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Tocilizumab Versus Baricitinib in Patients Hospitalized With COVID-19 Pneumonia and Hypoxemia: A Multicenter Retrospective Cohort Study

OBJECTIVES: In patients hospitalized with COVID-19 pneumonia, both tocilizumab and baricitinib have been shown to have clinical benefit compared with placebo. To date, there are few data comparing the two treatments, and their relative benefits and harms are unknown. This study aims to evaluate the effectiveness of tocilizumab versus baricitinib in patients hospitalized with COVID-19 pneumonia and hypoxemia.

DESIGN: Retrospective cohort study.

SETTING: Seven inpatient acute-care hospitals in Wisconsin.

PARTICIPANTS: Patients hospitalized with COVID-19, hypoxemia, and PaO_2 -to- FiO_2 ratio less than or equal to 300 mm Hg, who received either tocilizumab or baricitinib.

INTERVENTIONS: Electronic chart review.

MEASUREMENTS AND MAIN RESULTS: Patients were divided into tocilizumab and baricitinib cohorts based on actual medication received. The primary outcome was hospital discharge alive and free from mechanical ventilation within 60 days, assessed by logistic regression. Three hundred eighty-two patients were included: 194 in the tocilizumab cohort and 188 in the baricitinib cohort. Most baseline characteristics in the two cohorts were similar. All patients received dexamethasone. Two patients were lost to follow-up. In the remaining 380 patients, probability of successful discharge in the two cohorts was quantitatively similar in unadjusted, multivariate-adjusted, and propensity score-matched analyses. Hospital length of stay, rates of thromboembolic events, and rates of hospital-acquired infections were all similar in the two cohorts.

CONCLUSIONS: In patients hospitalized with COVID-19 pneumonia and hypoxemia who receive dexamethasone, treatment with tocilizumab or baricitinib appears to result in similar outcomes.

KEY WORDS: acute lung injury; baricitinib; coronavirus; COVID-19; hypoxemia; tocilizumab

The COVID-19 pandemic has created a global health emergency (1). In severe cases, COVID-19 can cause pneumonia, acute respiratory distress syndrome, and death (2). An excessive inflammatory response involving several cytokines due to infection is thought to play an important role in the pathophysiology of severe COVID-19 infection (3, 4). Anti-inflammatory treatment with dexamethasone was shown to reduce mortality in patients hospitalized with COVID-19 and requiring respiratory support (5). Subsequent trials have shown possible clinical benefit of the interleukin-6 (IL-6) inhibitors tocilizumab and sarilumab (6–10) and of the Janus kinase (JAK) inhibitors baricitinib and tofacitinib (11–13), both with and without concurrent steroid treatment (11–16),

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DOI: 10.1097/CCE.0000000000000702

although data are not dispositive. Despite this uncertainty, current guidelines for anti-inflammatory therapy recommend tocilizumab or baricitinib, and recommend sarilumab or tofacitinib as alternatives (17).

In patients with severe COVID-19 infection, the relative efficacy of IL-6 inhibitors compared with JAK inhibitors is not known. Clinical trials have compared these treatments with placebo, and two small single-center studies report on comparative experience with these classes (18, 19), but no published study has robustly compared the two classes of medications. Cross-study comparison is difficult due to variability in inclusion criteria and the use of concomitant treatments such as glucocorticoids and the antiviral medication remdesivir. The absence of head-to-head comparisons of efficacy and variability in supply and cost of these medications warrant a study to compare these treatments.

This multicenter retrospective cohort study aims to assess the benefits and harms of tocilizumab versus baricitinib in patients hospitalized with COVID-19 pneumonia and hypoxemia.

MATERIALS AND METHODS

The study was approved by the institutional review board (Ascension Wisconsin Institutional Review Board, study identification number RWI20210109). All study procedures were in accordance with the ethical standards of the institutional review board and with the Helsinki Declaration of 1975. The institutional review board provided this study a waiver for informed consent. We conducted a retrospective study of hospitalized patients receiving tocilizumab or baricitinib for COVID-19 pneumonia. Seven hospitals across the Milwaukee, WI, region participated in the study.

Patients were grouped into tocilizumab and baricitinib cohorts based on study medication received. Treatment allocation was determined primarily by medication availability. In August 2021, baricitinib became widely available within the hospital system. Due to shortages in tocilizumab supply, the hospital system issued statewide guidelines stating that for patients hospitalized with COVID-19 meeting criteria for immunomodulator therapy, tocilizumab be used as first-line treatment and baricitinib be used as the alternative treatment if tocilizumab were unavailable. Thus, in the absence of specific contraindications, assignment to tocilizumab or baricitinib treatment was based on availability at time of hospitalization.

Inclusion criteria were age greater than or equal to 18 years, inpatient admission to one of the seven participating hospitals, admitting diagnosis of COVID-19 pneumonia proven by molecular testing, new treatment with at least one dose of either tocilizumab or baricitinib for treatment of COVID-19 infection (patients receiving both treatments concurrently or continuation of prior outpatient treatment were excluded), and hypoxemia requiring supplemental oxygen with P_{aO_2} -to- F_{iO_2} (P/F) ratio less than or equal to 300 mm Hg. Exclusion criteria were pregnancy, end-stage renal disease requiring maintenance dialysis (due to the contraindication of baricitinib in this population), extracorporeal membrane oxygenation treatment at time of study drug initiation, transfer into participating hospital from another inpatient facility without available medical records, and goals of care documented as comfort-measures and/or hospice. Pharmacy records were used to identify the charts of all patients prescribed either tocilizumab or baricitinib between August 1, 2021, and December 31, 2021. All charts were then reviewed manually for data collection. Baseline data were documented at the time of tocilizumab or baricitinib initiation. Respiratory support category was defined per the Adaptive Covid-19 Treatment Trial-1 study (20). P_{aO_2} was measured using arterial blood gas analysis or estimated using pulse oximetry (21). F_{iO_2} was documented using respiratory device-reported values or estimated using oxygen flow rate (22). To assess change in oxygenation, a second P/F ratio measurement was documented approximately 48 hours after drug initiation. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease-4 equation (23). Comorbidities were documented based on chart review. Lung disease was defined as chronic obstructive pulmonary disease or asthma requiring medication, or other parenchymal lung disease (excluding sleep-disordered breathing).

The primary outcome was defined as hospital discharge alive and free from mechanical ventilation within 60 days of study drug initiation. Secondary outcomes were hospital length of stay from time of study drug initiation in patients meeting the primary outcome, change in P/F ratio at 48 hours, arterial or venous thromboembolism, and hospital-acquired infections occurring after starting study drug (central-line-associated bloodstream infection, catheter-associated urinary tract infection, and *Clostridium difficile* infection).

Prior to data collection, we estimated required sample sizes of $n = 332$ and $n = 580$ to detect 20%

and 15% relative differences, respectively, in the primary outcome with 80% power and 5% type I error rate. For the available sample of $n = 380$, power is 87% and 62% for relative differences of 20% and 15%, respectively. For power and sample size calculations, the probability of the primary outcome was taken from a large randomized trial (24). The primary outcome was assessed using binary logistic regression. For the multivariate model, fixed effects for individual hospital location were included. Additional baseline characteristics for multivariate models were chosen to include known predictors of outcome (25–28) and to adjust for baseline covariates that were not balanced in the treatment cohorts. Goodness-of-fit for the logistic regression model was assessed using visual plots of observed versus predicted probabilities, tests of link function, and the Hosmer-Lemeshow test. Additional analysis of the primary outcome was performed in propensity score-matched cohorts. For this analysis, probability of treatment group assignment was predicted with baseline variables using logistic regression. Matching was then performed in a 1:1 ratio using a greedy matching algorithm, with a caliper to ensure adequate matches. Baseline variables and secondary outcomes were compared using unpaired t test, Wilcoxon rank-sum test, Pearson chi-square test, or Fisher exact test, as appropriate. Baseline variables with excessively skewed distributions were log or square-root transformed for multivariate regression. Missing values for baseline characteristics were imputed using stochastic regression imputation (no more than 10% of values missing for all variables except lactate dehydrogenase). All data are presented as mean (SD), median (interquartile range), or number (%), unless otherwise indicated. All p values reported are two-tailed. All statistical analyses were done using Stata Statistical Software: Release 17. College Station, TX (StataCorp LLC).

RESULTS

Seven hospitals participated in the study. Four hundred three consecutive hospitalized patients who were prescribed tocilizumab or baricitinib were identified. Of these, 382 patients met all inclusion/exclusion criteria and form the basis for this study. Twenty-one patients were excluded due to concurrent treatment with both tocilizumab and baricitinib ($n = 1$), study drug never administered ($n = 5$), transfer from another external

facility ($n = 5$), COVID-19 not an admitting diagnosis ($n = 7$), study drug treatment prescribed in outpatient setting ($n = 2$), pregnancy ($n = 1$), and end-stage renal disease ($n = 2$) (some patients had more than one exclusion criterion).

Of the 382 patients included in the study, 194 (50.8%) received tocilizumab, and 188 (49.2%) received baricitinib. Most baseline characteristics in the two cohorts were similar, with notable exceptions being aspartate aminotransferase (AST) and C-reactive protein (**Table S1, Supplementary Digital Content**, <http://links.lww.com/CCX/A997>). Minor differences in baseline characteristics were equalized in the propensity score-matched cohorts (**Table S2, Supplementary Digital Content**, <http://links.lww.com/CCX/A997>). Dosages of tocilizumab and baricitinib administered during hospitalization are shown in Table S1 (Supplementary Digital Content, <http://links.lww.com/CCX/A997>). All patients received dexamethasone (ranging from 6–20 mg per day), and most received remdesivir. Most patients required high-flow oxygen or noninvasive ventilation. Sixty-day follow-up data for assessment of the primary outcome were available for 380 patients (99.4%). The primary outcome could not be ascertained for two patients (both in the tocilizumab cohort), who were transferred to inpatient facilities outside of the hospital system prior to day 60.

Odds for the primary outcome, and hospital discharge within 60 days alive and free from mechanical ventilation were quantitatively similar in the tocilizumab and baricitinib cohorts (**Table 1**). Results were similar in unadjusted (odds ratio [OR] for baricitinib, 1.19; $p = 0.42$), multivariate (OR for baricitinib, 1.33; $p = 0.37$), and propensity score-matched (OR for baricitinib, 1.13; $p = 0.71$ in 89 matched pairs) analyses. Two hundred forty three patients (64%) were discharged successfully by day 60. The observed probabilities for successful discharge were similar in the two cohorts (66% for baricitinib, 62% for tocilizumab, and absolute difference 4.0%; 95% CI [–5.7 to 13.6%]; p value = 0.42). The vast majority of the 137 patients not successfully discharged by day 60 had died (95% for tocilizumab vs 98% for baricitinib). Five patients remained alive and hospitalized beyond 60 days (four in the tocilizumab cohort and one in the baricitinib cohort). Results for the primary outcome were similar when redefined as successful discharge at 30 days, rather than 60 days (OR for baricitinib, 1.56; $p = 0.16$). ORs for included

TABLE 1.
Odds of Discharge Free From Mechanical Ventilation Within 60 d

Logistic Regression Model	OR for Baricitinib (95% CI)	<i>p</i>
Bivariate unadjusted	1.19 (0.78–1.81)	0.42
Multivariate	1.33 (0.72–2.45)	0.37
Propensity score-matched	1.13 (0.60–2.15)	0.71

OR = odds ratio.

For ORs of other covariates in multivariate model, see Table 2.

baseline covariates in the multivariate model are shown in **Table 2**. For the multivariate regression model, tests of link function and the Hosmer-Lemeshow test showed no evidence of model misspecification.

Secondary outcomes were similar in the tocilizumab and baricitinib cohorts (**Table 3**). No appreciable differences were observed in hospital length of stay, change in oxygenation at 48 hours, thromboembolic events, or hospital-acquired infections. Due to skewness of hospital length of stay, additional exploratory analysis using negative binomial regression was performed; in this analysis, assignment to

TABLE 2.
Multivariate Analysis for Primary Outcome^a

Predictor	OR (95% CI)	<i>p</i>
Baricitinib	1.33 (0.72–2.45)	0.37
Age (per 10 yr)	0.60 (0.48–0.75)	0.00
Cardiac disease ^b	0.45 (0.20–1.03)	0.06
Chronic lung disease	0.61 (0.32–1.15)	0.12
Glomerular filtration rate (per 10 mL/min)	1.11 (1.02–1.20)	0.02
Invasive mechanical ventilation	0.12 (0.02–0.56)	0.01
PaO ₂ /FIO ₂ ratio (per 10 mm Hg)	1.20 (1.07–1.35)	0.00
Respiratory rate (per min)	0.97 (0.93–1.01)	0.11
Aspartate aminotransferase (U/L) (log)	0.49 (0.30–0.79)	0.00
C-reactive protein (mg/L) (sqrt)	0.94 (0.88–1.01)	0.08

OR = odds ratio, sqrt = square-root.

^aORs for individual hospital locations and constant term not shown. Vasopressor use not included due to collinearity with invasive mechanical ventilation. Lactate dehydrogenase not included due to large number of imputed values and collinearity with C-reactive protein and aspartate aminotransferase.

^bcardiac disease defined as congestive heart failure or coronary artery disease.

tocilizumab or baricitinib treatment did not predict length of stay.

DISCUSSION

This study shows that in hospitalized patients with hypoxemia due to COVID-19 infection, tocilizumab and baricitinib added to dexamethasone result in quantitatively similar rates of successful hospital discharge. To our knowledge, this is the first multicenter study directly comparing these two treatments for COVID-19. Both treatments are thought to be beneficial and are recommended in this patient population, but the relative merits of each have not previously been evaluated.

Although statistical tests were conducted with hypotheses of equality rather than equivalence, the results strongly suggest that outcomes with tocilizumab and baricitinib are truly similar. The point estimates and CIs for the OR and estimated probabilities of the primary outcome argue that any true differences in the benefit of tocilizumab versus baricitinib are likely to be clinically insignificant. Specifically, outcomes with baricitinib appear to be at least as good as those with tocilizumab. This is of particular importance to clinicians; our study suggests that if immunomodulatory treatment is warranted but tocilizumab is unavailable, baricitinib could be substituted without loss of efficacy or increase in adverse events.

The consistency of our results in multiple different analyses gives confidence to the conclusion that outcomes with tocilizumab and baricitinib are similar. Results were robust to changes in specification of the primary outcome (i.e., successful discharge at 30 vs 60 d). Results from the propensity score-matched cohorts, in which baseline characteristics were virtually identical, confirmed the results of the primary multivariate analysis. Most baseline characteristics were similar in the tocilizumab and baricitinib cohorts. The higher baseline levels of AST in the tocilizumab cohort are likely explained by the relative contraindication for baricitinib in the setting of severe hepatic impairment (29). However, even in patients with liver dysfunction, in the vast majority, the degree of hepatic impairment was mild, permitting clinicians to prescribe baricitinib. Further, multivariate and propensity score-matched models accounted for liver dysfunction.

In contrast to the nil effect of study drug assignment, several baseline characteristics were predictive of outcome (Table 2). Results were consistent with previously published predictors of outcome in COVID-19.

TABLE 3.
Secondary Outcomes

Outcome	Tocilizumab (n = 194)	Baricitinib (n = 188)	p
Hospital length of stay (d)	10 (6–19)	9 (6–17)	0.72
PaO ₂ /FIO ₂ ratio change at 48 hr (mm Hg)	9.7 (–6.6 to 40.9)	7.1 (–5.1 to 32.2)	0.45
Thromboembolism	18 (9.3%)	15 (8.0%)	0.65
Hospital-acquired infection ^a	7 (3.6%)	3 (1.6%)	0.34
Central-line-associated bloodstream infection	4 (2.1%)	0 (0.0%)	
Catheter-associated urinary tract infection	2 (1.0%)	1 (0.5%)	
<i>Clostridium difficile</i> infection	2 (1.0%)	2 (1.1%)	
Opportunistic infection	1 (0.5%) ^b	0 (0%)	

^aIndividual hospital-acquired infections sum to greater than total due to multiple infections per patient.

^bInvasive pulmonary aspergillosis.

The use of glucocorticoid treatment deserves mention. Dexamethasone use varied widely in published trials of tocilizumab and baricitinib for COVID-19. The impact of concurrent steroid treatment and dose on the effectiveness of tocilizumab and baricitinib is a matter of debate. Data are at least suggestive of benefit of additional immunomodulator treatment when given with steroids. In previous studies that used steroids, dexamethasone dose (or equivalent) ranged from 6 to 20 mg (12, 30, 31). The doses used in the present study were within this range. In the present study, all patients in both cohorts were treated with dexamethasone, as would be expected given its proven benefit in this patient population (5). Therefore, the results of this study may not be applicable to patients not treated with glucocorticoids.

There are several limitations to this study. Most importantly, the study is retrospective, and patients were not randomized. The possibility of unobserved selection bias cannot be ruled out. However, it is believed that most patients were assigned to treatment cohort based on medication availability (in the absence of specific medication contraindications). Therefore, after adjustment for baseline characteristics, the likelihood of major unobserved selection bias is low. The second important limitation is the relatively modest sample size. Compared with published placebo-controlled trials, which varied widely in sample size, the present study is intermediate in size and had 62% power to detect a 15% relative difference in the primary outcome. For reference, the Randomised Evaluation of COVID-19 Therapy study of tocilizumab versus placebo showed a 14% relative increase in the rate of successful discharge (our primary outcome) (24). Based on results from this study, it is estimated that a study of noninferiority of baricitinib to

tocilizumab with 80% power and noninferiority margin of 5% absolute difference in probability of successful discharge would require 700 patients. Another limitation is the assessment of secondary infections. We reported on infections with clear-cut diagnostic criteria, but based on chart review, we were unable to confidently assess the frequency of secondary bacterial pneumonia in patients with severe viral pneumonia. It is, therefore, possible that the frequency of pulmonary bacterial superinfection is different in the treatment arms. Finally, very few patients in either treatment arm were receiving invasive mechanical ventilation at baseline, so results may not apply to this population. Notably, patients needing invasive ventilation have a high mortality rate (28) and were excluded from many of the placebo-controlled trials of tocilizumab and baricitinib (8, 10).

In conclusion, this is the first published study to compare the effectiveness of tocilizumab and baricitinib in COVID-19 pneumonia. The results show that outcomes are similar with either treatment. A large prospective randomized study would be required to confirm these results.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccejjournal>).

The authors have disclosed that they do not have any potential conflicts of interest.

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