Baricitinib Versus Tocilizumab for the Treatment of Moderate to Severe COVID-19

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Abstract

Background: To date, minimal data directly compare tocilizumab with baricitinib for treatment in moderate to severe COVID-19. Objective: To compare the rates of in-hospital mortality with progression to mechanical ventilation in patients with COVID-19 who received either tocilizumab or baricitinib. Methods: The authors conducted a single-centered, institutional review board–approved, retrospective cohort study. Patients who were 18 years or older who were hospitalized with COVID-19 and who received tocilizumab or baricitinib were included. The primary end point is a composite outcome of progression to mechanical ventilation or in-hospital mortality. Secondary end points include components of the composite outcome and progression to higher level of care, duration of mechanical ventilation, and hospital and intensive care length of stay. Safety end points include the incidence of infections and thrombosis. Results: A total of 176 patients were included, of whom 61 (34.7%) received tocilizumab and 115 (65.3%) received baricitinib. In the primary outcome, there was no difference between the groups (52.5% tocilizumab vs 44.3% baricitinib, \( P = 0.305 \)). For safety outcomes, there was a higher instance of thrombosis (11.5% tocilizumab vs 3.5% baricitinib, \( P = 0.042 \)) and rates of antibiotic use after initiation of therapy (55.7% tocilizumab vs 38.3% baricitinib, \( P = 0.026 \)) in the tocilizumab group. Conclusion and Relevance: There was no significant difference in the composite outcome in patients who received tocilizumab or baricitinib for the treatment of COVID-19. However, there was an increase in rates of thrombosis in those receiving tocilizumab compared with baricitinib. These results need to be confirmed in larger prospective, randomized trials.

Keywords
tocilizumab, baricitinib, COVID-19, pneumonia

Background

Coronavirus disease 2019 (COVID-19) is caused by the virus SARS-CoV-2 and was first discovered in December 2019 in Wuhan, China.¹ As of June 2022, COVID-19 has led to 6.3 million deaths worldwide.² Severe COVID-19 is associated with a dysregulated immune response that can lead to a hyperinflammatory response.³⁵ In this state, the progressive release of proinflammatory cytokines, including interleukin (IL)-6, IL-1, IL-10, interferon-\( \gamma \), and granulocyte–macrophage colony-stimulating factor, occurs, causing a “cytokine storm.”⁶⁵ Corticosteroids, primarily dexamethasone, have been successful in providing anti-inflammatory effects and reducing mortality in hospitalized patients needing supplemental oxygen with COVID-19.⁷ Additional immunomodulators have been studied in this population, including tocilizumab and baricitinib with or without dexamethasone, with mixed results.⁸¹³

Tocilizumab is a recombinant antihuman IL-6 receptor monoclonal antibody that binds to IL-6 receptors and prevents further inflammatory cascades.¹⁴ Baricitinib is a selective Janus kinase (JAK)1 and JAK2 intracellular route inhibitor that inhibits multiple cytokines, including IL-2, IL-6, IL-10, interferon-\( \gamma \), and granulocyte–macrophage colony-stimulating factor.¹⁵ There is also some evidence that baricitinib acts against SARS-CoV-2 by impairing adaptor protein (AP)2-associated protein JAK1 and prevents SARS-CoV-2 cellular entry and infectivity.¹⁶ Both agents carry boxed warnings for the risk of serious infections. Baricitinib

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also has a boxed warning for thrombosis, and tocilizumab’s package insert lists an increased risk for deep vein thrombosis among its adverse effects.

The National Institutes of Health (NIH) guidelines recommend adding tocilizumab or baricitinib to dexamethasone in hospitalized patients with rapidly increasing oxygen requirements and systemic inflammation. As of June 2022, the NIH guidelines do not recommend one agent over the other. This study was developed to compare the rates of in-hospital mortality with progression to mechanical ventilation in patients with moderate to severe COVID-19 who received either tocilizumab or baricitinib.

Methods

The institutional review board (Valley Health/Winchester Medical Center Institutional Review Board, study identification number 20220102) approved this study on January 25, 2022. All study procedures were in accordance with the ethical standard of the institutional review board and with the Helsinki Declaration of 1975. The institutional review board provided this study with a waiver for informed consent. This study was a single-center, retrospective cohort study conducted at a 495-bed community hospital with a 48-bed intensive care unit (ICU). Originally, only tocilizumab was on the institution’s formulary and baricitinib was added to the formulary on August 24, 2021, due to shortages of tocilizumab. In the absence of any contraindications, the use of baricitinib or tocilizumab was based on their availability at time of hospitalization. Tocilizumab and baricitinib orders were placed using an order set. Patients receiving tocilizumab were given 8 mg/kg once, rounded to the nearest 200 mg, not to exceed 800 mg, and administered over 60 minutes. Patients receiving baricitinib received 4 mg daily or the dose was adjusted based on the patient’s renal function as per the package insert. Per the hospitals’ criteria for use, tocilizumab or baricitinib therapy was not allowed to be initiated if the patient was on concomitant antibiotic therapy.

Patients were included if they were aged older than 18 years, diagnosed with COVID-19, and received at least 1 dose of tocilizumab or at least 3 doses of baricitinib. Patients were excluded if they were pregnant, on mechanical ventilation prior to the first dose of study agent, received both study medications, and anyone who remained hospitalized at the time of data collection. A list of patients for whom either tocilizumab or baricitinib was ordered for between August 24, 2021, and December 31, 2021, was generated from the electronic health record (EHR) and evaluated for inclusion in the trial.

The primary end point was a composite outcome of progression to mechanical ventilation or in-hospital mortality. Secondary end points included components of the composite outcome and progression to a higher level of care, progression to tracheostomy, duration of mechanical ventilation, hospital length of stay (LOS), and ICU LOS. Safety end points included rates of infections, antibiotic use after administration of study drugs, and thrombosis.

The SPSS software Version 28.0.1.1 was used to analyze the outcomes. Categorical data, including the primary outcome, was evaluated using χ² or Fischer’s exact test when appropriate. Continuous data, including the secondary outcomes duration of mechanical ventilation, hospital LOS, and ICU LOS, were tested for normality, using the Kolmogorov–Smirnov and Shapiro–Wilk tests. All outcomes were determined to be not normally distributed and thus were evaluated using Mann–Whitney U test. Two-sided alpha was set at 0.05%. The authors assumed a moderate effect size of 10% between groups. Assuming equal distributions of patients, 388 patients in each group would be needed to reach 80% power.

Results

Study Population

Upon data extraction, 201 patients were identified as having orders for tocilizumab or baricitinib between August 24, 2021, and December 31, 2021. Of these patients, 25 patients were excluded. Twelve patients received less than 3 doses of baricitinib, 10 did not receive a dose of tocilizumab despite the medication being ordered, 2 were intubated prior to the first dose, and 1 received concurrent treatment with both tocilizumab and baricitinib. Of the 176 included patients, 61 (34.7%) received tocilizumab and 115 (65.3%) received baricitinib. No patients received more than 1 dose of tocilizumab. The median duration of baricitinib therapy was 9 days (interquartile range = 6–13.25). The most common dose of tocilizumab was 800 mg (86.9%) followed by 600 mg (8.2%) and 400 mg (4.9%). Ten patients (8.7%) in the baricitinib group had renally dosed therapy. For most patients, premature discontinuation of baricitinib (n = 52) was due to hospital discharge (n = 23, 44.2%), development of infection (n = 10, 19.2%), or comfort care (n = 7, 13.5%). Demographics and baseline characteristics are summarized in Table 1. The median age was 62 years, and most of the population were white men. There was a higher percentage of patients with hypertension, diabetes, and prior history of deep vein thrombosis (DVT)/pulmonary embolism (PE) in the baricitinib group. Both agents were frequently ordered for patients in the ICU, and there was a higher number of baricitinib patients with treatment initiated on the medical floor. Concurrent treatments are also summarized in Table 2. All patients in the study received dexamethasone. In both groups, most patients received greater than or equal to 10 mg of dexamethasone per day and for more than 10 days. In terms of venous thromboembolism prophylaxis, both groups had similar use of intermediate-dose anticoagulation (heparin 7500...
units every 8 hours or enoxaparin 40 mg subcutaneously every 12 hours, with weight-based and renal dose adjustments). In contrast, a higher percentage of tocilizumab patients had received therapeutic anticoagulation (heparin infusion or enoxaparin 1 mg/kg every 12 hours with renal dose adjustments). More baricitinib patients received standard-dose anticoagulation (heparin subcutaneous 5000 units every 8–12 hours or enoxaparin 40 mg subcutaneously daily, with weight-based and renal dose adjustments). In addition, fewer patients had received antibiotics before the first dose of tocilizumab (21 patients, 34.43%) compared with baricitinib (54 patients, 46.96%).

Primary and secondary outcomes are shown in Table 3. The primary outcome, in-hospital mortality and progression to mechanical ventilation, occurred in 52.5% (n = 32) of patients in the tocilizumab group and 44.3% (n = 51) of patients in the baricitinib group (P = 0.305). For the secondary outcomes, there were no statistically significant differences noted between the groups in regards to progression to mechanical ventilation, in-hospital mortality, progression to higher level of care, hospital LOS, and ICU LOS. The rate of thrombosis was higher in the tocilizumab group. There was no difference in the rate of positive cultures, but there was a significant difference in the rate of antibiotic use (Table 3).

Table 1. Baseline Characteristics.

| Characteristics                        | TCZ (n = 61) | BARI (n = 115) |
|----------------------------------------|-------------|----------------|
| Age, years (median, IQR)              | 62 (51–70)  | 61 (51.5–71)   |
| Female gender, n (%)                  | 22 (36.07)  | 38 (33.04)     |
| Body mass index (median, IQR)         | 33.11 (30.26–39.14) | 34.8 (29.91–38.41) |
| Race, n (%)                           |             |                |
| White                                  | 57 (93.44)  | 105 (91.3)     |
| Black or African American              | 1 (1.64)    | 2 (1.74)       |
| Hispanic/Latino                        | 2 (3.28)    | 6 (5.22)       |
| Asian                                  | 0           | 1 (0.87)       |
| Other                                  | 1 (1.64)    | 1 (1.64)       |
| Past medical history, n (%)           |             |                |
| Prior DVT or PE                        | 1 (1.64)    | 5 (4.35)       |
| Hypertension                           | 29 (47.54)  | 67 (58.26)     |
| Cardiovascular disease                 | 10 (16.39)  | 22 (19.13)     |
| Diabetes                               | 17 (27.87)  | 40 (34.78)     |
| Chronic lung disease                   | 8 (13.11)   | 14 (12.17)     |
| MAB prior to admission, n (%)          | 4 (6.56)    | 6 (5.22)       |
| Vaccinated,a n (%)                     | 5 (8.2)     | 11 (9.57)      |
| Vaccine received,b n (%)               |             |                |
| J&J                                    | 3 (4.92)    | 4 (3.48)       |
| Pfizer-BioNTech                        | 2 (3.28)    | 4 (3.48)       |
| Moderna                                | 0           | 3 (2.61)       |
| Location at time of order, n (%)       |             |                |
| ICU                                    | 40 (65.57)  | 69 (60)        |
| ED                                     | 6 (9.84)    | 7 (6.09)       |
| Oxygen requirement, n (%)              |             |                |
| CPAP (0–10 L/min)                      | 5 (8.2)     | 9 (7.83)       |
| HFNC (30–60 L/min)                     | 48 (78.69)  | 93 (80.87)     |
| BiPAP (0–10 L/min)                     | 3 (4.92)    | 3 (2.61)       |
| Midflow (6–10 L/min)                   | 1 (1.64)    | 7 (6.09)       |
| Other oxymizer (1–15 L/min)            | 4 (6.56)    | 3 (2.61)       |
| Labs on admission (median, IQR)        |             |                |
| C-reactive protein (mg/L)              | 12.78 (9.28–17.91) | 9.4 (6.03–15.79) |
| Ferritin (mcg/L)                       | 1611.8 (678.7–2593.4) | 1504.95 (827.95–2852.8) |
| Procalcitonin (ng/mL)                  | 0.16 (0.1–0.28) | 0.14 (0.09–0.27) |

Abbreviations: BARI, baricitinib; CPAP, continuous positive airway pressure; DVT, deep vein thrombosis; ED, emergency department; HFNC, High-flow nasal cannula; ICU, intensive care unit; IQR, interquartile range; MAB, monoclonal antibody; PE, pulmonary embolism; TCZ, tocilizumab.

*aVaccinated was defined as having received either 2 doses of an mRNA vaccine (Pfizer-BioNTech, Moderna, or a mix) or 1 dose of the J&J vaccine.

*bWe did not identify any patients in either group who mix and matched vaccines.
Figures 1 and 2 illustrate the positive cultures obtained from the tocilizumab and baricitinib patients and the associated microbes. Fungal infections (n = 21) were isolated in the urine (n = 5) and respiratory cultures (n = 20). One incident of aspergillus pneumonia occurred in the baricitinib group, there were no incidences of invasive candidiasis.

**Discussion**

In this retrospective cohort study, tocilizumab and baricitinib did not have significantly different rates of the composite outcome, progression to mechanical ventilation, or in-hospital mortality. Few studies have directly compared tocilizumab with baricitinib in patients with COVID-19. Roddy et al., in a study of 382 patients, found no difference in the rate of hospital discharge of patients alive and free from mechanical ventilation within 60 days of treatment, with either tocilizumab or baricitinib; unadjusted bivariate odds ratio (OR) = 1.19, 95% CI = [0.78-1.81], P = 0.42, multivariate OR = 1.33, 95% CI = [0.72-2.45], P = 0.37. Similarly, a smaller retrospective medical record review that evaluated 60 patients, with COVID-19 and interstitial pneumonia treated with baricitinib and/or tocilizumab versus no treatment, found no difference in mortality at 1 to 15 and 16 to 30 days in those receiving tocilizumab and baricitinib. However, an additional study of 98 patients published in *Medicina* found that tocilizumab (13/64 patients, 20.2%) was associated with higher rates of 28-day mortality compared with baricitinib (1/34 patients, 2.94%) in the univariate analysis (OR = 8.41, 95% CI = [1.05-67.37], P = 0.045), but failed to be a predicting factor for mortality in the multivariate analysis (OR = 13.28, 95% CI = [0.45-392.92]).

Our study found a similar trend toward patients treated with tocilizumab having higher in-hospital mortality. This is an underpowered outcome, and the results could be a type II error. In addition, higher rates of remdesivir use
in the baricitinib group may accentuate the difference between groups. Evidence on the use of remdesivir in patients receiving tocilizumab or baricitinib is limited and conclusions regarding the effects of remdesivir in this population cannot be made in the absence of more robust confirmation of its effects.17

Our study found a higher instance of thrombosis in tocilizumab patients despite higher utilization of therapeutic
anticoagulation prior to thrombotic events. This difference was not reported in similar studies, including the larger Roddy et al.\textsuperscript{19} study.\textsuperscript{19} In addition, although there was no difference in the rate of positive cultures, a higher rate of antibiotic utilization in the tocilizumab group was reported. The difference in antibiotic use without a variance in rates of positive cultures may also be related to variable sensitivity and specificity of sputum cultures. The rates of positive blood cultures may be more indicative of the rates of infection without further clinical correlation that is beyond this retrospective study. Furthermore, positive urine cultures were not further characterized as urinary tract infections or asymptomatic bacteriuria and thus may overrepresent infections. Other studies comparing tocilizumab with baricitinib have not found differences in hospital-acquired infections\textsuperscript{18} or secondary infections.\textsuperscript{20}

Based on the findings of the study, the choice of tocilizumab versus baricitinib may be dependent on multiple factors. Tocilizumab’s long half-life, intravenous administration, and lack of contraindication in patients with renal dysfunction may make it a more desirable agent in selected populations. However, baricitinib’s shorter half-life allows discontinuation upon suspicion of infection. At this time, there appears to be minimal cost difference between these 2 agents. An individualized approach based on patient characteristics is prudent.

In addition to the aforementioned limitations, several additional study deficiencies should be noted. These limitations include tocilizumab supply constraints causing a larger baricitinib population, ICU capacity limitations leading to some critically ill patients being managed on the medical floor, and the study’s observational design. In addition, due to the observational design, a patient’s vaccination status could not be confirmed through interview, although records from the institution’s state and surrounding states’ departments of health immunization records were reviewed. In addition, the exclusion of patients on mechanical ventilation limits generalizability to this population. Although there was no difference in efficacy between tocilizumab and baricitinib, this study adds to the limited data comparing the use of these agents in COVID-19.

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