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# Addition of Baricitinib to Usual Therapeutic Regimen in Hospitalized Patients with Severe Covid-19: A Prospective Cohort Study

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## Abstract

**Background-Purpose:** The ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has affected our everyday lives for the last three years, leading to in numerous patient hospitalizations all over the world and a plethora of therapeutic interventions being implemented in an effort to combat the disease. Baricitinib is an oral selective Janus kinase (JAK) inhibitor approved for the treatment of rheumatic disease that was hypothesized to bear positive effect on the more severe forms of the novel coronavirus disease 2019 (COVID-19) based on its antiviral and anti-cytokine properties. The purpose of the current prospective cohort study was to study the effect of adding baricitinib to the usual drug regimen of patients hospitalized with severe COVID-19 in the infectious disease unit of a third-level hospital.

**Patients-Methods:** The current prospective cohort study was conducted at the Infectious Disease Unit of the 401 General Military Hospital of Athens, recruiting a total of 74 patients who were hospitalized with severe COVID-19 based on the COVID-19 severity index. Relevant demographic data, personal and family medical history and turnout of the cases was documented. Laboratory examinations as well as arterial blood gases (ABGs) were recorded and analysed both upon admission and discharge of the patients. An oral dose of 4 mg baricitinib daily (or an adjusted dose of 2 mg daily in cases of renal disease) was added to the usual therapeutic regimen of the patients.

**Results:** For the purpose of the current study, we recruited 74 patients (male sex 81.1%, mean age 52,8±17,2 years old). Six patients (8.1%) were fully vaccinated and 32 patients (43.2%) presented at least one comorbidity (chronic cardiovascular disease, chronic liver disease, chronic kidney disease, immunosuppression, diabetes mellitus or obesity). Mean hospitalization time reached 10.9 ± 5.8 days while mean time of baricitinib administration was 9.2 ± 2.9 days. Regarding outcomes of hospitalizations, 12 patients (16.2%) needed to be transferred to the intensive care unit (ICU), with 6 of them finally succumbing to the disease. Administration of the drug led to a statistically significant drop of inflammatory markers as well as a statistically significant improvement of respiratory function as evaluated by ABGs. No serious adverse events were recorded.

**Conclusion:** The addition of oral baricitinib to the standard drug regimen of hospitalized patients with severe COVID-19 proved safe and efficacious in managing symptoms of the disease, leading to swift clinical complaint and laboratory profile improvements.

**Keywords:** severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); coronavirus disease 2019 (COVID-19); baricitinib; treatment; hospitalization

## Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that was first described in Wuhan, China, has affected the globe for the last three years [1]. The disease can manifest in various ways, ranging from a mild upper respiratory infection to severe acute manifestations from virtually every human body system and tissue, having led to hundreds of thousands of hospitalizations all over the globe [2-4]. Main clinical complaints of the disease consist of fever and upper respiratory system symptomatology, including cough, anosmia, ageusia and sore throat, while other mild clinical insults

include general fatigue and malaise, headache, exanthems and gastrointestinal irritation [5,6]. Risk factors for severe illness from SARS-CoV-2 are older age and male sex as well as a plethora of comorbidities, the most important being cardiovascular disease, chronic respiratory disease, diabetes mellitus and obesity, malignancy and immunosuppression [7,8].

Various studies have analyzed clinical images of patients presenting with COVID-19 in order to define groups of the population that need hospitalization as well as predict need for respiratory support and/or transfer to intensive care unit (ICU) settings [9], one of them being the COVID-19 severity index. The aforementioned algorithm not only can be used as a triage tool for use by emergency department (ED) staff to identify high-risk patients, but at the same time evaluate admitted patients in terms of possible need for oxygen supplementation and negative outcomes. Within the algorithm, a sum of clinical, laboratory and radiographic variables are evaluated to determine a numerical score for each patient [10]. After a multitude of drugs being tested in various healthcare settings as possible therapeutic measures to combat symptomatology of the disease, the antiretroviral remdesivir in combination with corticosteroids, most commonly in the form of dexamethasone, are the standard of care for hospitalized COVID-19 patients at present [11-13]. Given the lack of disease-specific drugs, though, drugs already approved for use in similar conditions are being tested to potentially alleviate symptoms of severe COVID-19 [14,15]. Since it has been proposed that severe forms of COVID-19 stem from a dysregulated inflammatory response due to excessive interleukin and cytokine production, it has been hypothesized that inhibition of the cytokine storm may modulate the immune response in order to alleviate symptoms of the disease [16].

Inhibition of the inflammatory cascade can be achieved via use of Janus kinase (JAK) inhibitors, traditionally used to treat chronic inflammatory disorders. Drugs of the aforementioned category were first recognized to bear efficiency in Rheumatoid Arthritis, and have since been trialled in a multitude of immune-mediated diseases, including psoriatic arthritis, irritable bowel disorder, dermatological disorders and even genetic disorders [17]. JAKs carry the name of the two-faced Roman God Janus and consist of a four-member group, namely JAK1, JAK2, JAK3 and TYK2, all of which carry their effects through interleukins and interferons [18]. Baricitinib blocks the interleukin-6 receptor and is a selective inhibitor of JAK 1 and 2, originally approved for the treatment of rheumatoid arthritis unresponsive or resistant to other traditionally used drugs for the disease [14]. A double-blind, randomized trial of combined remdesivir and baricitinib treatment showed shortened recovery times and faster clinical resolution in hospitalized COVID-19 patients as compared to patients receiving remdesivir plus a placebo drug [19]. Other studies have also offered value in the use of the drug as a therapeutic measure against severe COVID-19, especially in combination with corticosteroids for enhanced improvement of respiratory complaints. Apart from a profound positive effect in overall survival, administration of the drug was safe, without occurrence of relevant adverse events [20,21].

## Patients-Methods

### Study Design

Seventy-four patients with polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection and clinical symptomatology were recruited at the Emergency Department of the 401 General Military Hospital of Athens, Greece for the purposes of the current prospective cohort study. Patients were selected based on the severity of their presenting symptoms as evaluated by the COVID-19 severity index. More specifically, patients presenting with a moderate (3-5 points), high (6-7 points) or critical (8 or more points) clinical risk were recruited for inclusion in the study. The index guidelines were followed, according to which moderate clinical risk equals transfer to ward under frequent nursing surveillance, high clinical risk denotes intensive nursing surveillance as well as possible ICU admission, whereas critical clinical risk signifies immediate transfer to ICU [10]. Patients not eligible to receive baricitinib due to kidney disease [e-glomerular filtration rate (eGFR) <15 mL/min/1.73 $m^2$, patients on dialysis, patients with end-stage renal disease or with acute kidney injury] as well as severe hepatic disease (transaminases > 5 x upper normal limit) were excluded from the recruitment process. Pregnant women or patients younger than 18 years old were also not included in the recruitment process.

Selected patients were admitted to the hospital and placed on the usual therapeutic regimen of intravenous remdesivir (200 mg on day 1 followed by 100 mg daily on days 2-5) plus dexamethasone (6 mg daily) along with oral administration of 4 mg baricitinib daily. In cases of moderate (eGFR 30 to <60 mL/min/1.73 $m^2$) or severe (eGFR 15 to <30 mL/min/1.73 $m^2$) renal disease, the administered dose was adjusted to 2 mg or

1 mg respectively. The drug was administered until the day of discharge or for a total of fourteen days, whichever came first.

Oral informed consent for initiation of the therapeutic regimen was received from selected patients or the patients' proxies in case they were unable to provide consent by themselves due to severity of their medical condition or owing to language barriers. The study protocol was approved by the 401 General Military Hospital of Athens Ethics and Bioethics Committee.

## Data Collection

Demographic data as well as full personal and family medical history were received from the patients, with emphasis on risk factors for progression to severe disease. Risk factors included age ≥ 60 years, cardiovascular or cerebrovascular disease (coronary heart disease and/or stroke), chronic lung disease (chronic obstructive pulmonary disease, asthma, interstitial lung disease), diabetes mellitus (fasting plasma glucose ≥126 mg/dl and/or self-reported treatment with antidiabetic medication), obesity (body mass index ≥30 kg/m2) and immunosuppression (prescription for immunosuppressive drugs at the time of presentation) or malignancy (active neoplasm/hematologic malignancy or under palliative care at the time of presentation). Biochemical profiling was made upon patient presentation at the ED, including examinations that have been associated with progression to severe forms of the disease and higher mortality, namely C-reactive protein (CRP), D-dimers, lactate dehydrogonase (LDH), ferritin and procalcitonin (PCT) [22-25]. Arterial blood gases (ABGs) were also drawn for the estimation of respiratory function through oxygen saturation ($SaO_2$) and partial pressure of oxygen ($pO_2$) and carbon dioxide ($pCO_2$).

## Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Science (SPSS) data suite version 26.0 (SPSS, IBM, Armonk, US). Arithmetic means, extreme values and standard deviations were calculated for quantitative variables and frequencies of occurrence for quantitative values. Qualitative variables were compared between groups using the chi-square ($\chi 2$) test or Fisher exact method for small-sized samples. For the comparison of means, Welch's t-test was used. For the purposes of this study, a statistical importance level of $p = 0.05$ was set.

## Results

### Patient Demographics and Baseline Characteristics

Complete patient characteristics are depicted. A total of 74 patients were enrolled in the trial, with a mean age of 52.8 ± 17,2 years, 60 (81.1%) of them being male and 6 (8.1%) being fully vaccinated against SARS-CoV2 infection. Regarding coexisting underlying medical conditions, the most prevalent was age ≥ 60 years old (63.5%) followed by cardiovascular/cerebrovascular disease (41.9%), chronic lung disease (35.1%), diabetes mellitus (32.4%), obesity (25.7%) and immunosuppression or malignancy (24.3%). Patients presented at the ED after a mean of 6.7 ± 2.6 days of symptoms and were hospitalized for 10.9 ± 5,8 days.

Upon examination at the ED, selected patients presented on average abnormal values of all negative predictive parameters. More specifically, mean values for each adverse prognostic biochemical parameter can be found. Mean $SaO_2$ and $pO_2$ upon admission at the hospital were 91.3 ± 4.2 % and 55.7 ± 6.4 mm Hg, respectively.

## Patient Outcomes

Sixty-two patients (83.8%) were eventually discharge from the Infectious Disease Unit whereas twelve (16.2%) needed transfer to the ICU. No deaths occurred within the hospital ward, while six of the twelve ICU patients died (8.1% of all patients). Regarding individuals who were discharged from the Infectious Disease Unit, thirty-eight patients (61.3% of discharged patients) needed at-home supplemental oxygen administration (supplemental at-home oxygen was administered on the basis of a room air $SaO_2 < 92\%$ or $pO_2 < 60$ mmHg on discharge day). Adverse prognostic biochemical tests were drawn again on discharge day, with all of them presenting significant improvements with the exception of LDH.

## Discussion

Baricitinib, marketed under the name Olumiant, is a selective Janus kinase inhibitor immunomodulatory drug that has been approved for the treatment of active rheumatoid arthritis resistant or nonresponsive to other therapies. The drug maintains its efficacy in the context of autoimmune disease by shifting the imbalance between pro- and anti-inflammatory cytokines [26]. Baricitinib has the ability to interrupt

signaling pathways of inflammatory cytokines, including interleukins (IL-2, IL-6, IL-10), interferons (INF-γ) and growth factors (GM-CSF), all of which appear elevated in the cascade of inflammation caused by the SARS-CoV-2 infection [27,28]. Clinical trials including baricitinib have substantiated its role in the management of hospitalized patients with COVID-19, significantly reducing the risk of both death and invasive means of respiratory support [mechanical ventilation or extracorporeal membrane oxygenation (ECMO)], all while maintaining an excellent safety profile [29,30]. A number of different combination therapies including baricitinib for COVID-19 patients have been studied, including its administration alongside hydroxychloroquine [31], tocilizumab [32] and remdesivir plus dexamethasone [33].

While baricitinib is authorized for use in hospitalized adults and paediatric COVID-19 patients, its introduction as an emergency condition drug raised concerns, especially given the limited information regarding potential adverse risks arising from wider use of the drug. The most serious concern for a wider use of the drug would be side effects stemming from immunomodulation, such as upper respiratory tract infections or reactivation of chronic infections (tuberculosis, hepatitis B, Epstein-Barr virus, varicella-zoster virus, herpes simplex virus) in individuals treated with it. At the same time, the drug has been associated with thrombosis, hypersensitivity reactions, cardiovascular and liver toxicity, as well as gastrointestinal irritation [34]. It becomes easily apparent that a careful laboratory profiling including renal and liver function as well as complete blood count should be performed before introduction of baricitinib therapy.

While prompt identification and isolation of SARS-CoV-2 infected individuals remain the mainstay of the disease management, JAK inhibitors such as baricitinib have been suggested as emergency therapeutic measures against the disease. In conclusion, as long as a definite treatment strategy against COVID-19 remains elusive, baricitinib as a part of combination therapies maintains an important role in the pandemic battle.

## Conclusion

The addition of oral baricitinib to the therapeutic regimen of hospitalized patients with moderate to severe and critical COVID-19 along with the traditional antiviral drug and corticosteroids yields positive outcomes not only in terms of improved survival rates but also in terms of reduced hospitalization times and healthcare costs. Immunomodulation achieved by baricitinib alters the host's inflammatory cascade, alleviating IL- and IFN-mediated pathways and thus symptomatology of the disease. It becomes apparent that JAK inhibitors have a definite role in the COVID-19 therapeutic strategy against more severe forms of the disease. The excellent safety profile and suitability for co-administration with traditional COVID-19 regimens make baricitinib a viable treatment approach for the continuing battle against the SARS-CoV-2 pandemic.

## Declarations

### Author Contributions

Conceptualization: N.K.; methodology: I.G.; software: C.G.; validation: I.G.; formal analysis: N.K.; data curation: A.P.; writing-original draft preparation: N.K.; writing-review and editing, A.P, N.K.; visualization: I.G.; supervision: C.G. All authors read and approved the final version of the manuscript.

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### Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki.

### Informed Consent Statement

Oral informed consent for initiation of the therapeutic regimen was received from selected patients or the patients' proxies in case they were unable to provide consent by themselves due to severity of their medical condition or owing to language barriers.

### Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon request.

### Conflicts of Interest

The authors declare no conflict of interest.

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