.

In the ACTT-2 trial, the beneficial effects of the combination treatment with baricitinib and remdesivir included a 1-day shorter time to recovery and a greater improvement in clinical status as assessed on the ordinal scale [10]. In contrast, we did not evaluate the time to clinical improvement or recovery, since we could not validate these data that were collected retrospectively for control patients. The assessment of time to recovery was even more challenging in patients with normal oxygen saturation. Therefore, the hard end-points of death or invasive ventilation seemed to be more suitable criteria of efficacy for our non-randomised clinical study.

The use of glucocorticoids was prohibited by the protocol of the ACTT-2 trial, although these medications were permitted for standard indications including septic shock and acute respiratory distress syndrome. In the ACTT-2 study, dexamethasone was administered to only 6.0% of patients in the baricitinib group. On the contrary, systemic glucocorticoids were used in 82% of patients who were enrolled in the tocilizumab arm of the RECOVERY study. Addition of tocilizumab to glucocorticoids resulted in 20% reduction in the risk of all-cause mortality, whereas this benefit was not seen in patients who did not receive glucocorticoids [7]. These findings suggest that in patients with COVID-19 tocilizumab and probably other immunomodulators should be considered in addition to glucocorticoids, particularly in those who do not respond to initial anti-inflammatory therapy or present with severe or progressive disease. In our study, 31.2% of patients received intravenous dexamethasone. Addition of tofacitinib to glucocorticoids was associated with a more than two-fold reduction in the occurrence of the composite end-point of death or mechanical ventilation compared to controls among patients with low oxygen saturation (12.9% vs. 28.2%). Both the need of mechanical ventilation and all-cause mortality rates were lower in the tofacitinib group. However, the differences between the two groups were not significant, probably as a result of limited number of enrolled patients. The incidence of the primary and secondary end-points was low in patients with normal oxygen saturation and did not differ between the two groups. Tofacitinib was well tolerated in the studied population and was discontinued in only 5.4% of patients.

Our findings are in contrast with the results of the STOP-COVID Trial, in which treatment with tofacitinib compared to placebo resulted in a lower cumulative incidence of death or respiratory failure through day 28 (risk ratio, 0.63; 95% CI, 0.41 to 0.97; p = 0.04) and reduction in the proportional odds of having a worse score on the eight-level ordinal scale (0.54, 95% CI, 0.27 to 1.06) at day 28, whereas the difference in the mortality rates between the tofacitinib and placebo groups did not reach statistical significance [11]. A higher rate of glucocorticoids administration (78.5%) and a higher dose of tofacitinib (10 mg twice daily) are the possible explanations of the better outcomes of JAK-inhibitor use in the STOP-COVID Trial.

Our study has several limitations. First, we could not account for confounders inherent to the study design, although we adjusted the baseline model for inverse propensity score weighting. Control patients were selected randomly from the population of COVID-19 patients who were hospitalised during the first wave of the pandemic in Russia. Nevertheless, selection biases cannot be ruled out. Second, the statistical power of our study was limited, particularly among patients with normal oxygen saturation given the low incidence of events. However, we evaluated tofacitinib' efficacy in a relatively large sample of patients with COVID-19.

In summary, tofacitinib in addition to standard of care therapy did not reduce the risk of invasive mechanical ventilation or death in patients with moderately severe COVID-19. Analysis of the composite primary end-point and the secondary end-points favoured tofacitinib, particularly among patients with low oxygen saturation who received intravenous dexamethasone. However, all the differences between tofacitinib users and controls were not significant.

Notes

Acknowledgments. The authors thank all patients who were enrolled in this study and all physicians who participated in their care.

Role of the funding source. There was no funding source for this study. The first author and two last authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Potential conflicts of interests. A. Kronbichler received speaking fees from Novartis, TerumoBCT, Miltenyi Biotech, and Vifor Pharma, and received consulting fees from Alexion and Vifor Pharma. All other authors have no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflict of Interest.

References

1. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med **2020** ; 383(23): 2255-73.

2. Kim JS, Lee JY, Yang JW, Lee KH, Effenberger M, Szpirt W, et al. Immunopathogenesis and treatment of cytokine storm in COVID-19. Theranostics **2021** ; 11(1): 316-29.

3. Cavalli G, Farina N, Campochiaro C, De Luca G, Della-Torre E, Tomelleri A, Dagna L. Repurposing of biologic and targeted synthetic anti-rheumatic drugs in COVID-19 and hyper-Inflammation: A comprehensive review of available and emerging evidence at the peak of the pandemic. Front Pharmacol **2020** ; 11: 598308.

4. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med**2021** ; 384(8): 693-704.

5. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: A randomized clinical trial. JAMA Intern Med **2021** ; 181(1): 32-40.

6. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med **2020** ; 383(24): 2333-44.

7. Horby PW, Campbell M, Staplin N, Brightling CE, Sarkar R, Thomas K, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. medRxiv preprint doi: https://doi.org/10.1101/2021.02.11.21249258.

8. Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmaco-immunomodulatory therapy in COVID-19. Drugs **2020** ; 80(13): 1267-92.

9. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet **2020** ; 395(10223): e30-e1.

10. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med **2021** ; 384(9): 795-807.

11. Guimarães PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al; STOP-COVID Trial Investigators. Tofacitinib in patients hospitalized with Covid-19 pneumonia. N Engl J Med. 2021 Jun 16. doi: 10.1056/NEJMoa2101643. Epub ahead of print.

12. Prokop M, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, et al. CO-RADS: A categorical CT assessment scheme for patients suspected of having COVID-19 definition and evaluation. Radiology **2020** ; 296(2): E97-E104.

13. Dhillon S. Tofacitinib: a review in rheumatoid arthritis. Drugs**2017** ; 77(18): 1987-2001.

14. Moiseev S, Avdeev S, Brovko M, Bulanov N, Tao E, Fomin V. Outcomes of intensive care unit patients with COVID-19: a nationwide analysis in Russia. Anaesthesia **2021** ; 76 Suppl 3: 11-2.

Table 1. Baseline demographic and clinical characteristics of patients with reduced oxygen saturation

Characteristic	Tofacitinib group, n=72	Control group, n=185	p
Age, years	61 (50-68)	61 (52-71)	0.95
Male gender, n (%)	39 (54.2)	102 (55.1)	0.89
BMI, kg/m^2	29.7 (26.9-33.0)	30.8 (26.3-33.9)	0.57
Time from disease onset to enrollment, days	10 (7-12)	8 (6-10)	<0.01
Persistent fever, n (%)	60 (83.3)	133 (71.9)	0.08
CRP>50 mg/L, n (%)	60 (83.3)	182 (98.4)	<0.01
Comorbidities, n (%)			
Hypertension	41 (56.9)	111 (60.0)	0.67
Diabetes	13 (18.1)	40 (21.6)	0.61
Obesity	29/61 (47.5)	77/150 (51.3)	0.65
History of stroke	2 (2.8)	11 (5.9)	0.53
History of myocardial infarction	3 (4.2)	16 (8.6)	0.29
Malignancy	2 (2.8)	7 (3.8)	1.00
COPD	2 (2.8)	7 (3.8)	1.00
Other*	34 (47.2)	91 (49.2)	0.78
Oxygen support at enrollment, n (%)			
Nasal oxygen	71 (98.6)	184 (99.5)	0.48
Non-invasive ventilation	1 (1.4)	1 (0.5)	0.48
Oxygen saturation, %	90 (87-92)	90 (88-92)	0.93
Extent of lung involvement on CT, n (%)			
0-24%	2 (2.8)	3 (1.6)	0.62
25-49%	37 (51.4)	55 (29.7)	<0.01
50-74%	26 (36.1)	105 (56.7)	<0.01?¿?
75	7 (9.7)	17 (9.2)	1.00
Missing data			
Body temperature (axillary), °C	38.0 (38.5-38.7)	37.6 (37.2-38.1)	<0.01
Blood parameters			
White cells, $\times 10^9$/L	5.9 (4.2-7.5)	6.1 (4.8-8.1)	0.70
Neutrophils, $\times 10^9$/L	4.1 (2.9-5.6)	4.6 (3.4-6.3)	0.19
Lymphocytes, $\times 10^9$/L	1.0 (0.7-1.3)	0.9 (0.7-1.3)	0.45
CRP, mg/L	89.4 (62.6-154.2)	106.5 (79.0-148.5)	0.02
LDH, U/L	654.5 (532.5-871.3)	732.0 (566.5-894.0)	0.46
Creatinine, mcmol/L	93.4 (87.0-115.0)	95.5 (84.7-115.9)	0.81
Concomitant therapy, n (%)			

Characteristic	Tofacitinib group, n=72	Control group, n=185	p
Antimalarials	63 (87.5)	173 (93.5)	0.13
Lopinavir-ritonavir	10 (13.9)	80 (43.2)	<0.01
Glucocorticoids	31 (43.7)	39 (21.1)	<0.01
Azithromycin	54 (75.0)	157 (84.9)	0.07
Other antibiotics	47 (65.3)	145 (78.4)	0.04
Low molecular weight heparins	69 (95.8)	160 (86.5)	0.04

*CAD with no history of myocardial infarction, chronic heart failure I-II class, atrial fibrillation, peripheral artery disease, chronic gastritis, gastroesophageal reflux disease, gallstone disease, stone kidney disease, gout, chronic ENT infections, hypothyroidism, Alzheimer's disease, epilepsy, asthma

Data are median (IQR) or n/N (%). P values were calculated with Mann-Whitney U-test or $\chi 2$, as appropriate. BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 2. Baseline demographic and clinical characteristics of patients with normal oxygen saturation

Characteristic	Tofacitinib group, n=59	Control group, n=68	p
Age, years	52 (45-62)	57 (44-65)	0.38
Male gender, n (%)	33 (55.9)	38 (55.9)	1.00
BMI, kg/m^2	29.2 (27.2-32.8)	28.7 (26.5-33.5)	0.76
Time from disease onset to enrollment, days	9 (7-12)	8 (5-11)	0.12
Persistent fever, n (%)	48 (81.4)	43 (63.2)	0.03
CRP>50 mg/L, n (%)	30 (50.8)	65 (95.6)	<0.01
Comorbidities, n (%)			
Hypertension	27 (45.8)	32 (47.1)	1.00
Diabetes	11 (18.6)	11 (16.2)	0.82
Obesity	16/42 (38.1)	22/49 (44.9)	0.53
History of stroke	2 (3.4)	1 (1.5)	0.60
History of myocardial infarction	3 (5.1)	2 (2.9)	0.66
Malignancy	3 (5.1)	2 (2.9)	0.66
COPD	1 (1.7)	2 (2.9)	1.00
Other*	26 (44.1)	32 (47.1)	0.86
Oxygen saturation, %	95 (94-96)	94 (94-95)	**<0.01**
Extent of lung involvement on CT, n (%)			
0-24%	10 (16.9)	2 (2.9)	0.01
25-49%	41 (69.5)	22 (32.4)	<0.01
50-74%	8 (13.6)	32 (47.1)	<0.01?¿?
75	0	6 (8.8)	0.03
Missing data	0	6 (8.8)	0.03
Body temperature (axillary), °C	38.0 (37.5-38.5)	37.4 (37.0-38.3)	**<0.01**
Blood parameters			
White cells, $\times 10^9$/L	5.3 (4.3; 6.5)	6.1 (4.8; 8.1)	0.05
Neutrophils, $\times 10^9$/L	3.5 (2.7; 4.8)	4.3 (3.2; 6.2)	0.27
Lymphocytes, $\times 10^9$/L	1.1 (0.8; 1.6)	1.2 (0.8; 1.5)	0.71
CRP, mg/L	53.0 (35.6; 87.6)	79.2 (60.3; 155.0)	**<0.01**
LDH, U/L	479.0 (406.0; 615.8)	608.0 (489.0; 792.5)	**0.01**
Creatinine, mcmol/L	96.5 (84.5; 110.0)	98.9 (84.8; 110.1)	0.58
Concomitant therapy, n (%)			

Characteristic	Tofacitinib group, n=59	Control group, n=68	p
Antimalarials	45 (76.3)	60 (88.2)	0.10
Lopinavir-ritonavir	5 (8.5)	9 (13.2)	0.57
Glucocorticoids	33 (57.9)	15 (22.1)	<0.01
Azithromycin	38 (64.4)	53 (77.9)	0.12
Other antibiotics	35 (59.3)	50 (73.5)	0.13
Low molecular weight heparins	56 (94.9)	43 (63.2)	<0.01

*CAD with no history of myocardial infarction, chronic heart failure I-II class, atrial fibrillation, peripheral artery disease, chronic gastritis, gastroesophageal reflux disease, gallstone disease, stone kidney disease, gout, chronic ENT infections, hypothyroidism, Alzheimer's disease, epilepsy, asthma

Data are median (IQR) or n/N (%). P values were calculated with Mann-Whitney U-test or χ^2, as appropriate. BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 3. Effect of treatment with tofacitinib versus standard of care alone on primary and secondary outcomes

End-points	Unadjusted HR (95% CI)	p	Adjusted HR (95% CI)	p
Patients with reduced oxygen saturation				
Death or invasive mechanical ventilation	0.91 (0.42–1.97)	0.82	0.92 (0.33-2.56)	0.87
Invasive mechanical ventilation	0.67 (0.25–1.78)	0.42	0.46 (0.11-1.99)	0.30
Death	1.24 (0.54–2.84)	0.62	1.25 (0.44-3.54)	0.67
Patients with normal oxygen saturation				
Death or invasive mechanical ventilation	0.76 (0.07–8.57)	0.83	0.83 (0.07-9.44)	0.88
Invasive mechanical ventilation	NA		NA	
Death	0.99 (0.09–11.08)	0.99	1.10 (0.10 – 12.46)	0.94

Table 4. Adverse events in 131 patients treated with tofacitinib

Adverse events	n (%)
Elevated liver enzymes	14 (10.7)
Bacterial pneumonia	6 (4.6)
Urinary tract infection	2 (1.5)
Bacterial sepsis	2 (1.5)
Bacterial colitis	1 (0.8)
Anaemia	2 (1.5)
Leukopenia	1 (0.8)
Jugular vein thrombosis	1 (0.8)
Skin rash	1 (0.8)
Periodontitis	1 (0.8)
ST-elevation myocardial infarction	1 (0.8)
Acute kidney injury that required dialysis	1 (0.8)
Gastrointestinal bleeding	1 (0.8)

Figure 1. Kaplan-Meier curves for composite end-point in patients with reduced saturation

Figure 2. Kaplan-Meier curves for composite end-point in patients with reduced saturation