Clinical Infectious Diseases

BRIEF REPORT

Use of Baricitinib in Patients With Moderate to Severe Coronavirus Disease 2019

Boghuma K. Titanji,[1] Monica M. Farley,[1,2] Ashish Mehta,[3,4] Randi Connor-Schuler,[4] Abeer Moanna,[1,2] Sushma K. Cribbs,[3,4] Jesse O'Shea,[1] Kathryn DeSilva,[2] Bonnie Chan,[2] Alex Edwards,[5] Christina Gavegnano,[6] Raymond F. Schinazi,[6] and Vincent C. Marconi[1,2,5,7]

[1]Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia, USA, [2]Infectious Diseases, Atlanta Veterans Affairs Medical Center, Decatur, Georgia, USA, [3]Pulmonary Medicine, Atlanta Veterans Affairs Medical Center, Department of Medicine, Decatur, Georgia, USA, [4]Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Emory University, Atlanta, Georgia, USA, [5]Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA, [6]Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, USA, [7]Emory Vaccine Center, Emory University, Atlanta, Georgia, USA

(See the Editorial Commentary by Lenz et al on pages 1251–2.)

Hyperinflammation is associated with increased mortality in coronavirus disease 2019 (COVID-19). In this retrospective, uncontrolled patient cohort with moderate -severe COVID-19, treatment with baricitinib plus hydroxychloroquine was associated with recovery in 11 of 15 patients. Baricitinib for the treatment of COVID-19 should be further investigated in randomized, controlled clinical trials.

Keywords. COVID-19; baricitinib; hyper-inflammation.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to more than 8 million confirmed infections worldwide, with an estimated global mortality of 5.6% as of 17 June 2020 [1]. Virus-driven hyperinflammation and cytokine storm syndrome are important features of severe COVID-19 [2]. A multicenter, retrospective study of 150 patients with severe COVID-19 showed a strong association between elevated ferritin and interleukin (IL)-6 levels and adverse clinical outcomes [3]. Recognizing and treating cytokine storm may present a viable approach to reducing the mortality from COVID-19. The Janus kinase (JAK) 1/2 inhibitor, baricitinib, is an attractive candidate due to its properties as a potent anti-inflammatory agent and its hypothesized off-target antiviral effects against SARS-CoV-2 [4, 5]. In this brief report of 15 patients, we present the clinical use of baricitinib for the treatment of patients with moderate to severe COVID-19.

Received 9 May 2020; editorial decision 18 June 2020; accepted 22 June 2020; published online June 29, 2020.

Correspondence: V. C. Marconi, Health Sciences Research Building, 1760 Haygood Dr NE, Room W325, Atlanta, GA 30322, USA (Vincent.marconi@va.gov; vcmarco@emory.edu; vmarconi@gmail.com).

Clinical Infectious Diseases® 2021;72(7):1247–50

DOI: 10.1093/cid/ciaa879

METHODS

This study was conducted at the Atlanta Veterans Affairs Medical Center (VAMC) with approvals from the Emory University Institutional Review Board and Atlanta VAMC Office of Research and Development. Data were abstracted from electronic health records between 1 March 2020 and 18 April 2020.

Patients had laboratory-confirmed COVID-19, diagnosed by quantitative reverse-transcriptase polymerase chain reaction testing of oropharyngeal, nasopharyngeal, or tracheal aspirate samples. The patients were treated at the discretion of the medical team with a combination of hydroxychloroquine and baricitinib if they fulfilled at least 1 of the following criteria: evidence of pneumonia on lung imaging and requiring supplemental oxygen on admission or development of a new oxygen requirement during the course of their hospitalization; moderate disease requiring hospitalization (eg, severe diarrhea requiring volume resuscitation, encephalopathy, evidence of end-organ damage); elevated or rising inflammatory markers during hospitalization. Statistical analyses were performed using GraphPad and R software.

DISEASE CLASSIFICATION AND OUTCOMES

Moderate COVID-19 patients met any of the following criteria: fever, confusion, severe diarrhea, dyspnea, evidence of pneumonia on lung imaging, or requiring hospitalization for ongoing medical care but not intensive care unit (ICU)–level care. Severe COVID-19 patients met any of the following criteria: respiratory rate >30 times/min, oxygen saturation by pulse oximetry ≤93% at rest, or ratio of partial pressure of oxygen to fraction of inspired oxygen <300 mm Hg. Critical COVID-19 patients required high-flow oxygen therapy or invasive mechanical ventilation for any length of time during the course of their hospitalization. Patient outcomes were classified into 1 of the following 3 mutually exclusive categories: (1) recovered, further defined as: (a) hospitalized, not requiring supplemental oxygen, and no longer requiring ongoing medical care; (b) discharged, limitation on activities, and/or requiring home oxygen; or (c) discharged, no limitations on activities; (2) not recovered, further defined as hospitalized, requiring supplemental oxygen, and intensive care unit (ICU) level care; or (3) died.

RESULTS

The demographic characteristics, comorbidities, presenting symptoms, and clinical courses of patients in this cohort are summarized in Supplements 1 and 2. Patients received 2–4 mg of baricitinib daily and hydroxychloroquine

200–400 mg once daily orally by mouth or via nasogastric tube. Patients with underlying kidney disease and a glomerular filtration rate of 30–60 mL/min/m^2 received a reduced dosage of 2 mg baricitinib daily. A summary of treatments, complications, and outcomes for all patients is provided in Supplement 3. Nine of 15 (60%) patients required ICU-level care, with 4 (26.7%) requiring 6–20 days of mechanical ventilation. Baseline inflammatory markers (including C-reactive protein [CRP], IL-6, and erythrocyte sedimentation rate [ESR]) were elevated for all patients. Following initiation of baricitinib, 13 of 15 (86.7%) patients had a significant reduction in body temperature and CRP levels over the course of treatment (Figure 1 and Supplement 4). Clinical improvement in oxygen requirements, presenting

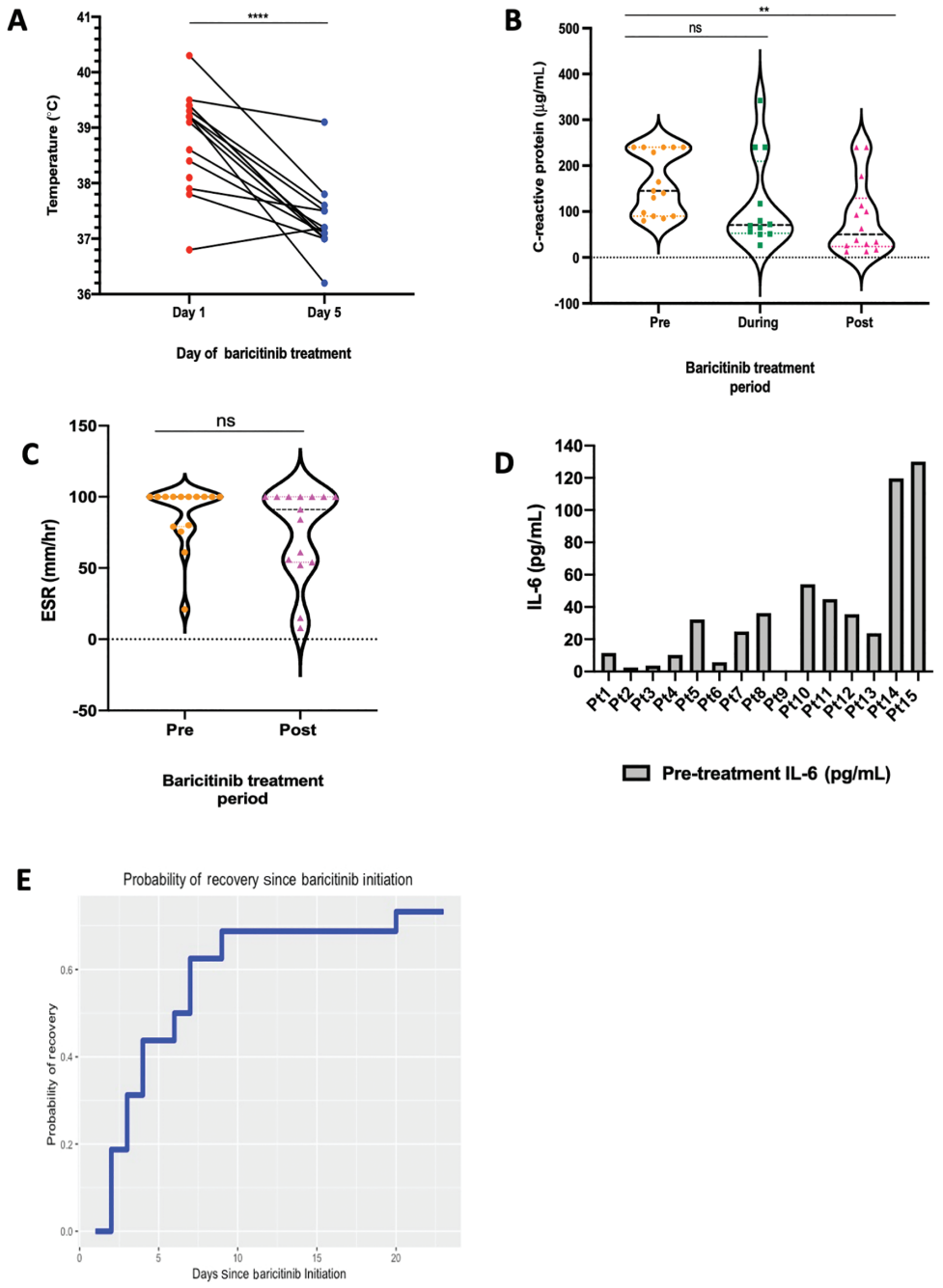

Figure 1. Body temperature, C-reactive protein (CRP), ESR, IL-6, and survival of patients with moderate to severe coronavirus disease 2019 treated with baricitinib. *A*, Highest recorded body temperature on day 1 of treatment with baricitinib (red dots) compared with day 5 of therapy (blue dots); temperature significantly decreased ($P < .0001$) and normalized for 13/15 patients. *B*, CRP levels before, during, and after baricitinib treatment. Levels were significantly lower post-treatment compared with pretreatment ($P < .01$). *C*, ESR levels before and after baricitinib treatment. *D*, Pretreatment IL-6 levels for all patients in the cohort. *E*, Kaplan-Meier curve showing time to recovery after baricitinib initiation with death right-censored. Abbreviations: ESR, erythrocyte sedimentation rate; IL, interleukin; ns, not significant; Pt, patient.*$p < .05$, ***$p < .0005$.

symptoms (cough, diarrhea, confusion, shortness of breath), and recovery were observed in 12 of 15 treated patients, representing 80% survival at the end of the study period (Supplement 3). Three patients died: 1 patient with underlying dementia and normal pressure hydrocephalus developed severe hypoxic respiratory failure but had a do-not-resuscitate (DNR)/do-not-intubate (DNI) advance directive; 1 patient with underlying lymphoma, developed candidemia, progressed to severe hypoxic respiratory failure, and requested a DNI/DNR advance directive; and 1 patient developed cardiogenic shock 8 days into his ICU course and had a DNR advance directive in place. Patient 1 developed rhabdomyolysis temporally associated with initiation of hydroxychloroquine as well as a deep venous thrombus (DVT) associated with a peripherally inserted central catheter in his left upper extremity (Supplement 3). Patient 8 developed a pulmonary embolism during his hospital course for which he received therapeutic anticoagulation. Patient 13 required mechanical ventilation associated with barotrauma, pneumomediastinum, and methicillin-sensitive *Staphylococcus aureus* pneumonia in the ICU. All patients received standard DVT prophylaxis with unfractionated heparin or low-molecular-weight heparin on admission. Those patients who developed thrombotic complications where treated with therapeutic doses of intravenous heparin.

DISCUSSION

In this retrospective cohort, 15 patients with moderate to severe COVID-19 were treated with baricitinib and hydroxychloroquine. Twelve of 15 recovered, and 3 died. We observed temporally associated clinical improvement following initiation of baricitinib in 11 of the 15 (73.3%) patients. This improvement was characterized by a normalization of body temperature, a decline in inflammatory markers and oxygen requirements, and recovery. Two of the 15 (13.3%) developed secondary bacterial or fungal infections during prolonged ICU stays.

Richardson et al [4] suggested a potential role for baricitinib in the treatment of COVID-19 based on artificial intelligence algorithms. They hypothesized that baricitinib, a JAK1/2 inhibitor, could directly mitigate the inflammatory response triggered by SARS-CoV-2 infection. In addition, baricitinib was [4] identified as a numb-associated kinase inhibitor with high affinity for AP2-associated protein kinase 1 (AAK1). AAK1 was previously described as a crucial regulator of clathrin-mediated endocytosis of coronavirus and other viruses [5]. In light of this, baricitinib may have direct antiviral effects by preventing virus entry into target cells [4, 5]. This mechanism could be complementary to potential anti-inflammatory benefits in the setting of the cytokine storm associated with severe COVID-19. Two case series of 4 and 12 patients have been published on the use of baricitinib in mild to moderate COVID-19 [6, 7] with findings similar to those from our study. These studies, however, did not include any patients with severe disease.

An approach using a JAK1/2 inhibitor to treat a viral infection may appear counterintuitive given the importance of the JAK-Signal transducer and activator of transcription (STAT) signaling pathway in mediating the antiviral effects of type I (alpha and beta) interferons. Interferon therapy for treating other coronavirus syndromes, that is, middle eastern respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), yielded inconclusive results on antiviral effects and clinical benefit [8]. About 80% of patients who contract SARS-CoV-2 are able to clear the virus and make a full recovery without additional treatments [9]. However, 20% of patients progress to moderate to severe disease and require hospitalization; peak viral loads occur approximately 1 week after the initial onset of symptoms [2]. Disease severity is marked by hyperinflammation and cytokine storm syndromes with increased levels of type II (gamma), which drives IL-6 expression through the JAK-STAT pathway [2].

In animal models of SARS and MERS, the initial (type I) interferon response had beneficial effects in the early phases of disease but may have become damaging in the latter phases (type II) [8]. This suggests that the patients most likely to benefit from treatment with JAK1/2 inhibitors are those with evidence of disease progression and hyperinflammation characterized by rising levels of inflammatory markers, progressive pulmonary disease, and overall clinical deterioration. In addition, at a 2- to 4-mg daily dosage, baricitinib primarily inhibits type II interferon and less likely type I interferon responses. Baricitinib is approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis [10]. Long-term use has been associated with increased risk for infections and thromboembolic events [11]. These adverse events are less likely to occur with a limited course of therapy as received by patients in this cohort. However, it is unclear whether the thrombotic events noted in 3 of the 15 patients were related to baricitinib therapy, were general nosocomial complications, or occurred as part of the pathogenesis of COVID-19 disease.

This study has several limitations. It was a small, nonrandomized cohort and did not include controls. Thus, it is unclear if these patients would have improved without baricitinib treatment. All patients were concomitantly treated with hydroxychloroquine, which has in vitro antiviral activity against SARS-CoV-2 as well as anti-inflammatory properties [12]. As such, it is uncertain whether the clinical improvements in this cohort can be attributed to the effects of baricitinib alone, a potentially synergistic response in combination with the purported antiviral and anti-inflammatory effects of hydroxychloroquine, or is consistent with the natural history of the disease unrelated to either intervention.

CONCLUSIONS

In this noncontrolled, retrospective cohort study of 15 patients with moderate to severe COVID-19, a short course of baricitinib in combination with hydroxychloroquine was tolerated and temporally associated with clinical improvement in 11 of 15 patients and recovery in 12 of 15 patients. A causal relationship between clinical improvement and the use of baricitinib in combination with hydroxychloroquine cannot be established in this observational study. However, these findings provide support for conducting a formal evaluation of JAK1/2 inhibitors in randomized, controlled clinical trials for treatment of COVID-19. The ongoing ACTT-2 trial (ClinicalTrials.gov; NCT04280705), which is investigating baricitinib in combination with remdesivir for the treatment of COVID-19, should provide more clarity on this intervention.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Financial support. V. C. M. and R. F. S. are partially funded by the Emory University Center for AIDS Research (AI050409). R. F. S. and C. G. are funded, in part, by the National Institutes of Health (grant 5-R01-MH116695).

Potential conflicts of interest. V. C. M. has consulted or received research support from ViiV, Gilead, Lilly, and Bayer. R. F. S. served as an unpaid consultant for Eli Lilly whose drugs are being evaluated in the research described here. In addition, R. F. S. owns shares in Eli Lilly and Gilead and has been issued patents 20190134039, 10022378, and 9662332. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. World Health Organization. Coronavirus disease 2019—situation report number 148. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200613-covid-19-sitrep-145.pdf?sfvrsn=bb7c1dc9_2. Accessed 17 June 2020.
2. Mehta P, McAuley DF, Brown M, et al; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet **2020**; 395:1033–4.
3. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med **2020**; 46:846–8.
4. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet **2020**; 395:e30–1.
5. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis **2020**; 20:400–2.
6. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: a pilot study on safety and clinical impact. J Infect **2020**; S0163-4453:30228.
7. Stebbing J, Krishnan V, de Bono S, et al. Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. EMBO Mol Med **2020**; doi:10.15252emmm.20212697.
8. Channappanavar R, Fehr AR, Zheng J, et al. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. J Clin Invest **2019**; 129:3625–39.
9. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis **2020**; 20:P669–77.
10. Kubo S, Nakayamada S, Tanaka Y. Baricitinib for the treatment of rheumatoid arthritis and systemic lupus erythematosus: a 2019 update. Expert Rev Clin Immunol **2019**; 15:693–700.
11. Strand V, Ahadieh S, DeMasi R, et al. THU0211 Meta-analysis of serious infections with baricitinib, tofacitinib and biologic dmards in rheumatoid arthritis. Ann Rheum Dis **2017**; 76:284.
12. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis **2020**; doi: 10.1093/cid/ciaa237.