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Evaluating the Efficacy and Safety of Baricitinib in Reducing COVID-19 Mortality: A Comprehensive Review of Clinical Evidence and Pharmacological Strategies

Authors:

Paulina Kwaśniewska, student

Faculty of Medicine, Medical University of Warsaw Żwirki i Wigury 61, 02-091 Warsaw, Poland

paulinakwasniewska12@gmail.com, https://orcid.org/0009-0009-4677-3387

Patryk Graczyk, student

Faculty of Medicine, Poznan University of Medical Sciences Aleksandra Fredry 10, 61-701 Poznań

patrykg1234@o2.pl, https://orcid.org/0009-0006-8963-6882

Anna Wilewska, student

Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

wilewskaanna2000@gmail.com, https://orcid.org/0009-0001-5136-4598

Kinga Borowiec, student

Faculty of Medicine, Medical University of Warsaw Żwirki i Wigury 61, 02-091 Warsaw, Poland

kingaborowiec07@gmail.com, https://orcid.org/0009-0000-5546-9787

Agnieszka Borowiec, MD
The Regional Specialist Hospital in Biala Podlaska Terebelska 57-65 21-500 Biala Podlaska, Poland
borowiec.agn@gmail.com, https://orcid.org/0000-0002-1428-170X
Julia Biernikiewicz, student
Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
biernikiewiczjulia@gmail.com, https://orcid.org/0009-0004-1192-9365
Konstanty Alabrudziński, student
School of Medicine Collegium Medicum University of Warmia and Mazury in Olsztyn, Oczapowskiego 2, 10-719 Olsztyn, Poland
konstanty.alabrudzinski@gmail.com, https://orcid.org/0009-0008-4729-0937
Milena Biernikiewicz, student
Faculty of Medicine, Wroclaw Medical University Wybrzeże Ludwika Pasteura 1, 50-367 Wroclaw, Poland
milenabiernikiewicz@gmail.com, https://orcid.org/0009-0006-7288-6965
Bartosz Pomirski, student
Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
bartosz.pomirski@gmail.com, https://orcid.org/0009-0004-4868-0073
Agata Pomirska, student
Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
pomirska.agata@gmail.com, https://orcid.org/0009-0009-5367-7123

Corresponding author:
Paulina Kwaśniewska
Medical University of Warsaw,
ul. Żwirki i Wigury 61,
02-091 Warszawa,
Poland
paulinakwasniewska12@gmail.com

Abstract

Introduction: COVID-19 manifests with symptoms ranging from mild to severe, including respiratory and cardiovascular complications. Severe cases are often marked by a cytokine storm, causing pulmonary damage and multi-organ dysfunction. Current treatments lack a specific antiviral, though several pharmacological options, including immunomodulatory and antiviral drugs, are under investigation.

Purpose: The purpose of this article is to provide an evaluation of the efficacy and safety of baricitinib, a JAK inhibitor, combined with standard care for hospitalized adults with COVID-19. By reviewing recent literature, it aims to assess baricitinib's effectiveness in improving patient outcomes.

Material and methods: A systematic review of clinical trials and case studies was conducted to analyze baricitinib's impact on COVID-19 mortality. Data includes treatment-emergent adverse events and patient outcomes in moderate to severe cases.

Discussion: Baricitinib has demonstrated potential in managing hyperinflammation in severe COVID-19 by inhibiting multiple proinflammatory cytokines and enhancing immune response. Clinical trials show that baricitinib, particularly in combination with corticosteroids, reduces mortality and serious infections compared to standard care alone. Due to potential adverse events, continuous monitoring of hematological and lipid levels is essential. These findings highlight baricitinib's dual role as an immunomodulatory and antiviral agent, suggesting its importance in treating severe COVID-19. Future research should focus on optimizing treatment regimens and further exploring the long-term implications of baricitinib therapy.

Keywords: COVID-19; baricitinib; JAK inhibitors; immunomodulatory therapy; SARS-CoV

Introduction:

Coronavirus disease 2019 (COVID-19) is an infectious illness caused by the SARS-CoV-2 virus, which is transmitted from person to person. The disease can present as asymptomatic or with mild symptoms, including loss of smell, fatigue, fever, cough, and dyspnea. In severe cases, it can lead to significant pulmonary and cardiac damage due to a dysregulated immune response, characterized by a sudden surge of proinflammatory mediators like cytokines and chemokines.[1,2]

COVID-19 is typically classified into four stages: the first stage involves upper respiratory tract infection; the second is marked by the onset of dyspnea and pneumonia; the third is defined by a worsening clinical state dominated by a cytokine storm and hyperinflammation; and the fourth results in either recovery or death. Currently, there is no specific treatment for SARS-CoV-2 infection. However, several pharmacological approaches are being explored, particularly for patients with moderate to severe disease. These include antiviral agents, anti-inflammatory/immunomodulatory drugs, low molecular weight heparins, convalescent plasma, and hyperimmune immunoglobulins.[1,2]

Research indicates that baricitinib effectively manages hyperinflammation during severe stages of illness. Its ability to inhibit specific inflammatory pathways makes it a valuable option in addressing the cytokine storm often seen in critical patients. By reducing inflammation, baricitinib may help improve outcomes and recovery times. Ongoing clinical trials are actively exploring its role in combination with other therapies to enhance treatment efficacy and address potential challenges in patient management.[1,2]

Purpose:

This review aims to assess the efficacy and safety of baricitinib, a selective Janus kinase (JAK) inhibitor, in combination with standard care for hospitalized adults with COVID-19. Through an analysis of recent literature and clinical cases, we aim to determine the effect of baricitinib on reducing mortality from COVID-19 and improving outcomes in infected patients.

Material and methods:

This study is a review of the literature focused on the role of baricitinib in reducing COVID-19 mortality, examining its efficacy and safety in combination with standard care for hospitalized patients. Additionally, it includes an analysis of relevant clinical cases and outcomes associated with baricitinib treatment in the context of severe COVID-19.

Mechanism of action:

Interleukin-6 (IL-6) receptor antagonists and JAK inhibitors are immune modulators that have shown positive effects on survival in patients with severe COVID-19. These treatments, when

used alongside corticosteroids, have contributed to improved outcomes for affected individuals [3,4,5]. IL-6 is known to be a key factor in the immune dysregulation seen in COVID-19 pneumonia. Higher levels of this cytokine have been linked to greater disease severity [6].

Tocilizumab is a monoclonal antibody that competitively inhibits IL-6 from binding to its receptor. This action effectively blocks IL-6 signaling and helps to reduce inflammation [7]. Baricitinib exhibits broader anti-cytokine activity compared to tocilizumab. In vitro studies have demonstrated that it reduces the SARS-CoV-2-specific response mediated by several cytokines, including interferon gamma (IFN-γ), interleukin 17 (IL-17), interleukin 1β (IL-1β), interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), interleukin 4 (IL-4), interleukin 13 (IL-13), interleukin 1ra (IL-1ra), interleukin 10 (IL-10), granulocyte-macrophage colony-stimulating factor (GM-CSF), fibroblast growth factors (FGF), Interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1) , and macrophage inflammatory protein 1β (MIP-1β). Additionally, baricitinib enhances overall immune response by promoting a rapid recovery of circulating T- and B-cell frequencies [10]. Furthermore, baricitinib may function as a potential antiviral agent by inhibiting clathrin-mediated endocytosis, which is the process that allows SARS-CoV-2 to enter cells [11].

Severe COVID-19 is characterized by a dysregulated immune response to infection with SARS-CoV-2. This imbalance results in cytokine dysregulation and significant immuno-inflammatory disruptions, thus causing lung damage and multi-organ dysfunction [12].

In this context, therapeutic strategies involve a combination of antiviral and primarily immunomodulatory therapies. However, there is currently no consensus on the best composition of these treatment regimens [13,14] and mortality remains unacceptably high [15]. Dexamethasone is one of the immune modulators that has been shown to reduce mortality. It is currently regarded as the primary treatment for severe and critical COVID-19 cases [13,14,16]. Recently, Janus kinase (JAK) inhibitors have been linked to a reduced risk of mortality. These findings suggest their potential importance in SARS-CoV-2 treatment [4,17,18].

Baricitinib is a selective inhibitor of JAK1 and JAK2, primarily used for treating rheumatoid arthritis. Recently, evidence has emerged indicating its efficacy against COVID-19, as documented by studies such as those by Favalli et al. (2020) and Jorgensen et al. (2020). This drug works by transiently and reversibly inhibiting the production of various proinflammatory cytokines, which play a significant role in the dysregulated immune response often seen in severe COVID-19 cases, including the cytokine storm phenomenon. In addition to its

immunomodulatory effects, baricitinib also binds to AP2-associated protein kinase 1 (AAK1). This protein is a critical regulator of clathrin-mediated endocytosis, a process that viruses, including SARS-CoV-2, utilize to enter host cells. By inhibiting AAK1, baricitinib may reduce the virus's ability to infect target cells, thus providing an antiviral effect alongside its immunomodulatory action. Moreover, the convenience of oral administration and the minimal interactions with cytochrome P450 (CYP) enzymes enhance baricitinib's appeal as a treatment option. These characteristics position it as one of the most promising therapies currently available for managing not only COVID-19 but also various chronic inflammatory diseases. Therefore, baricitinib represents a dual mechanism of action, functioning effectively as both an immunomodulatory and antiviral agent in the fight against COVID-19 [19,20].

Clinical trials:

The safety of baricitinib in hospitalized COVID-19 patients has been assessed in three clinical trials. Most of these patients required oxygen supplementation. The studies reported the proportions of patients who experienced treatment-emergent adverse events (TEAEs). [3,4,21]. In the study conducted by Marconi et al. [4], adults hospitalized with laboratory-confirmed SARS-CoV-2 infection, along with evidence of pneumonia or symptomatic COVID-19 and at least one elevated inflammatory marker, were given either baricitinib or a placebo (83%). Most participants (83%) received treatment for 14 days in addition to standard care. Following a protocol amendment, the requirement for baseline oxygen support was introduced, indicated by a National Institute of Allergy and Infectious Disease Ordinal Scale (NIAID-OS) score of 5 or 6. Participants were excluded if they required invasive mechanical ventilation (IMV; NIAID-OS score 7) at the time of study entry, were receiving immunosuppressants, or had previously received convalescent plasma or intravenous immunoglobulin for COVID-19 [4].

In the study by Kalil et al. [3], adults with laboratory-confirmed SARS-CoV-2 infection received either baricitinib or a placebo, both in combination with remdesivir. This treatment lasted for 14 days or until the patients were discharged from the hospital, which occurred in 98% of cases. At the time of enrollment, participants met at least one of the following criteria indicating lower respiratory tract infection: radiographic infiltrates observed on imaging, peripheral oxygen saturation of 94% or less on room air, or the need for supplemental oxygen, mechanical ventilation, or ExtraCorporeal Membrane Oxygenation (ECMO). Notably, 11% of the patients had an NIAID-OS score of 7 [3].

In the study by Ely et al. [21], adults hospitalized with laboratory-confirmed SARS-CoV-2 infection were assessed. At the time of study entry and randomization, 3% of participants

were receiving IMV or ECMO. These patients showed evidence of pneumonia or exhibited clinical symptoms of COVID-19. Additionally, they had at least one elevated inflammatory marker indicating a risk of disease progression. Participants were randomly assigned to receive either baricitinib or a placebo, both in combination with standard care, for a median duration of 11 and 12 days, respectively [21].

In a study involving 1,502 hospitalized patients with severe COVID-19 infection and multiple comorbidities, the risk of serious non-COVID-19 infections was assessed. Among these patients, 33% were obese, 30% had diabetes mellitus, and nearly half had hypertension. Additionally, almost 90% required some form of supplemental oxygen at study entry. The rates of serious infections were similar for those receiving baricitinib at 4 mg (8.5%) and those receiving a placebo (9.8%), both in conjunction with standard care, which included systemic glucocorticoids and, in some cases, remdesivir. Notably, 91% of patients who experienced a serious infection while on baricitinib and 85% of those on placebo were also receiving glucocorticoids [4]. In a study involving 99 patients with more severe COVID-19 infection, where participants were using invasive mechanical ventilation (IMV) or ECMO at baseline, the prevalence of comorbidities was similar between groups. Among these patients, serious infections occurred in 44% of those receiving baricitinib and in 53% of those receiving a placebo [21].

In another trial involving 1,033 hospitalized patients with COVID-19, specific serious infections were reported less frequently in those treated with baricitinib plus remdesivir compared to those receiving placebo plus remdesivir. The rates were as follows: septic shock occurred in 0.8% of the baricitinib group versus 1.6% in the placebo group; pneumonia was seen in 0.4% of patients on baricitinib compared to 1.6% on placebo; and sepsis was reported in 0.2% of the baricitinib group versus 1.0% in the placebo group. Additionally, the use of glucocorticoids was once again linked to a higher risk of infection. [3].

Side effects:

Potential side effects of baricitinib, such as secondary infections and venous thrombosis, are associated with alterations in inflammatory and coagulation processes. However, these side effects have been infrequent in patients with rheumatoid arthritis, which is the approved indication for the drug. While continuous inhibition of JAK2 might typically lead to anemia and decreased white blood cell and platelet counts, the effects of baricitinib are different. Since baricitinib reversibly inhibits JAK2 signaling for only part of the dosing cycle at approved doses, changes in hematological parameters tend to be small to moderate and often temporary. Despite this, product guidelines recommend monitoring absolute neutrophil and

lymphocyte counts, as well as hemoglobin levels, before starting baricitinib treatment. Ongoing monitoring should continue according to standard patient management practices, and treatment should not be started or interrupted in patients with low blood cell counts [23,26].

The increases in lipid levels, especially cholesterol and triglycerides, noted during baricitinib treatment may not indicate a heightened cardiovascular risk. This is in contrast to what is typically seen in individuals with high lipid levels who lack significant inflammation. Instead, these changes may be a predictable response to the reduction of inflammation associated with the treatment [24,27]. In patients undergoing treatment with baricitinib, lipid levels should be monitored 12 weeks after starting the medication. After this initial assessment, monitoring should continue based on international clinical guidelines for hyperlipidemia. Patients should be managed in accordance with these guidelines moving forward [23,28,29]. In a post-marketing study conducted in Japan, both anemia and hyperlipidemia were reported infrequently. Specifically, these conditions occurred in just 1% of the 3,445 patients with rheumatoid arthritis (RA) involved in the study [25,30,31].

Summary:

Baricitinib is a JAK inhibitor initially used for rheumatoid arthritis that has shown promise in treating severe COVID-19. It works by reducing hyperinflammation and may also inhibit the entry of SARS-CoV-2 into cells, thereby functioning as both an immunomodulatory and antiviral agent. Clinical trials indicate that baricitinib, often administered alongside standard care, significantly improves outcomes in hospitalized patients, with comparable rates of serious infections to those receiving placebo. It has been particularly effective in patients exhibiting high levels of inflammatory markers. Despite some potential side effects, including secondary infections and elevated lipid levels, these have generally been manageable and infrequent. Monitoring of hematological parameters and lipid levels is recommended during treatment. Overall, baricitinib represents a dual mechanism approach that could enhance COVID-19 management strategies. In conclusion, its efficacy and safety profile make it a valuable option for clinicians treating severe COVID-19, warranting further exploration and application in clinical settings.

Discussion:

The findings from this review underscore the significant role of baricitinib, a selective Janus kinase (JAK) inhibitor, in the management of severe COVID-19. COVID-19 presents a spectrum of clinical manifestations, ranging from mild to severe, with the latter often characterized by a hyperinflammatory response known as a cytokine storm. This hyperinflammation results in substantial pulmonary and systemic complications, necessitating

the exploration of innovative treatments that can address both the viral infection and the associated immune dysregulation.

Baricitinib functions through a dual mechanism of action: it not only inhibits the signaling pathways of multiple proinflammatory cytokines but also exhibits potential antiviral properties. By targeting JAK1 and JAK2, baricitinib effectively reduces the production of cytokines such as interleukin-6 (IL-6), which is pivotal in driving the inflammatory response observed in severe COVID-19 cases. Clinical trials have consistently shown that the addition of baricitinib to standard care, particularly corticosteroids, is associated with a significant reduction in mortality rates and an improvement in clinical outcomes. For instance, studies by Kalil et al. and Marconi et al. reported that patients receiving baricitinib alongside corticosteroids demonstrated a lower risk of progression to invasive mechanical ventilation and a higher likelihood of recovery compared to those receiving standard care alone.

The evidence suggesting that baricitinib does not significantly increase the risk of serious infections compared to placebo is particularly noteworthy. This finding is crucial, as secondary infections are a common concern in severely ill patients, often complicating treatment and adversely affecting outcomes. In the trials reviewed, the rates of treatment-emergent adverse events (TEAEs) associated with baricitinib remained comparable to those observed in the placebo groups. This suggests that the therapeutic benefits of baricitinib, especially in patients with elevated inflammatory markers, may outweigh the potential risks, making it a compelling option in the management of severe COVID-19.

Additionally, baricitinib's mechanism of inhibiting clathrin-mediated endocytosis further enhances its profile as an antiviral agent. By interfering with the cellular entry of SARS-CoV-2, baricitinib not only mitigates the immune response but also directly affects the virus's ability to infect host cells. This dual action—reducing hyperinflammation while simultaneously targeting viral entry—highlights the importance of a multimodal treatment approach that can tackle the complex pathophysiology of COVID-19 more effectively.

Despite the promising results associated with baricitinib treatment, careful consideration must be given to its potential side effects. Changes in hematological parameters, such as neutrophil and lymphocyte counts, and elevations in lipid levels have been observed in patients receiving baricitinib. While these alterations are typically mild and manageable, they necessitate regular monitoring to ensure patient safety and to mitigate any potential complications. The recommendation to monitor lipid levels and blood cell counts reflects a prudent approach to patient management, especially in populations with pre-existing comorbidities such as obesity, diabetes, and cardiovascular disease, which are prevalent in severe COVID-19 cases.

Moreover, the variability in patient responses to baricitinib therapy highlights the need for further research into optimizing treatment regimens. Understanding which patient demographics—based on factors such as age, sex, comorbidities, and the severity of disease—are most likely to benefit from baricitinib will be critical in refining treatment protocols.

Conclusion:

In conclusion, baricitinib emerges as a promising therapeutic option for the treatment of severe COVID-19, demonstrating both efficacy and a manageable safety profile when administered alongside standard care. Its dual mechanism of action—as an immunomodulatory agent and a potential antiviral—addresses the multifaceted challenges posed by COVID-19, making it a valuable addition to the treatment arsenal. The evidence from clinical trials indicates that baricitinib significantly improves outcomes in hospitalized patients, with a noteworthy reduction in mortality and serious complications compared to standard care alone.

As the understanding of COVID-19 evolves, further research is essential to refine treatment protocols, assess long-term safety and efficacy, and explore the full potential of baricitinib in diverse patient populations. Investigating optimal dosing strategies and identifying specific biomarkers that predict response to therapy will be crucial in enhancing the personalized treatment of severe COVID-19. Integrating baricitinib into clinical management strategies could lead to substantial improvements in survival rates and overall patient quality of life, providing a much-needed advancement in the fight against COVID-19.

DISCLOSURE

Author's contribution

Conceptualizatio: Paulina Kwaśniewska, Patryk Graczyk;

Methodolog: Paulina Kwaśniewska, Kinga Borowiec;

Software: Paulina Kwaśniewska, Anna Wilewska;

Check, Bartosz Pomirski, Julia Biernikiewicz, Agnieszka Borowiec;

Formal analysis: Paulina Kwaśniewska, Konstanty Alabrudziński, Milena Biernikiewicz;

Investigation: Paulina Kwaśniewska, Patryk Graczyk;

Resources: Konstanty Alabrudziński, Milena Biernikiewicz;

Data curation: Paulina Kwaśniewska, Agnieszka Borowiec;

Writing - rough preparation: Paulina Kwaśniewska, Anna Wilewska;

Writing - review and editing: Konstanty Alabrudziński;

Supervision: Kinga Borowiec, Julia Biernikiewicz;

Project administration: Paulina Kwaśniewska, Anna Wilewska;

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