Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

Tocilizumab versus baricitinib in hospitalized patients with severe COVID-19: an open label, randomized controlled trial

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ABSTRACT

Objective: Randomized controlled trials comparing tocilizumab and baricitinib in patients with coronavirus disease 2019 (COVID-19) are needed. This was an open-label, randomized controlled trial aiming to address this unmet need.

Methods: To determine whether baricitinib was non-inferior to tocilizumab, we assessed whether the upper boundary of the two-sided 95% CI of the hazard ratio (HR) did not exceed 1.50. The primary outcome was mechanical ventilation or death by day 28. Secondary outcomes included time to hospital discharge by day 28 and change in WHO progression scale at day 10.

Results: We assigned 251 patients with COVID-19 and a PaO_2/FiO_2 ratio of <200 to receive either tocilizumab ($n = 126$) or baricitinib ($n = 125$) plus standard of care. Baricitinib was non-inferior to tocilizumab for the primary composite outcome of mechanical ventilation or death by day 28 (mechanical ventilation or death for patients who received baricitinib, 39.2% [$n = 49/125$]; mechanical ventilation or death for patients who received tocilizumab, 44.4% [$n = 56/126$]; HR, 0.83; 95% CI, 0.56−1.21; p 0.001 for non-inferiority). Baricitinib was non-inferior to tocilizumab for the time to hospital discharge within 28 days (patients who received baricitinib- discharged alive: 58.4% [$n = 73/125$] vs. patients who received tocilizumab- discharged alive: 52.4% [$n = 66/126$]; HR, 0.85; 95% CI, 0.61−1.18; $p < 0.001$ for non-inferiority). There was no significant difference between the baricitinib and tocilizumab arms in the change in WHO scale at day 10 (0.0 [95% CI, 0.0−0.0] vs. 0.0 [95% CI, 0.0−1.0]; p 0.83).

Discussion: In the setting of this trial, baricitinib was non-inferior to tocilizumab with regards to the composite outcome of mechanical ventilation or death by day 28 and the time to discharge by day 28 in patients with severe COVID-19. **Theodoros Karampitsakos, Clin Microbiol Infect 2022;▪:1**

Introduction

The emergence of coronavirus disease 2019 (COVID-19) has led to a growing global public health crisis. Despite major advances in the prevention and treatment of COVID-19, a substantial proportion of infected individuals still experiences severe respiratory failure [1]. Emerging data suggest that hypoxic respiratory failure may be, in part, due to dysregulated inflammatory responses [2]. Thus, despite the benefits of anti-viral compounds, such as remdesivir, extensive research efforts have aimed to test the efficacy of compounds that are able to mitigate an immune response. Corticosteroids have been consistently associated with improved survival

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across multiple studies. However, mortality has remained high, and the need for agents targeting deregulated immune responses is amenable [1,2].

An interleukin 6R antagonist, tocilizumab, has led to survival benefit among patients with COVID-19 [3–5]. Most recently, an oral selective Janus kinase 1/2 inhibitor, baricitinib, has been associated with reduced mortality in hospitalized patients with COVID-19 [6–8]. Both compounds had been originally introduced as therapeutic modalities for autoimmune diseases [5,8].

On the basis of the above, the U.S. Food and Drug Administration issued an emergency use authorization for the use of both compounds in hospitalized patients with severe COVID-19. To this end, there is a paucity of high-quality, randomized controlled trials comparing tocilizumab and baricitinib in patients with COVID-19. Limited data arise from retrospective, observational studies [9,10]. To our knowledge, this is the first head-to-head randomized controlled trial aiming to investigate whether baricitinib was non-inferior to tocilizumab in patients with severe COVID-19.

Methods

Trial design and oversight

We conducted an investigator-initiated, open-label, randomized controlled trial and enrolled consecutive patients admitted to our hospital between 20 October 2021 and 7 May 2022 who underwent nasopharyngeal swab and had a positive PCR test result for SARS coronavirus 2 (SARS-CoV-2). Trial sites were three different COVID-19 departments of the University Hospital of Patras, Greece. Each patient or the patient's legally authorized representative provided written informed consent. The trial was conducted in accordance with the International Conference on Harmonisation E6 guidelines for Good Clinical Practice, Declaration of Helsinki, and local regulations. Our study was approved by the institutional review board and the local ethics committee of the University Hospital of Patras, Greece (protocol number: 26651/18-10-21). This was a registered clinical trial (NCT05082714, https://clinicaltrials.gov/ct2/show/NCT05082714). The study design is provided in Fig. 1.

Participants

Patients aged ≥18 years who presented with a partial pressure of oxygen in the arterial blood (PaO_2)/fraction of inspired oxygen (FiO_2) ratio of <200 at any time during their hospitalization were included in the analysis. The exclusion criteria were as follows: age of <18 years, pregnancy, estimated glomerular filtration rate of <30 mL/min/1.73 m^2, and mechanical ventilation before patients' transfer to our hospital.

Randomization and interventions

Day 1 was considered the first day when a patient reached a PaO_2/FiO_2 ratio of <200. Patients were randomly assigned through a random sequence generator (derived from http://www.randomization.com) to tocilizumab or baricitinib in a 1:1 ratio. We used simple sequential randomization without blocks. Randomization was not stratified by the COVID-19 unit. The randomization sequence was maintained by an investigator (APK) not involved in the recruitment process or patient care, and study arm allocation was assigned after the patient provided informed consent. Treatment with tocilizumab or baricitinib was started on day 1. The time between inclusion and administration of the study drug was minimal. Tocilizumab was administered as a 60-minute intravenous drip infusion at 8 mg/kg. A second infusion of tocilizumab within 48 hours was administered at the clinician's discretion in case of very rapid deterioration. Baricitinib was administered orally at a dose of 4 mg/d (administered daily for up to 14 days or until discharge from the hospital, whichever occurred

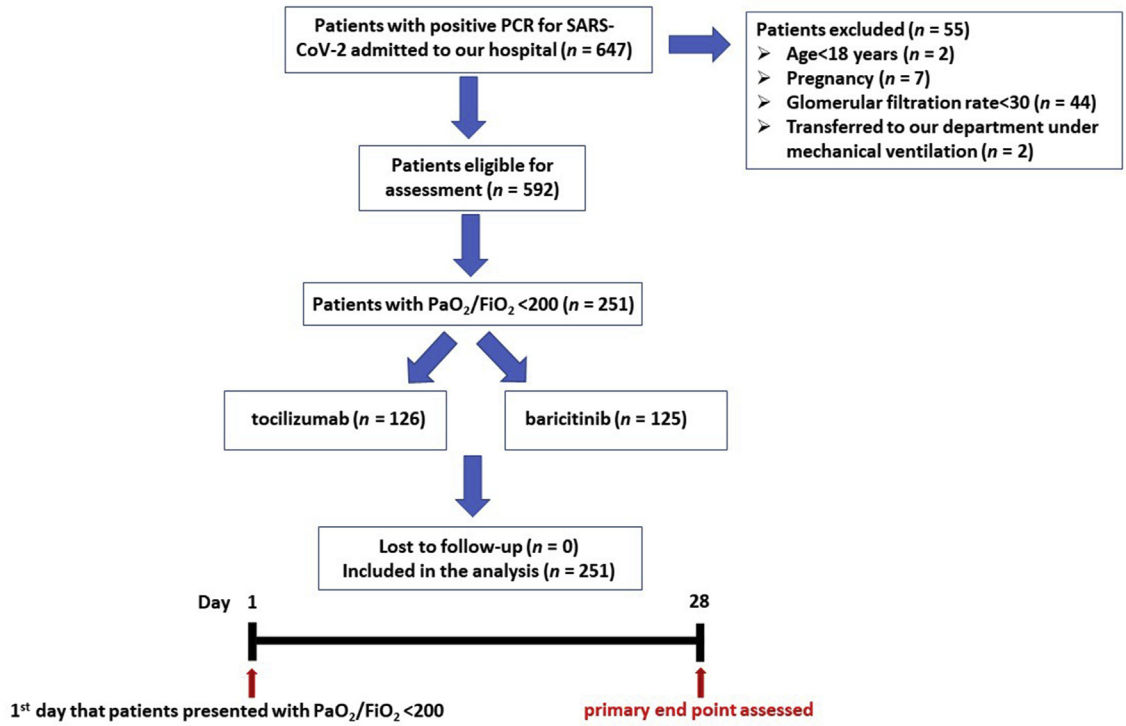

Fig. 1. Schematic representation of the study design. SARS-CoV-2, SARS coronavirus 2. PaO2: partial pressure of oxygen in the arterial blood; FiO2: fraction of inspired oxygen.

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first) or at a dose of 2 mg/d in case of an estimated glomerular filtration rate of 30 to <60 mL/min/1.73 m^2. All patients included in the analysis received standard of care on admission (for details, please see supplementary material). The study design is summarized in Fig. 1.

Outcome measures

The primary endpoint was the time to death or mechanical ventilation by day 28. Our secondary outcomes were time to discharge by day 28 and disease progression as indicated by change in WHO clinical progression scale at day 10 (ΔWHO scale [day 10 to day 1]). Safety outcomes included a platelet count of $>450 \times 10^9$/L, a five-fold increased level of creatine phosphokinase compared with the reference value, a three-fold increased level of transaminases compared with the reference value, lobar consolidation, major bleeding, cardiac event, and septic shock. Moreover, we recorded the primary outcome separately in the elderly (patients older than the median age of our cohort) and patients with rapid progression (as indicated by a drop in the PaO_2/FiO_2 ratio to >50 in the first 48 hours).

Data collection

We recorded the PaO_2/FiO_2 ratio, demographics, comorbidities, laboratory parameters, arterial blood gas test results at least twice per day, WHO clinical progression scale, and time to outcomes for each patient [11]. The WHO clinical progression scale was used as a measure of illness severity across a range from 0 (not infected) to 10 (dead), with data elements being easily obtainable from clinical records [12].

Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Sample size

We initially planned for a total sample size of 164 patients. However, on the basis of fast recruiting, we submitted a protocol modification and increased the total sample size to 251 patients without changing outcome measures. The final sample size was estimated under the following assumptions: (1) a randomization ratio of 1:1 for tocilizumab and baricitinib; (2) a two-sided type I error of 0.05; (3) a hazard ratio (HR) (θ) of 1; (4) an HR θ_0 of 1.5 (the upper boundary of the two-sided 95% CI of the HR for the risk of the primary composite endpoint not exceeding 1.50); (5) a power of 80%; (6) based on our previous records, 60% of patients receiving standard of care required mechanical ventilation or died within 28 days after a PaO_2-to-FiO_2 ratio of <200 was reached. Given the absence of high-quality data comparing tocilizumab and baricitinib at the time that the protocol was designed, we chose the margin of 1.50 on the basis of the literature, as this was the median non-inferiority margin used in previous high-quality non-inferiority trials [13]. In this setting and on the basis of the differences between the two compounds with regards to availability, route of administration, drug–drug interactions, and metabolism, we aimed to investigate whether baricitinib was non-inferior to tocilizumab in hospitalized patients with severe COVID-19.

Statistical analysis

Continuous data were denoted as mean ± standard deviation or median with interquartile range following Kolmogorov-Smirnov test for normality. The primary outcome was presented using the Kaplan–Meier method, and cumulative incidence curves were compared between the two groups. We assessed the primary non-inferiority hypothesis by investigating whether the upper boundary of the two-sided 95% CI of the HR for the risk of the primary composite endpoint did not exceed 1.50. The absolute risk difference (ARR) with CI for the primary outcome and mortality was also calculated using the Miettinen and Nurminen method. The time to discharge was presented with the use of the Kaplan–Meier approach. We assigned the 'worst outcome' for individuals who died before day 28; therefore, these patients were managed as those with the longest hospital stay (hospitalized by day 29) [3,14]. Non-inferiority was assessed for the secondary outcome of time to hospital discharge. Mann-Whitney U test was used to detect differences in ΔWHO scale between the two arms. Statistical significance was set at $p < 0.05$.

Results

Patients

Two hundred fifty-one patients ($n = 251$) were randomly allocated to receive either tocilizumab plus standard of care ($n = 126$) or baricitinib plus standard of care ($n = 125$). Five patients ($n = 5$/126, 4.0%) received a second infusion of tocilizumab. No participant was lost to follow-up, and all patients were compliant with the treatment; hence, we did not present intention-to-treat and per-protocol analyses separately. Baseline characteristics were similar between the study groups (please see Table 1 and supplementary material).

Primary outcome

Baricitinib was non-inferior to tocilizumab for the primary composite outcome of mechanical ventilation or death by day 28 (HR, 0.83; 95% CI, 0.56–1.21; p 0.001 for non-inferiority) (Fig. 2a). Mechanical ventilation or death by day 28 occurred in 39.2% ($n = 49/125$) and 44.4% ($n = 56/126$) of patients in the baricitinib and tocilizumab arms, respectively. ARR for the primary outcome was −5.2% (95% CI, −17.3 to 7.0%).

Secondary outcomes

Baricitinib was non-inferior to tocilizumab for the time to hospital discharge within 28 days (HR, 0.85; 95% CI, 0.61–1.18; $p < 0.001$ for non-inferiority) (Fig. 2b). Seventy-three patients ($n = 73/125$, 58.4%) in the baricitinib group and 66 patients ($n = 66$/126, 52.4%) in the tocilizumab group had been discharged alive within the 28-day period. Among patients that were discharged alive within the 28-day period, median days of hospitalization were 8.0 (95% CI, 6.0–10.0) and 8.0 (95% CI, 6.6–9.0) in the baricitinib and tocilizumab groups, respectively. There was no significant difference between the baricitinib and tocilizumab arms in the risk of disease progression by day 10, as assessed by the change in WHO scale at day 10 (ΔWHO scale [day 10 to day 1] for baricitinib, 0.0 [95% CI 0.0–0.0] vs. ΔWHO scale [day 10 to day 1] for tocilizumab, 0.0 [95% CI 0.0–1.0]; p 0.83) (Fig. 3).

Other outcomes and subgroup analysis

Forty ($n = 40/125$, 32.0%) patients in the baricitinib arm died within the 28-day period, whereas 50 patients ($n = 50/126$, 39.7%) died within the 28-day period in the tocilizumab arm (HR, 0.73; 95% CI, 0.49–1.09; $p < 0.001$ for non-inferiority). The ARR for mortality was −7.7% (95% CI, −19.4 to 4.2%). Forty-seven ($n = 47$/125, 37.6%) and 54 ($n = 54/126$, 42.9%) patients were transferred in

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Table 1
Characteristics of patients at baseline

Characteristics	Tocilizumab group	Baricitinib group
Number of patients, *n*	126	125
Age (y), median (interquartile range)	72.0 (62.0–83.0)	73.0 (61.0–83.0)
Male sex/Female sex, *n* (%)/*n* (%)	74 (58.7)/52 (41.3)	74 (59.2)/51 (40.8)
Symptom onset to admission (d), median (interquartile range)	7 (6–7)	7 (5–8)
Admission to inclusion (d), median (interquartile range)	1 (0–2)	1 (0–2)
Weight (kg), median (interquartile range)	83.9 (78.7–89.3)	84.8 (80.4–87.8)
Current smokers, *n* (%)	17 (13.5)	14 (11.2)
Arterial hypertension, *n* (%)	67 (53.2)	67 (53.6)
Dyslipidemia, *n* (%)	38 (30.2)	37 (29.6)
Chronic heart disease, *n* (%)	31 (24.6)	29 (23.2)
Diabetes mellitus, *n* (%)	29 (23.0)	32 (25.6)
COPD or asthma, *n* (%)	15 (11.9)	16 (12.8)
Cancer, *n* (%)	12 (9.5)	11 (8.8)
Obesity, *n* (%)	10 (7.9)	10 (8)
Hypothyroidism, *n* (%)	6 (4.8)	8 (6.4)
Depression, *n* (%)	8 (6.3)	9 (7.2)
Immunocompromised (corticosteroids or steroid-sparing agent), *n* (%)	2 (1.6)	2 (1.6)
Vaccinated with at least one booster dose, *n* (%)	25 (19.8)	26 (20.8)
4C Mortality Score, median (interquartile range)	11.0 (9.0–14.0)	11.0 (8.0–14.0)
WHO clinical progression scale day1, median (interquartile range)	5.0 (5.0–5.0)	5.0 (5.0–5.0)
PaO_2/FiO_2 day 1, median (interquartile range)	144.5 (135.5–161.5)	145.0 (137.0–150.0)
C-reactive protein (mg/L), median (interquartile range)	81.5 (44.7–147.3)	81.8 (36.5–141.9)
D-dimer (μg/ml), median (interquartile range)	1.0 (0.6–1.7)	1.0 (0.6–1.9)
White blood cells (/μL), median (interquartile range)	6955.0 (4900.0–9440.0)	6940.0 (4912.5–9980.0)
Polymorphonuclear leukocytes (/μL), median (interquartile range)	5185.0 (3640.0–8170.0)	5520.0 (3722.5–8552.5)
Lymphocytes (/μL), median (interquartile range)	805.0 (610.0–1260.0)	820.0 (595.0–1187.5)

COPD, chronic obstructive pulmonary disease. PaO2: partial pressure of oxygen in the arterial blood; FiO2: fraction of inspired oxygen.

the intensive care unit and received mechanical ventilation in the baricitinib and tocilizumab arms, respectively.

With regards to patients aged ≥73 years, mechanical ventilation or death by day 28 occurred in 47.7% (31/65) of patients in the baricitinib group and 55.7% (34/61) of patients in the tocilizumab group. Finally, 133 patients presented with a drop in the PaO_2/FiO_2 ratio to >50 during the first 48 hours ($n = 133/251$, baricitinib: 67, tocilizumab: 66). Among those patients, the primary outcome occurred in 47.8% (32/67) and 63.6% (42/66) in the baricitinib and tocilizumab arms, respectively.

Safety outcomes

There were 33 ($n = 33/126$, 26.2%) and 25 ($n = 25/125$, 20%) patients with at least one adverse event in the tocilizumab and baricitinib arms, respectively (Table 2). There was a statistically significant difference in the number of patients presenting with three-fold increased levels of transaminases between the tocilizumab ($n = 10/126$, 7.9%) and baricitinib arms ($n = 3/125$, 2.4%) (p 0.04).

Discussion

In the setting of this trial, baricitinib was non-inferior to tocilizumab with respect to the primary composite outcome of mechanical ventilation or death by day 28 in hospitalized patients with severe COVID-19. Baricitinib was non-inferior to tocilizumab for the time to hospital discharge within 28 days. There was no significant difference between baricitinib and tocilizumab in the change of WHO progression scale at day 10.

Our study exhibited many important attributes that should be presented upfront. First, we enrolled a relatively homogenized group of patients under a standardized algorithm. Thus, outcomes were not affected by heterogeneous approaches. Second, our results could limit the dramatic upswing in health system budgets. To this end, there is a paucity of biologically enriched studies able to demonstrate patients who are more likely to experience benefit from tocilizumab than from baricitinib. On the other hand, baricitinib has a lower cost, is administered per os in tablet form, has few drug–drug interactions, and has a favourable safety profile. Therefore, adopting baricitinib as the first-line treatment for severe COVID-19 might be rational.

Our results are in line with those from previous high-quality trials for COVID-19. Baricitinib has shown the largest effect size on the mortality of hospitalized patients with COVID-19 among immunomodulatory compounds [7,8]. Baricitinib has demonstrated benefit in addition to the use of corticosteroids alone [8]. A recent head-to-head trial between baricitinib and dexamethasone in COVID-19 showed similar rates of mechanical ventilation–free survival by day 29; yet, fewer adverse events were encountered in the baricitinib arm [15]. This might be explained by the fact that baricitinib has a shorter half-life than that of dexamethasone, exerts its anti-inflammatory role by acting on targeted critical pathways, and, thus, biologic redundancy is minimized with less immunosuppression [7]. Furthermore, baricitinib may exert synergistic effects with the antiviral properties of remdesivir [16,17].

Contrary to the results of baricitinib trials in COVID-19, studies investigating the efficacy profile of tocilizumab in hospitalized patients with COVID-19 have yielded contradictory results [3,4,18–27]. The RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial, including a total of 4116 patients with COVID-19, and further future studies have shown beneficial effects of tocilizumab with regards to hospitalization, clinical recovery, need for mechanical ventilation, and survival [3,25]. The aforementioned results have led to a debate on whether the timing of administration influenced the efficacy of tocilizumab [28]. Our group had previously shown that tocilizumab was efficacious when administered at the time point when a PaO_2/FiO_2 ratio of <200 was observed [5]. Therefore, we adopted that approach in this trial.

Baricitinib has shown consistent efficacy independent of disease severity [14,22,23]. Our 'not too early, not too late' approach with regards to the time point administration was based on three concepts. First, we aimed to avoid further immunomodulation at the early phases of SARS-CoV-2 replication. Second, patients with the most severe disease status might not benefit accordingly from

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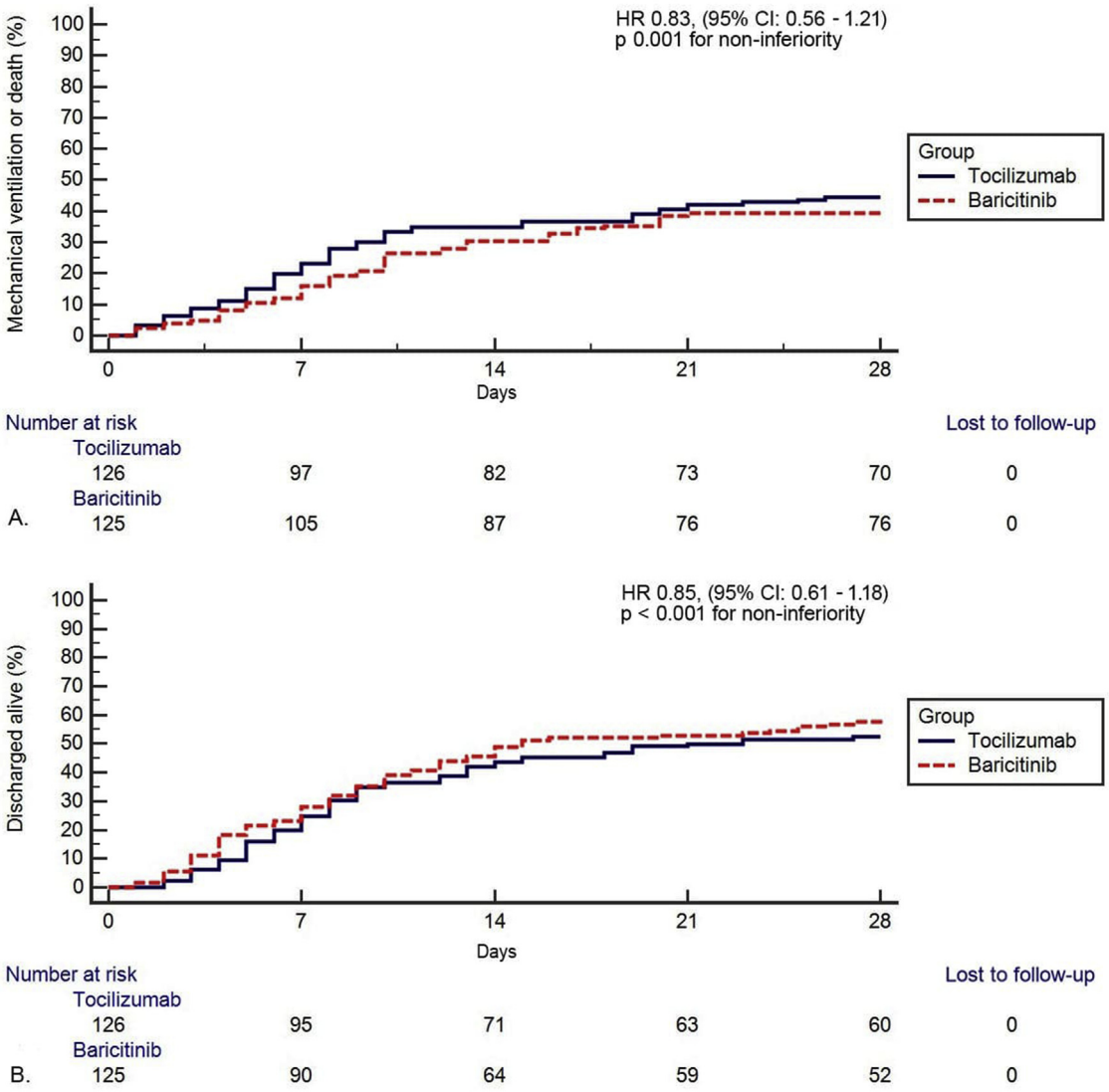

Fig. 2. Kaplan-Meier curve showing the effect of allocation to baricitinib or tocilizumab on (A) mechanical ventilation or death by day 28 and on (B) discharge from hospital within 28 days of randomization. HR, hazard ratio.

these compounds because inflammatory cascade might be too advanced to be reversible [7,16]. The ideal time window to intervene might correlate with the time around clinical deterioration, as assessed by a PaO_2/FiO_2 ratio of <200 [5]. Third, the administration of baricitinib or tocilizumab at the time point of clinical deterioration might limit their irrational use, maximize cost-effectiveness, and reduce immunocompromisation-related side effects.

Our trial has some limitations. First, this is an open-label, randomized controlled trial. Decision for the implementation of mechanical ventilation, time to discharge, and score in WHO progression scale are operator-dependent. Limitations associated with the use of WHO progression scale as a secondary outcome include the lack of proportionality among categories, absence of an established minimum clinically important difference, and heterogeneity in local clinical practice. However, the management of our cohort from clinicians of the same hospital with a homogeneous approach represents the optimal way to maximize the value of the aforementioned outcomes. Second, we did not have data about the specific variant or sub-variant of each patient in our cohort. Third, cycle thresholds of SARS-CoV-2 PCRs were not available; yet, the enrolment of patients with a PaO_2/FiO_2 ratio of <200 considerably limits the possibility of bacterial surinfection and low residual viral load. Fourth, our sample size was moderate yet adequate to assess non-inferiority based on our pre-specified plan. Fifth, event rates might be different compared from those reported in other countries, partially owing to the very strict lockdown in Greece before the Delta era and the fact that 26.2% of the population in Greece was not vaccinated for COVID-19 by the end of the study. This further highlights the role of vaccination as the most cost-effective way to contain the pandemic. Finally, given that this was, to our knowledge, the first head-to-head trial of these compounds in COVID-19, we chose as margin the value that represented the median non-inferiority margin used in previous high-quality non-inferiority trials [13]. On the basis of the literature published more recently than the time point of our study design, we could have chosen a different margin i.e. on the basis of the recent tocilizumab meta-analyses; however, it is important to note that our analysis resulted in HRs that far exceeded both the pre-specified margin and margins that could have been set on the basis of most recent meta-analyses. Moreover, the upper CI bounds derived from ARR, a clinically relevant approach, further strengthen the argument of baricitinib being non-inferior to tocilizumab.

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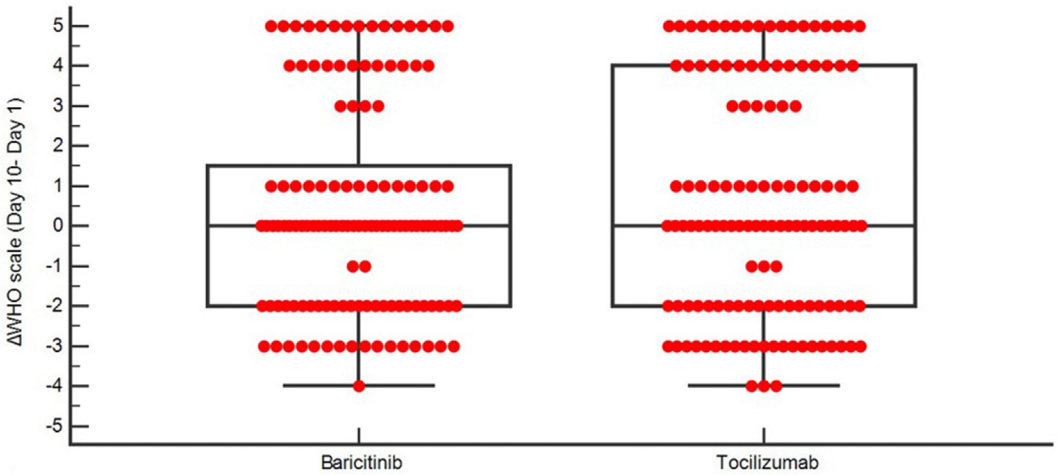

Fig. 3. Box plot of the difference in change in WHO scale at day 10 (ΔWHO scale [day 10 to day 1]). Lines represent lower and upper extremes, lower and upper quartile, as well as median value.

Table 2
Adverse events by day 28

Adverse events	Tocilizumab group (n = 126), n (%)	Baricitinib group (n = 125), n (%)	p
Lobar consolidation	7 (5.5)	5 (4.0)	0.57
Cardiac event	9 (7.1)	5 (4.0)	0.28
Major bleeding	0 (0.0)	2 (1.6)	0.15
Septic shock	2 (1.6)	4 (3.2)	0.41
Thrombocytosis	8 (6.3)	7 (5.6)	0.82
Increased CPK 5 times greater than the upper reference value	2 (1.6)	1 (0.8)	0.56
Increased SGOT/SGPT 3 times greater than the upper reference value	10 (7.9)	3 (2.4)	**0.04**

CPK, creatine phosphokinase; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase. Bold denotes statistical significance.

Collectively, this is, to our knowledge, the first head-to-head trial between baricitinib and tocilizumab in COVID-19. The concept that baricitinib might be non-inferior to tocilizumab in hospitalized patients with severe COVID-19 is interesting and deserves further investigation. Given the absence of theragnostic biomarkers able to guide decision between tocilizumab and baricitinib for the treatment of this highly contagious disease, cost effectiveness and optimal safety profiles should be taken into consideration. Biologically enriched studies aiming to identify subgroups of patients that are more likely to benefit from targeted immunomodulatory compounds are eagerly awaited.

Author contributions

TK and AT conceptualized the study. TK, OP, PT, MK, AK, APK, EM, EZ, GT, VG, VS, EK, CC, AM, ML, FS, KA, MM, and AT curated the data and performed the investigation. TK and AT developed the methodology, performed the software analysis and visualization of the data. TK, AK, APK, and AT performed the formal analysis.TK and AT validated the study. MM supervized the study. AT was the project administrator. TK and AT wrote the original draft of the article. OP, PT, MK, AK, APK, EM, EZ, GT, VG, VS, EK, CC, AM, ML, FS, KA, and MM reviewed and edited the article. TK and OP contributed equally to this research work. All authors gave final approval of the version to be submitted.

Transparency declaration

AT has received grants and honoraria from GlaxoSmithKline, Astra Zeneca, Chiesi, Roche, and Boehringer Ingelheim outside the submitted work. TK has received grants and honoraria from Roche and Boehringer Ingelheim outside the submitted work. KA has received grants and honoraria from Pfizer, MSD, Angelini, Gilead, 3M, Norma Hellas, GlaxoSmithKline, and ViiV outside the submitted work. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.10.015.

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