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Baricitinib vs tocilizumab treatment for hospitalized adult patients with severe COVID-19 and associated cytokine storm: a prospective, investigational, real-world study

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ABSTRACT

Objectives: Our aim was to compare outcomes of hospitalized adults with severe COVID-19 and cytokine storm treated with tocilizumab or baricitinib.

Methods: A prospective, investigational, real-world study was performed from April 2020 to April 2021 at our center. COVID-19 severity was classified by World Health Organization criteria, and cytokine storm was documented along predefined criteria. Eligible patients were enrolled at diagnosis if they fulfilled *a priori* inclusion criteria and received standard-of-care plus tocilizumab or baricitinib for >48 hours. Patients were followed per protocol for 28 days post-diagnosis. The primary outcome was all-cause mortality; secondary outcomes were invasive mechanical ventilation and major infectious complications.

Results: Of 463 patients, 102/463 (22.1%) received tocilizumab, and 361/463 (77.9%) baricitinib. Baseline characteristics were balanced. At 28 days, there was no difference in all-cause mortality (22/102, 21.6% vs 64/361, 17.7%; *P*-value = 0.38). Requirement for invasive mechanical ventilation was more frequent after tocilizumab (52/102, 50.9% vs 96/361, 26.6%; $P < 0.01$), rate of major infectious complications was similar (32/102, 31.4% vs 96/361, 26.6%; *P*-value = 0.34). In logistic regression, the immunomodulatory drug was not retained as a predictor of all-cause mortality. Kaplan–Meier analysis revealed statistically similar survival distributions.

Conclusion: All-cause mortality was similar between adults treated with baricitinib or tocilizumab for severe COVID-19 with cytokine storm.

Introduction

The ongoing COVID-19 pandemic caused by SARS-CoV-2 has devastated countries. The race to find adequate therapies is ongoing, but significant progress has been made since 2019. Our understanding of COVID-19 pathogenesis revealed the need for targeting the dysregulated immune response. The term cytokine storm first appeared 30 years ago, describing a potentially life-threatening condition triggered by various pathogens, hematologic and immunological disorders, and is characterized by peripheral hyperactivation of T-lymphocytes, resulting in elevated cytokines levels, systemic inflammation, and end-organ damage (Chatenoud et al., 1991; Osuchowski et al., 2021). The recognition of COVID-19-associated cytokine storm is challenging, as no clinically validated universal criteria exist yet (Fajgenbaum and June, 2020). Dexamethasone was the first drug to gain evidence in the treatment of severe COVID-19 pneumonia requiring additional oxygen (The RE-

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COVERY Collaborative Group, 2021). However, in 5-10% of cases, COVID-19 progresses to cytokine storm despite dexamethasone (Fajgenbaum and June, 2020; Tang et al., 2021). Further studies showed that the administration of tocilizumab, an interleukin-6 (IL-6) receptor-blocking monoclonal antibody, or baricitinib, a Janus kinase inhibitor, might associate with beneficial outcomes of COVID-19 (Gupta et al., 2021, Kalil et al., 2021; Marconi et al., 2021; Remap-Cap Investigators et al., 2021; Tleyjeh et al., 2021). Based on clinical data, the World Health Organization recommends baricitinib as an alternative to tocilizumab in severe COVID-19, while other guidelines discuss the role of baricitinib more cautiously, given the lack of comparative studies (Bartoletti et al., 2022, World Health Organization, 2021). Therefore, our aim was to compare the clinical characteristics and outcomes of patients treated with either tocilizumab or baricitinib for severe COVID-19 with cytokine storm.

Methods

Study design and settings

A prospective, investigational, real-world study was conducted from April 2020 to April 2021 among consecutive adult (aged ≥18 years at inclusion) patients diagnosed with COVID-19 and hospitalized at South Pest Central Hospital, National Institute of Hematology and Infectious Diseases (Budapest, Hungary), a tertiary-referral institution with >250 dedicated beds for COVID-19. The study was in accordance with national ethical standards and the Declaration of Helsinki. Our institutional review board approved the study protocol. Approval for the use of off-label drugs for COVID-19 was granted by the National Institute of Pharmacy and Nutrition. Written informed consent was obtained from each patient before study inclusion.

Patient eligibility, study inclusion

Patients hospitalized during the study period with COVID-19 of any illness duration, confirmed by respiratory SARS-CoV-2 polymerase chain reaction (PCR) during a compatible clinical case presentation with pulmonary infiltration on chest computed tomography, were eligible for inclusion at COVID-19 diagnosis. To overcome selection bias, all patients were screened for inclusion during daily investigator visits. After diagnosis establishment, inclusion was performed by using the following *a priori* criteria: (i) severe COVID-19, (ii) COVID-19–associated cytokine storm, and (iii) administration of the actual standard-of-care (SOC) plus either tocilizumab or baricitinib for >48 hours after diagnosis. Exclusion criteria were (i) death, anticipated hospital discharge or transfer to another hospital within ≤48 hours after diagnosis, or (ii) administration of SOC for ≤48 hours after diagnosis, (iii) any IL-6 or Janus kinase inhibitor treatment for ≥1 dose before COVID-19 diagnosis, (iv) pregnancy or breastfeeding, or (v) known allergy or absolute contraindications to study medications. Included patients were then subgrouped according to their respective immunomodulatory treatment.

Data collection

For study purposes, an anonymized database has been established by manual collection of patient data from electronic records to a standardized case report form. Data collected were (i) age and gender, (ii) comorbidities, (iii) requirement of intensive care unit (ICU) admission, length of hospital stay (LOS), ICU LOS, (iv) clinical characteristics at baseline (symptom onset, COVID-19 severity, requirement of oxygen support, partial arterial pressure of oxygen [PaO_2]/fraction of inspired oxygen [FiO_2] index, acute respiratory distress syndrome [ARDS]), (v) laboratory characteristics at baseline (blood absolute white blood cell, neutrophil granulocyte, lymphocyte and platelet counts, serum c-reactive protein, ferritin and lactate dehydrogenase [LDH], plasma IL-6, and D-dimer), (vi) imaging characteristics at baseline, (vii) microbiological characteristics during hospitalization, (viii) clinical outcomes. Baseline characteristics were recorded on the day of in-hospital COVID-19 diagnosis ascertainment.

Diagnostic evaluation, follow-up

At our center, COVID-19 patient care has been guided by a standardized, monthly-updated in-house protocol since March 2020. Diagnostic ascertainment of COVID-19 was done according to the European Centre for Disease Prevention and Control (2020) definition. Respiratory specimens could be collected by nasopharyngeal sampling (non-intubated patients) or bronchoalveolar lavage (intubated patients). Symptom onset of COVID-19 was defined as the first day of symptom appearance reported by the patient/caregiver or day of first positive respiratory SARS-CoV-2 PCR if symptoms were not reported. Day of COVID-19 diagnosis was defined as the day of first respiratory SARS-CoV-2 PCR positivity in a hospitalized, symptomatic patient.

Disease severity was determined according to the World Health Organization (2021) criteria. COVID-19-associated cytokine storm was defined if ≥1 clinical and ≥2 biochemical criteria were fulfilled during hospitalization in a patient. Clinical criteria (i) persistent fever for ≥3 consecutive days, despite systemic corticosteroids and non-steroid anti-inflammatory drugs, (ii) resting arterial O_2 saturation ≤94% or PaO_2/FiO_2 index <300 mmHg, with or without tachypnea (>22 breaths/min) on room air or oxygen support, (iii) acute respiratory failure, ARDS, circulatory shock, or multiple organ dysfunction. Biochemical criteria: (i) serum ferritin ≥600 µg/l, (ii) plasma IL-6 ≥3x above the upper limit of normal (2.0 pg/ml at our center), (iii) serum LDH level ≥1x above the upper limit of normal (480 IU/l at our center), (iv) serum c-reactive protein >75 mg/l, (v) plasma D-dimer >1000 ng/ml (Fajgenbaum and June, 2020). Acute respiratory failure and ARDS were defined according to the 2012 Berlin criteria (ARDS Definition Task Force et al., 2012). Fever was defined as a tympanal temperature of ≥38.0°C. Fully vaccinated status against COVID-19 was defined as receiving two doses, while partially vaccinated status was defined as receiving one dose of a nationally authorized vaccine (Janssen, Moderna, Oxford-AstraZeneca, Pfizer-BioNTech, Sinopharm, Sputnik V); after≥14 days of last vaccine administration.

Daily patient follow-up was done for 28 days from COVID-19 diagnosis until hospital discharge or death. If the patient was discharged within 28 days, a post-discharge follow-up was sought by attending physicians through e-mails, telephone calls, and the social security database of Hungarian National E-Health Infrastructure (National Directorate General for Hospitals, 2022). Physical examinations, laboratory studies, and arterial blood gas analyses were done on alternating days. Chest computed tomography scans were executed at COVID-19 diagnosis and if new-onset clinical instability occurred during hospitalization (recurrent fever, dyspnea or chest pain, circulatory shock, altered mental status). All febrile patients and those with new-onset clinical instability had ≥2 blood culture sets taken. Bloodstream infection was defined as the isolation of a virulent organism from a single blood culture, or a potential skin contaminant from the majority of blood cultures, during a compatible clinical scenario. Major infectious complications were diagnosed in accordance with current guidelines; microbiological diagnostics were performed at the Microbiology Laboratory of our

center (Cornely et al., 2012; Donnelly et al., 2020; Koehler et al., 2021; Mermel et al., 2009; Torres et al., 2017).

Treatment allocation

COVID-19 therapies were allocated per protocol according to disease severity in an open-label, non-randomized fashion, based on national and international guidelines detailing the actual literature evidence, but was also affected by drug availability (Bartoletti et al., 2022; Bobek et al., 2021). SOC for severe COVID-19 consisted of on-demand oxygen and respiratory support, intravenous fluids, antipyretics, antitussives, bronchodilators, remdesivir, and dexamethasone. All patients routinely received remdesivir after the drug became available nationally in May 2020. Before the advent of the remdesivir era and during drug shortages, available antivirals (with initially presumed activity against SARS-CoV-2) were hydroxychloroquine, lopinavir/ritonavir, and favipiravir. Dexamethasone was introduced to routine care of all patients requiring oxygen support in June 2020. Either tocilizumab or baricitinib was administered to patients with proven COVID-19-associated cytokine storm. The decision was based on drug availability for this indication (tocilizumab became available in April 2020, baricitinib in November 2020), the available route of administration (baricitinib was contraindicated in patients with documented or presumed difficulty of swallowing, and patients at ICU received it via nasogastric tube), at the discretion of the providing physician. Previous use of dexamethasone for COVID-19 was not regarded as a contraindication for tocilizumab/baricitinib. More details on treatments are given in Supplement File 1.

Outcomes

The primary outcome was all-cause mortality, defined as the death of a COVID-19 patient from any cause. Secondary outcomes were (i) requirement of invasive mechanical ventilation and (ii) documentation of any major infectious complication. The requirement of invasive mechanical ventilation was defined as a completed endotracheal intubation in relation to COVID-19, per decision of an ICU crash team. Major infectious complications were defined as bloodstream infection, and/or ventilator-associated pneumonia, and/or proven and putative/probable COVID-19-associated pulmonary aspergillosis. All outcomes were measured at 28 days from COVID-19 diagnosis.

Statistical analysis

Continuous variables are reported as median ± interquartile range, and categorical variables are reported as numbers (n) with percentages (%). Comparisons were done with Mann-Whitney U-test or Fisher's exact test. Normality was tested by the Shapiro-Wilk test. Assuming an 80% survival rate, an *a priori* sample size calculation revealed a minimum of 412 patients for the cohort (sampling ratio of 1:3) to detect a 15% difference margin for the primary outcome between subgroups at a statistical power of 1-β = 90%. The difference between the primary outcome of subgroups was examined by Kaplan–Meier survival analysis with log-rank testing. For identification of independent risk factors of the primary outcome, a forward-stepwise multivariate binomial logistic regression model (entry criterion: *P*-value = 0.05, removal criterion: *P*-value = 0.1) was built with plausible baseline parameters (including treatment modalities to overcome bias by indication), and those with a $P \leq 0.1$ in univariate logistic regression. The predictor number maximum was estimated by the 1:10 rule of thumb. Goodness-of-fit was tested by the Hosmer-Lemeshow test. The linearity of the logit was tested by the Box-Tidwell test. A 2-tailed

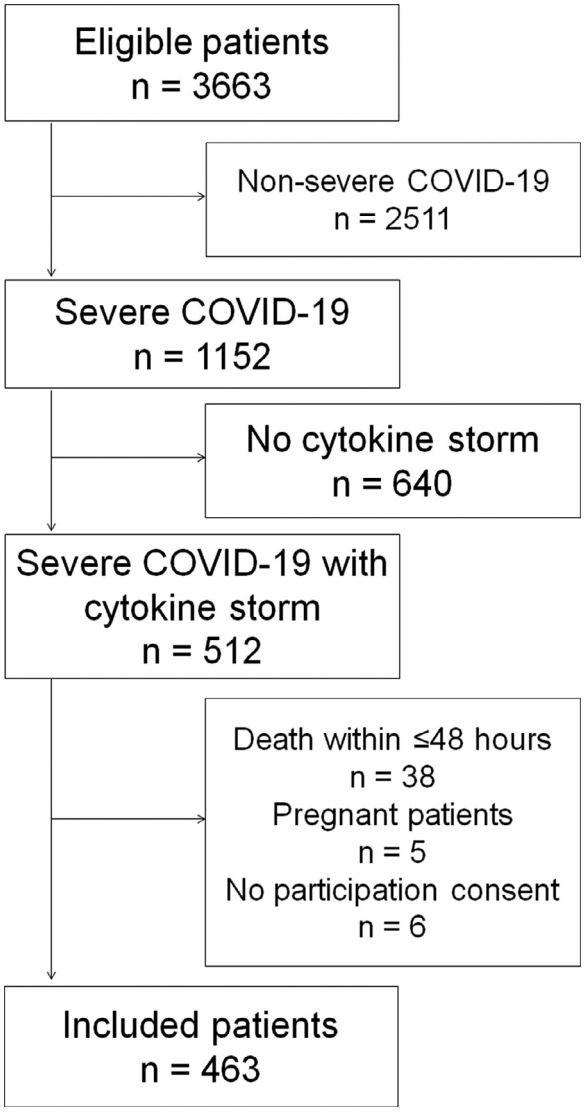

Figure 1. Flowchart of study inclusion.

$P < 0.05$ determined statistical significance. Tests were calculated using IBM SPSS Statistics 23, and Kaplan–Meier curves were plotted with MedCalc 14. For reporting, we adhere to Strengthening the Reporting of Observational Studies in Epidemiology Statement (von Elm et al., 2007).

Results

In total, 3663 eligible patients were admitted during the study period, and from these, 463 patients were enrolled: 102/463 (22.1%) were administered tocilizumab, 361/463 (77.9%) received baricitinib (Figure 1). Baseline and clinical characteristics are shown in Table 1. Median age, gender, and comorbidities were balanced between treatment subgroups. Non-vaccinated status was prevalent in the cohort (413/463, 89.2%). At baseline, the median PaO_2/FiO_2 index was 180 ± 91 mmHg; all patients required oxygen support. Between subgroups, types of oxygen support and laboratory parameters of COVID-19 at baseline were similar. Remdesivir was administered to 80.6% (373/463) and dexamethasone to 88.6% (410/463) of patients.

Outcomes are detailed in Table 2. There was no statistically significant difference in all-cause mortality between patients re-

Table 1
Baseline demographic and clinical characteristics of adult patients with COVID-19-associated cytokine storm, grouped by immunomodulatory treatment received.

PARAMETER	Total (n = 463)	Tocilizumab treatment (n = 102)	Baricitinib treatment (n = 361)	*P*-value
Age (years, median ± IQR, min-max)	63.1 ± 21.5 (26-98)	63.5 ± 27.4 (27-85)	63.1 ± 22.5 (26-98)	0.89
Male gender (n, %)	285 (61.6)	71 (69.6)	214 (59.3)	0.05
Comorbidities (n, %):				
- Chronic cardiovascular disease	277 (59.8)	64 (62.7)	213 (59.0)	0.56
- Chronic pulmonary disease	58 (12.7)	17 (16.7)	41 (11.4)	0.17
- Chronic renal disease	42 (9.1)	13 (12.7)	29 (8.0)	0.17
- Chronic hepatic disease	14 (3.0)	3 (2.9)	11 (3.0)	1.0
- Chronic cerebral disease	28 (6.1)	6 (5.9)	21 (5.8)	1.0
- Diabetes mellitus	124 (26.8)	25 (24.5)	99 (27.4)	0.61
- Active oncological malignancy	32 (6.9)	9 (8.8)	23 (6.4)	0.38
- Active hematologic malignancy	18 (3.9)	5 (4.9)	13 (3.6)	0.56
- Systemic autoimmune disease	16 (3.4)	1 (0.9)	15 (4.2)	0.21
- Tobacco smoking	35 (7.6)	11 (10.8)	24 (6.6)	0.20
- Chronic alcohol dependency	14 (3.0)	3 (2.9)	11 (3.0)	1.0
COVID-19 vaccination status at baseline (n, %):				
- Non-vaccinated	413 (89.2)	90 (88.2)	323 (89.5)	
- Partially vaccinated	48 (10.3)	11 (10.8)	37 (10.2)	0.63
- Fully vaccinated	2 (0.4)	1 (1.0)	1 (0.3)	
Clinical characteristics at baseline:				
- Partial arterial pressure of oxygen / Fraction of inspired oxygen index (mmHg, median ± IQR, min-max)	180 ± 91 (55-400)	185 ± 104 (100-400)	171 ± 89 (55-317)	0.69
- Requirement of any oxygen support (n, %)	463 (100.0)	102 (100.0)	361 (100.0)	1.0
Types of oxygen support started at baseline (n, %):				
- Low-flow nasal cannula	105 (22.7)	29 (28.4)	76 (21.1)	0.16
- Venturi mask or non-invasive mechanical ventilation	236 (50.9)	44 (43.1)	192 (53.2)	
- Invasive mechanical ventilation	122 (26,4)	29 (28.4)	93 (25.8)	
Laboratory characteristics at baseline (median ± IQR, min-max):				
- Blood absolute white blood cell count ($x10^9$/l)	6.9 ± 4.5 (1.3-55.7)	7.6 ± 4.4 (2.2-36.4)	6.8 ± 4.1 (1.3-55.7)	0.13
- Blood absolute neutrophil granulocyte count ($x10^9$/l)	5.3 ± 4.0 (0.9-34.1)	6.0 ± 4.6 (1.4-34.1)	5.3 ± 3.6 (0.9-20.3)	0.16
- Blood absolute lymphocyte count ($x10^9$/l)	0.8 ± 0.6 (0.2-137.7)	0.8 ± 0.6 (0.3-9.3)	0.8 ± 0.6 (0.2-137.7)	0.75
- Blood absolute platelet count ($x10^9$/l)	204 ± 113 (13-849)	215 ± 119 (13-510)	201 ± 108 (13-849)	0.13
- Serum c-reactive protein (mg/l)	131 ± 125 (7-379)	145 ± 156 (7-355)	129 ± 114 (8-379)	0.19
- Plasma interleukin-6 (pg/ml)	69.0 ± 124.6 (2.7-8963.0)	73.0 ± 123.5 (3.0-8963.0)	68.6 ± 120.8 (2.7-1129.0)	0.41
- Serum ferritin (μg/l)	1186 ± 1214 (45-20261)	1126 ± 1321 (81-1323)	1215 ± 1198 (45-20261)	0.72
- Serum lactate dehydrogenase (IU/l)	786 ± 356 (53-2323)	786 ± 585 (297-2323)	787 ± 334 (53-2113)	0.16
- Serum d-dimer (ng/ml)	1073 ± 1156 (15-122027)	1015 ± 1156 (203-122027)	1097 ± 1155 (15-76884)	0.47
Time from symptom onset to immunomodulatory treatment (days, median ± IQR, min-max)	9 ± 5 (0-40)	9 ± 4 (1-25)	9 ± 5 (0-40)	0.65
Remdesivir started at baseline (n, %)	373 (80.6)	78 (76.5)	295 (81.7)	0.24
Dexamethasone started at baseline (n, %)	410 (88.6)	85 (83.3)	325 (90.0)	0.06

IQR, interquartile range.

ceiving either tocilizumab or baricitinib at 28 days post-diagnosis (22/102, 21.6% vs 64/361, 17.7%; *P*-value = 0.38). In the baricitinib treatment subgroup, invasive mechanical ventilation was initiated at a lower rate (52/102, 50.9% vs 96/361, 26.6%; $P < 0.01$) but with a longer median duration (10 ± 10 days vs 15 ± 16 days, $P < 0.01$). Median ICU LOS values were comparable (12±14 days vs 15±15 days, *P*-value = 0.39). The rate of any major infectious complication was similar between treatment subgroups (32/102, 31.4% vs 96/361, 26.6%; *P*-value = 0.34).

Binomial logistic regression modeling of all-cause mortality is shown in Table 3. Six parameters were retained as independent predictors in the final model: the type of oxygen support started at baseline showed the most relative effect (Venturi mask or non-invasive mechanical ventilation: odds ratio (OR) 41.6, 95% CI 11.1-142.8; invasive mechanical ventilation: OR 15.8, 95% CI 7.24-35.7), followed by chronic renal disease (OR 8.92, 95% CI 3.43-23.26), systemic autoimmune disease (OR 8.33, 95% CI 1.11-62.5), age (OR 1.07, 95% CI 1.04-1.10), and serum LDH (OR 1.01, 95% CI 1.0-1.01). Immunomodulatory treatment with either of the two drugs dropped out from the final model. For both treatments, Kaplan–Meier survival analysis cumulated for the follow-up period is shown in Figure 2. A log-rank test showed no statistically significant difference between survival distributions of treatment subgroups (chi-square value = 1.25; *P*-value = 0.26).

Discussion

Present study

We performed a prospective, open-label, non-randomized investigational study to assess clinical characteristics and outcomes among 463 hospitalized adult patients with COVID-19-associated cytokine storm, receiving SOC plus either tocilizumab or baricitinib. We found that administration of baricitinib provided statistically similar all-cause mortality and overall major infectious complication rate at 28 days compared to tocilizumab, while invasive mechanical ventilation requirement was lower in the baricitinib treatment subgroup. This finding may be explained by the fact that in our COVID-19 center, the administration of tocilizumab in COVID-19-associated cytokine storm had been implemented in the protocol 3 months earlier than dexamethasone would gain evidence and become the basic drug of SOC worldwide and in our country. To our best knowledge, this is the largest parallel comparison of these treatment modalities in COVID-19 to date.

Studies from the literature

Findings from the literature might support our results that baricitinib shows comparable efficacy to tocilizumab in COVID-

Table 2
Outcome characteristics at 28 days post-diagnosis of adult patients with COVID-19-associated cytokine storm, grouped by immunomodulatory treatment received.

PARAMETER	Total (n = 463)	Tocilizumab treatment (n = 102)	Baricitinib treatment (n = 361)	*P*-value
All-cause mortality (n, %)	86 (18.5)	22 (21.6)	64 (17.7)	0.38
Requirement of invasive mechanical ventilation (n, %)	148 (31.9)	52 (50.9)	96 (26.6)	**<0.01**
Rate of any major infectious complication (n, %)	128 (27.6)	32 (31.4)	96 (26.6)	0.34
Types of major infectious complications (n, %):				
- Bloodstream-infection[a]	90 (19.4)	17 (16.7)	73 (20.2)	0.42
- Ventilator-associated pneumonia	77 (16.6)	20 (19.6)	57 (15.8)	0.36
- COVID-19-associated invasive pulmonary aspergillosis[b]	20 (4.3)	7 (6.9)	13 (3.6)	0.16
Time analysis (days, median ± interquartile range, min-max):				
- Length of hospital stay	16 ± 13 (2-233)	19 ± 15 (2-65)	15 ± 13 (2-233)	0.02
- Intensive care unit length of hospital stay	14 ± 15 (2-163)	12 ± 14 (2-65)	15 ± 15 (2-163)	0.39
- Time from diagnosis to death	16 ± 14 (2-66)	13 ± 8 (2-65)	21 ± 15 (2-66)	0.01
- Duration of mechanical ventilation[c]	13 ± 15 (0-150)	10 ± 10 (0-58)	15 ± 16 (0-150)	<0.01
- Time from diagnosis to first major infectious complication	9 ± 8 (1-115)	11 ± 5 (1-38)	8 ± 9 (1-115)	0.30

[a] Primary or catheter-related bacterial or fungal bloodstream infections.
[b] Proven and putative/probable.
[c] Duration from endotracheal intubation to extubation.

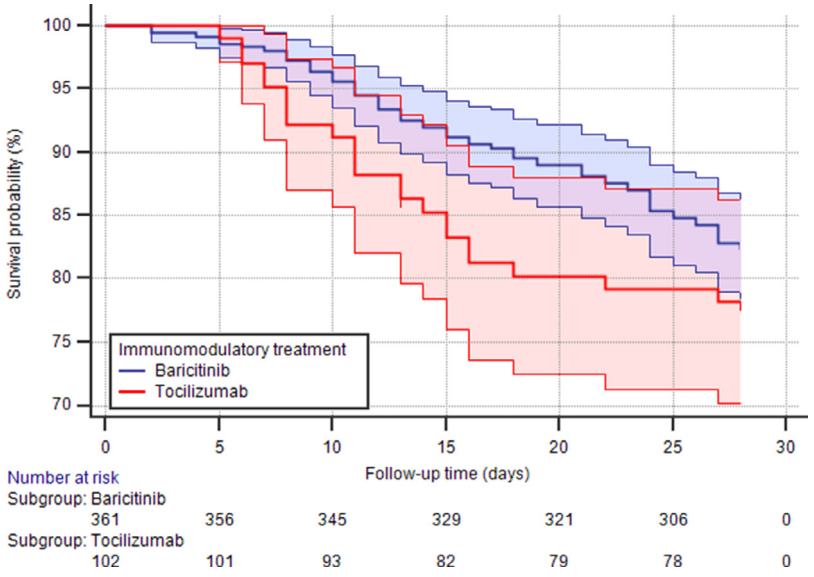

Figure 2. Kaplan–Meier survival analysis of adult patients with COVID-19-associated cytokine storm, grouped by immunomodulatory treatment received. Blue thick line: survival curve of patients receiving baricitinib, red thick line: survival curve of patients receiving tocilizumab. Thin lines represent 95% CI borders of the appropriate survival curve.

19-associated cytokine storm, while possibly maintaining a favorable adverse event profile. A retrospective single-center study from Japan with low case numbers examined outcomes of patients receiving either tocilizumab or baricitinib in similar clinical scenarios (Kojima et al., 2022). The study concluded that neither tocilizumab nor baricitinib increased the risk of death at day 28, and neither drug could be shown to be superior in the treatment of COVID-19. Another retrospective study evaluated the potential effects of baricitinib and/or tocilizumab along with corticosteroids. However, in this study, the exact timing of immunomodulatory drugs was not predefined, and 18% of patients received both baricitinib and tocilizumab, making overall interpretation more challenging (Rosas et al., 2020). In our study, there were no patients treated simultaneously with both drugs, which might translate into a more homogenous cohort. It is noteworthy that the authors highlighted that early introduction of baricitinib may prevent further deterioration of COVID-19, resulting in ICU admittance. Apparently, immunomodulatory drugs possess a narrow therapeutic window during the clinical course of COVID-19, and it could be hypothesized that baricitinib may have a wider one. A recently published multicentric, retrospective study compared the two therapeutic strategies by evaluating hospital discharge and ventilation-free hospital course within 60 days, but no statistically significant differences could be confirmed (Roddy et al., 2022). Our study might also mirror the results of these studies, mostly in terms of similar clinical efficacy of baricitinib and tocilizumab. Of note, two recent observational trials with lower case numbers, comparing outcomes of patients receiving dexamethasone plus either baricitinib or tocilizumab, confirmed similar findings to ours (Karolyi et al., 2022; Wong et al., 2022).

An immunomodulatory therapy might pose a risk in certain situations for developing secondary infections (Singh et al., 2015). Data, particularly from the early-pandemic period, suggested an augmented risk for secondary bacterial and fungal infections after biological treatment of COVID-19 (De Bruyn et al., 2022; Garcia-Vidal et al., 2021; Soriano et al., 2021). However, in the landmark placebo-controlled randomized trials with tocilizumab and baricitinib, the rate of documented secondary infections have not been found to be higher in the treatment subgroups (Marconi et al., 2021; Remap-Cap Investigators et al., 2021). In addition, observational studies did not find differences in secondary infection rates between baricitinib and tocilizumab subcohorts (Kojima et al.,

Table 3
Univariate and multivariate binomial logistic regression modeling of all-cause mortality of adult patients with COVID-19-associated cytokine storm, grouped by survival status.

PARAMETER	Alive (n = 377)	Dead (n = 86)	Univariate analysis Odds ratio (95% CI)	*P*-value	Multivariate analysis Odds ratio (95% CI)	*P*-value
Age (years, median ± IQR, min-max)	60.9 ± 19.8 (26-95)	72.5 ± 15.7 (29-98)	1.06 (1.04-1.08)	**<0.01**	1.07 (1.04-1.10)	**<0.01**
Male gender (n, %)	243 (64.5)	42 (48.8)	0.52 (0.32-0.83)	**<0.01**	1.16 (0.57-2.35)	0.66
Comorbidities (n, %):						
- Chronic cardiovascular disease	209 (55.4)	68 (79.1)	3.03 (1.74-5.30)	**<0.01**	1.37 (0.59-3.19)	0.45
- Chronic pulmonary disease	39 (10.3)	19 (22.1)	2.45 (1.34-4.51)	**<0.01**	1.49 (0.59-3.77)	0.39
- Chronic renal disease	17 (4.5)	25 (29.1)	8.68 (4.42-17.02)	**<0.01**	8.92 (3.43-23.26)	**<0.01**
- Chronic hepatic disease	9 (2.4)	5 (5.8)	2.52 (0.82-7.73)	0.1		
- Chronic cerebral disease	16 (4.2)	12 (14.0)	3.65 (1.66-8.06)	**<0.01**	1.36 (0.43-4.33)	0.61
- Diabetes mellitus	89 (23.6)	35 (40.7)	2.22 (1.35-3.63)	**<0.01**	1.01 (0.48-2.06)	0.99
- Active oncological malignancy	27 (7.2)	5 (5.8)	0.8 (0.29-2.17)	0.65		
- Active hematologic malignancy	14 (3.7)	4 (4.7)	1.26 (0.41-3.94)	0.68		
- Systemic autoimmune disease	9 (2.4)	7 (8.1)	3.62 (1.31-10.0)	**0.01**	8.33 (1.11-62.5)	**0.04**
- Tobacco smoking	30 (8.0)	5 (5.8)	0.72 (0.16-3.23)	0.67		
- Chronic alcohol dependency	12 (3.2)	2 (2.3)	0.71 (0.27-1.92)	0.49		
Received ≥1 COVID-19 vaccine (n, %)	42 (11.1)	8 (9.3)	0.81 (0.37-1.81)	0.62		
Types of oxygen support started (n, %):						
- Low-flow nasal cannula	101 (26.8)	4 (4.7)	ref.		ref.	
- Venturi mask or non-invasive mechanical ventilation	218 (57.8)	18 (20.9)	27.7 (9.62-83.3)	**<0.01**	41.6 (11.1-142.8)	**<0.01**
- Invasive mechanical ventilation	58 (15.4)	64 (74.4)	13.3 (7.35-24.4)	**<0.01**	15.8 (7.24-35.7)	**<0.01**
Laboratory characteristics (median ± IQR, min-max):						
- Blood absolute lymphocyte count	0.8 ± 0.6 (0.2-137.0)	0.8 ± 0.6 (0.3-23.3)	0.99 (0.94-1.04)	0.78		
- Serum c-reactive protein	126 ± 125 (7-379)	142 ± 104 (31-343)	1.01 (1.0-1.01)	0.1		
- Plasma interleukin-6[a]	63.7 ± 136.8 (2.7-5042.0)	109.3 ± 167.3 (5-8963.0)	1.01 (1.0-1.01)	**0.01**	n.a.	
- Serum lactate dehydrogenase	778 ± 431 (53-2113)	797 ± 389 (389-2323)	1.01 (1.0-1.02)	**0.01**	1.01 (1.0-1.01)	**<0.01**
- Serum ferritin	1158 ± 1113 (44-20261)	1545 ± 1378 (219-13232)	1.0 (1.0-1.01)	0.11		
Time from symptom onset to immunomodulatory treatment (days, median ± IQR, min-max)[a]	9 ± 5 (0-40)	8 ± 9 (0-28)	0.95 (0.9-1.01)	0.13	n.a.	
Remdesivir treatment (n, %)	303 (80.4)	70 (81.4)	0.93 (0.52-1.70)	0.83	0.87 (0.36-2.07)	0.74
Dexamethasone treatment (n, %)	337 (89.4)	73 (84.9)	0.67 (0.34-1.31)	0.24	0.35 (0.13-0.94)	0.05
Immunomodulatory treatment (n, %)	80 (21.2)	22 (25.6)	0.78 (0.46-1.35)	0.38	0.71 (0.31-1.58)	0.39

IQR, interquartile range; n.a., not applicable; ref., reference category.
[a] The parameter was not included in the final model as co-linearity was not proven by the Box-Tidwell test ($P < 0.05$).

2022; Roddy et al., 2022). We note that the overall susceptibility of patients to secondary infections might be a summation of other risk factors, such as the dysregulated host immune system, absolute peripheral lymphopenia, nosocomial environment with a potentially multiresistant pathogen,s and systemic corticosteroid administration. Whether tocilizumab or baricitinib unambiguously increases the risk of infectious complications during COVID-19 treatment remains controversial. These findings may be in line with our observations.

Study limitations

Our study had potential limitations. Shift of evidence about COVID-19 and shortages of drug supply might have affected patient care to some extent, as with all studies analyzing real-world data. A placebo-controlled arm was not deemed feasible due to ethical concerns, as cytokine storm is known as a potentially fatal disease without real clinical treatment. SARS-CoV-2 genomic sequencing is routinely not available at our center. We note that a tendentiously less frequent administration of dexamethasone among patients treated with tocilizumab might have contributed to higher rates of mechanical ventilation compared with those receiving baricitinib, and a higher rate of male gender representation in the tocilizumab group may also contribute to this difference. Lastly, there might be some residual bias concerning subjective variables (e.g., symptom onset determination).

Conclusion

In this study of hospitalized adult patients with severe COVID-19 and cytokine storm, treatment with either tocilizumab or baricitinib plus SOC resulted in similar survival rates at 28 days, while the requirement for invasive mechanical ventilation was more frequent in the tocilizumab group. Further trial data are needed to clarify the role of baricitinib in the armamentarium against COVID-19.

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Ethical approval

The study was in accordance with national ethical standards and the Declaration of Helsinki. The institutional review board of South Pest Central Hospital, National Institute of Hematology and Infectious Diseases approved the study protocol (No.13/EB/2020). Approval of use of *off-label* drugs for COVID-19 was granted by the National Institute of Pharmacy and Nutrition (www.ogyei.gov.hu/tajekoztato_a_veszelyhelyzet_megszunesevel_kapcsolatos_a_covid_19_jarvany_idejen_kulonos_meltanylast_erdemlo_betegellatasi_erdekhez_kotheto_gyogyszeralkalmazasok_bejelenteserol).

Author contributions

BL and BGSZ contributed equally to the manuscript (*in equo loco*). BL: management of patients, data collection, data analysis, preparation of study protocol, preparation of the manuscript, conception and design of the article, literature search and interpretation; BGSZ: management of patients, data collection, data analysis, preparation of study protocol, preparation of the manuscript, conception and design of the article, literature search and interpretation; IB: data collection, data analysis, management of patients; NKD: data analysis, management of patients, review of the manuscript; ZSG: data collection; AR: data collection; BP: data collection; BFF: data collection; GS: data collection; LG: preparation of study protocol, literature search and interpretation; GB: laboratory data analysis, review of the manuscript; JS: preparation of study protocol, preparation and review of the manuscript; PR: preparation of study protocol, preparation and review of the manuscript; JSZ: management of patients, review of the manuscript; DM: preparation of study protocol, preparation and review of the manuscript; IVN: preparation of study protocol, preparation and review of the manuscript. All authors have read and approved the final manuscript for publication.

Availability of data and material

Anonymized data of patients are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Consent to participate

Written informed consent was obtained from each patient before study inclusion.

Declaration of competing interest

The authors have no competing interests to declare.

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Supplementary materials

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