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Baricitinib for the treatment of COVID-19: A narrative review

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ABSTRACT

ABSTRAK: Baricitinib, one of the therapies for rheumatoid arthritis, is a JAK inhibitor. WHO recommended therapy with the combination of baricitinib and corticosteroids in COVID-19 patients with severe or critical conditions. Effectivity and safety assessment of Baricitinib use were carried out by reviewing the literature published between December 2019 – February 2022, and showed that the use of Baricitinib in COVID-19 patients resulted in an improvement of lung function, improvement of oxygen saturation, higher recovery rate, and lower mortality, with similar adverse event incidence. A loading dose or a higher dose can be recommended for patient with caution and consideration of higher possibility in the incidence of adverse events

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1. PENDAHULUAN

The first case of atypical pneumonia was reported on December 30th 2019, and the World Health Organization (WHO) determined that SARS-CoV-2 caused the coronavirus disease 2019 (COVID-19) (Cevik dkk., 2020; Liu dkk., 2020, p. 19). This disease has been declared a pandemic since the virus has become a global threat, growing rapidly and spreading to other countries (Liu dkk., 2020).

Since being declared a global pandemic, SARS-CoV-2 has spread to 223 nations with more than 281 cases and 5.4 million deaths worldwide. Omicron, known as the latest variant of SARS-CoV-2 has been reported in 76 countries. According to WHO, the fatality of COVID-19 cases is estimated at around 2.2% but this can be influenced by age, previous conditions, disease severity and varies widely between countries (Ahmad dkk., 2021).

Most COVID-19 patients experience cough, sore throat, asphyxiate, fever, dizziness, arthralgia, muscle aches, nasal congestion, and fatigue (Borges do Nascimento dkk., 2020). The most commonly found symptom is fever which is considered essential (Baj dkk., 2020). Another commonly found symptom in these patients is anosmia. The occurrence of anosmia is related to the presence of fever. This olfactory dysfunction persists in 56% of recovered patients from COVID-19(Lechien dkk., 2020).

Easy transmission of SARS-CoV-2 caused the rapid spread of COVID-19, and established it as a global issue. The active virus can spread through small droplets that are discharged when an infected person coughs. In one cough, it is estimated that 3000 droplets will be released which, if they contain a virus, can transmit disease to others. The COVID-19 virus can also be transmitted indirectly via the surfaces of objects like seats, elevator surfaces, door knobs that may be contaminated with patient secretions from the nasal cavity, oral cavity, or conjunctiva. Susceptible individuals can become infected by touching contaminated surfaces and touching the nostrils or rubbing the eyes (El-Wahab dkk., 2021).

SARS-CoV-2 can enter through the oral cavity and respiratory tract because hands, food, and water are contaminated by fecal content. SARS-CoV-2 is also transmitted via the ocular fluids in COVID-19 patients(El-Wahab dkk., 2021). The explanation of the transmission route from COVID-19 re-emphasized the importance of implementing health protocols such as wearing masks, washing hands frequently, and implementing physical distancing.

Baricitinib which is one of the therapies for rheumatoid arthritis is a JAK (Janus Kinase) inhibitor. In severe or critical COVID-19 patients, WHO recommended additional therapy with baricitinib and corticosteroids (Kmietowicz, 2022). Baricitinib is an agent with therapeutic potential in severe acute respiratory syndrome frequently observed in COVID-19 patients, and is affiliated with increased oxygenation and decreased inflammatory markers (Kalil dkk., 2021). Several mechanisms of action of Baricitinib contribute to the therapy of COVID-19. Thus, we will discuss the effectiveness and safety obaricitinib therapy in COVID-19 patients in clinical trials.

2. METHOD

We employed a few databases, including Google scholar, JAMA, PubMed, and ScienceDirect to collect the data. The keywords used included “COVID-19”, “SARS-CoV-2”, “baricitinib”, “mechanism action”, “effectivity”, “safety”, “clinical trials”. The inclusion parameters used were a) baricitinib given in the clinical trial and/or as a therapeutic treatment of COVID-19, b) Literature issued in December 2019 - January 2022 period.

3. RESULT AND DISCUSSION

The COVID-19 pandemic occurred due to the SARS-CoV-2, which began December 2019 with a report of a novel viral pneumonia case from the city of Wuhan with an unknown cause. The commonly found symptoms of the patients were fever, dry cough, dyspnea, and malaise, and later it was diagnosed as viral pneumonia (Liu dkk., 2020). COVID-19 was referred by WHO on February 12th, 2020, and the virus was concluded to be SARS-CoV-2 according to the International Committee on Taxonomy of Viruses based on the virus's taxonomy and phylogeny(Liu dkk., 2020; Zhou dkk., 2020). This disease was declared as a pandemic on March 11th 2020 by WHO since this virus has grown and spread rapidly to other countries around the world and becomes a global threat(Liu dkk., 2020). The median incubation period and the onset symptoms of SARS-CoV-2 infection consecutively are 5.1 days and 11.5 days (Lauer dkk., 2020).

Several risk factors can affect clinical conditions in COVID-19 patients including advanced age (>65 years old), cardiovascular diseases, respiratory diseases, diabetes, obesity, and hypertension. Fatal complications can occur in COVID-19 patients, such as pneumonia, sepsis, respiratory failure type 1, heart failure, septic shock, AKI, and acute cardiac injury. The most common complication that occurs in COVID-19 patients is acute respiratory distress syndrome(T. Chen dkk., 2020; Fu dkk., 2020; Gandhi dkk., 2020; Helmy dkk., 2020; Li dkk., 2020).

Clinical manifestations on the patients based on the severity can be classified into 5 stages; patients without any symptoms, patients with mild symptoms, patients with moderate symptoms, patients with severe symptoms, and critical patients. 80% of the patients are either asymptomatic or have a mild or moderate case-fatality rate. In the asymptomatic case, the patient did not experience specific or non-specific symptoms but was infected with SARS-CoV-2 with positive tests as the indicator. In mild case-fatality rates, patients generally experience typical symptoms, like fever, runny nose, non-producable cough, sore throat, malaise, myalgia, or loss of smell. Patients can also experience atypical symptoms, like nauseous vomit, abdominal pain, and diarrhea. In a moderate case-fatality rate, patients generally experience symptoms of pneumonia, prolonged fever with a body temperature of more than 37.8℃, and dry cough (Fu dkk., 2020; Nishiura dkk., 2020). The estimated prevalence of COVID-19 patients with severe fatalities is 15%. Clinical manifestations in these patients were dyspnea, hypoxia, diarrhea, vomiting, and nausea. For patients with a critical severity of the disease, it has an estimated prevalence of 5%. Clinical manifestations that occur in patients with critical clinical conditions are the severe difficulty of breathing, asphyxiate, chest pain, and movement impairment. Of the five severity of clinical manifestations, the majority of the severity in COVID-19 patients is moderate and asymptomatic (Fu dkk., 2020; Nishiura dkk., 2020).

COVID-19 patients generally have laboratory findings such as increased serum levels of C-reactive protein concentration, erythrocyte counts, myohemoglobin level, liver enzymes concentration, and increased muscle enzymes concentration(Helmy dkk., 2020). The severity of clinical conditions also affects laboratory findings. Higher levels of leukocyte count, D-dimer, procalcitonin, and lymphocytopenia were found in most patients with severe COVID-19 cases (Helmy dkk., 2020; Zhang dkk., 2020). In addition, laboratory results that indicate an increased risk are both higher alanine and aspartate aminotransferase, higher hydroxybutyrate dehydrogenase activity, and higher lactate dehydrogenase activity(G. Zhang dkk., 2020). COVID-19 patients may also have elevated interleukin 10, 6, 1, 2R as well as tumor necrosis factor alpha (TNF-α), and the level of these parameters might exceed the upper limit(G. Chen dkk., 2020; Mao dkk., 2020; Wang dkk., 2020).

3.1 Mechanism and effectivity of baricitinib

Baricitinib which is one of the therapies for rheumatoid arthritis is a JAK inhibitor and considered as potential medication for COVID-19 patients(Thoms dkk., 2022). Infections caused by the COVID-19 virus lead to excessive cytokine and chemokine activity with ARDS, which is one of the causes of death of COVID-19 patients. ARDS is highly associated with interleukin-6 (IL-6) as a predictor of mortality. It is also known that patients with moderate to severe symptoms do not have sufficient amounts of anti-viral cytokines. From this explanation, a restriction of the inflammatory response and improved viral clearance is needed as a therapy for COVID-19 (Stebbing dkk., 2020).

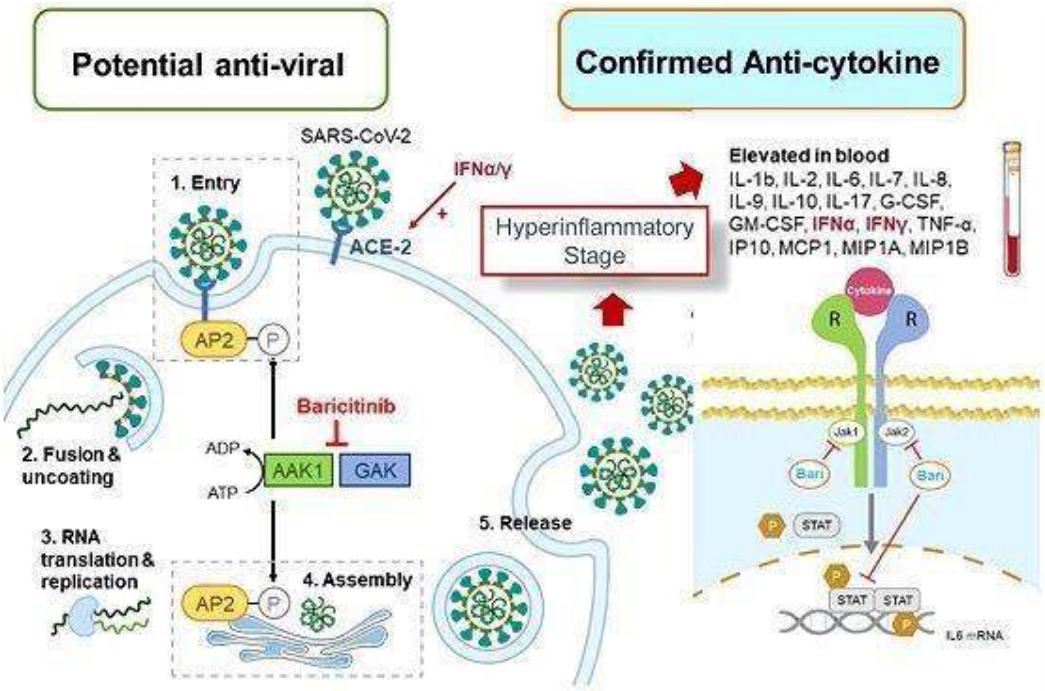

Figure 1. The mechanism of potential anti-viral effects of baricitinib (Stebbing dkk., 2020).

Baricitinib has an anti-cytokine activity which is hypothesized to reduce the inflammatory cascade response triggered by infection by the COVID-19 virus (Thoms dkk., 2022). Under normal conditions, JAK proteins play a role in activating the STAT protein which will canalize the nuclear signaling to express the gene transcription (Hempel dkk., 2022). Baricitinib reduces levels of the inflammatory genes IL-2,6,10, as well as IFN-γ, and also granulocyte macrophage colony stimulating factor (GM-CSF) in the hyper-inflammatory stage of the COVID-19 disease by inhibiting the intracellular cytokine signaling pathway in the T-Cell cytolytic response (Stebbing dkk., 2020).

Baricitinib also has a potential anti-viral effect by hindering the AP2 kinase 1 (AAK1), BMP-2-inducible kinase (BIKE), and Cyclin G-associated kinase (GAK), with a dose of baricitinib 2 mg and 4 mg once a day. AAK1 can be called a clathrin-mediated regulator of SARS-CoV-2 endocytosis (Stebbing dkk., 2020; Thoms dkk., 2022).

3.2 Potential role of baricitinib in COVID-19 treatment

Baricitinib originally indicated for severe rheumatoid arthritis (RA), but baricitinib has shown efficacy in controlling the inflammatory response that occurs in other diseases (Assadiasl dkk., 2021), including COVID-19, where baricitinib has shown protective and curative effects in COVID-19 patients.

3.2.1 Inhibition of Viral Transmission

It has known that the receptor that plays an important role in the occurrence of respiratory syndrome is angiotensin-converting enzyme 2 receptor (ACE-2), which is a cell-surface protein found in blood vessels, kidneys, and alveolar AT-2 epithelial cells. ACE-2 found in lungs is prone to viral infection and may lead to viral reproduction and transmission via endocytosis. Several promoters of endocytosis are AAK-1 and GAK, which increase viral assembly in the intracellular matrix. Baricitinib itself has an inhibitory mechanism of AAK-1 and GAK on alveolar type 2 endothelial cells, which will

prevent viral entrance, endocytosis, and reduce intracellular viral particle assembly(Assadiasl dkk., 2021; Praveen dkk., 2020; Richardson dkk., 2020).

3.2.2 As an anti-inflammatory

Baricitinib is known to be able to inhibit cytokines and growth factors so that the differentiation process of many immune cells will also be inhibited, both innate and adaptive immunity(Assadiasl dkk., 2021), which has a profitable effect on COVID-19 infection by inhibiting excessive inflammatory responses (Richardson dkk., 2020) Supported by in vitro studies which showed that both addition and monotherapy of baricitinib significantly decreased the IFN-γ response ($p<0.0001$) and significantly decreased specific responses mediated by IL-1β,1ra,10,6,4,13, and 17, as well as TNF-α, GM-CSF, FGF, MCP-1 and 1β ($p<0.02$). Those responses were seen mostly in patients with mild to moderate infection and COVID-19 patients with lymphocyte concentration at 1 × 103/ l (Petrone dkk., 2021). In vivo tests on animals with COVID-19 using baricitinib also showed reduced inflammation in lung tissue, decreased macrophage, and neutrophil recruitment compared to the control group (Hoang dkk., 2021).

3.3 Recommendation and clinical trial of baricitinib in COVID-19

Baricitinib therapy was associated with a good recovery rate, reduced mortality, and a good safety profile. The WHO 2022 guidelines recommend a dose of 4 mg daily orally in adults with a normal glomerular filtration rate for 14 days or until the patient becomes outpatient. In patients with decreased renal function (30<GFR≤60 mL/min/1.73 m2), the reduced dose could be recommended with 2 mg per day (Titanji dkk., 2021; WHO, 2022).

The addition of baricitinib in COVID-19 patients to standard treatment of antiviral therapy resulted in a beneficial outcome for the patient. Various end-point outcomes were used in clinical trials proving the effectivity of baricitinib, including improvement of lung function, oxygen saturation, recovery rate, and mortality (Bronte dkk., 2020; Chen dkk., 2021; Hasan dkk., 2021; Kalil dkk., 2021; Marconi dkk., 2021; Rodriguez-Garcia dkk., 2021). A phase 3 clinical trial examined both the effectiveness and the safety of baricitinib by comparing patients given baricitinib 4 mg daily vs. placebo. Studies have shown that patients given baricitinib had lower mortality (8%, n=62) than placebo (13%, n=100) (95% CI, 0.41–0.78)(Marconi dkk., 2021). The effectivity of baricitinib combined with corticosteroid was assessed and resulted in a greater improvement of SpO2/FiO2 (95% CI: 22-77, p<0,001), additional oxygen requirement at discharge (25,8% vs 62%; 95% CI, p<0,001) and after 1 month (12,9% vs 28%; 95% CI, p<0,001), compared with no addition of baricitinib (Rodriguez-Garcia dkk., 2021).

The study by Chen dkk. (2021) stated that the mortality rate between patients receiving JAK inhibitors, including ruxolitinib, baricitinib, and tofacitinib, compared with controls decreased significantly (4.1% vs. 7%, 95% CI, 1.09-0.92). Patients with JAK inhibitors were also associated with reduced healing time compared to controls (MD, -2.84; -5.56 to -0.12). Kalil dkk. (2021) compared the effectiveness of baricitinib with control and resulted in a median recuperate time of 7 days (95% CI, 6-8) compared with control of 8 days (95% CI, 7-9). Patients with combination therapy with baricitinib had a shorter recuperate time compared with control (10 vs 18 days) and lower mortality in 28 days (5,1% vs 7,8%). The improvement in COVID-19 patients treated with Baricitib was associated with a significant deflation of mediators involved in inflammation cascade, including IL-6, 1β, as well as TNF-α (Bronte dkk., 2020).

Table 1. Baricitinib Effectivity in COVID-19 Patients Based on Various Studies.

Reference	Published Year	Study Type	Result
Kalil dkk., 2021	2021	RCT	515 patients were assigned for a combination of remdesivir and baricitinib, and 518 patients as the control group. Median of days recovery : Combination 7 days vs Control 8 days Median of days recovery in patients with additional oxygen support : Combination 10 days vs Control 18 days
Marconi dkk., 2021	2021	RCT	1.525 patients were divided, with 764 patients as the therapy group and the remaining as the control. Baricitinib group had a 28-day mortality of 8% and 13% for the control group, the 60-days mortality for the Baricitinib group was 10% and 15% for the control. Serious adverse events for the baricitinib group was observed in 15% patients and 18% for the control group, with a similar percentage for both serious infection, which was 9% for baricitinib and 10% for control; and venous thromboembolic event, which was 3% for baricitinib and 3% for control.
Rodriguez-Garcia dkk., 2021	2021	Clinical Trial	62 patients were assigned to the combination of baricitinib and corticosteroid group, 50 patients in the corticosteroid group. Patients with baricitinib had a greater improvement of SpO2/FiO2, requirement for additional oxygen at both when the patients discharged and 1 month later.
Bronte dkk., 2020	2020	Clinical Trial	20 patients were treated with baricitinib as the sample group, 4 mg per 12 hours for 2 days, continued by 4 mg per 24 hours for 7 days; and 56 patients were treated as the control group. Patients showed a lower concentration of IL-6 and 1β, as well as the TNF-α; increased antibody production against COVID-19; a

			reduction supplemental oxygen requirement, and an increase of PaO2/FiO2 ratio.
Hasan dkk., 2020	2020	Clinical Trial	17 patients assigned to a control group received daily 4 mg baricitinib, and 20 patients assigned to a loading group, received 8 mg of baricitinib as a single dose and continued by 4 mg daily. Median days to reach SpO2 ≥ 95%, median days to reach normal breathing function, intensive aid requirement, and ventilation requirement, were less in the loading dose category, compared with the non-loading dose.
Hasan dkk., 2021	2021	Clinical Trial	116 patients were given the usual dose of baricitinib 4 mg per day, and 122 patients received 8 mg per day. Stabilization of oxygen saturation was found earlier in the higher dose group (8 mg per day). The study found a reduction of intensive care and intubation requirement in the 8 mg/day group. Mortality at 30-days and rehospitalization at 60-days were also reduced in the 8 mg/day group.

Contrary to the concern of adverse event incidence with the use of baricitinib, research showed that the adverse event was similar and even lower, than the placebo (Chen dkk., 2021; Kalil dkk., 2021; Marconi dkk., 2021). Marconi dkk.(Marconi dkk., 2021) showed that the relatively serious side effects were similar between baricitinib (15%) and placebo (18%). The incidence of serious infection (9% vs 10%) and venous thromboembolism (3% vs 3%) between Baricitinib and placebo was also similar. Similar to research by Marconi dkk. (2021), Chen dkk.(2021) stated that there is no significant difference in side effects both minor or serious, between the JAK Inhibitor and the control. Kalil dkk.(2021) found a lower frequency of serious adverse effect (16% vs 21%), and a lower percentage of new infections (5,9% vs 11,2%) in the baricitinib.

In general, the administration of baricitinib 4 mg once a day may result in a patient benefit, but the use of either a higher dose or a loading dose resulted in a better outcome. Research by Hasan dkk. (2020) stated that the addition of a loading dose of 8 mg continued by 4 mg daily resulted in faster normalization of oxygen saturation and faster return of lung function (29.4%/10%, $p<0.05$; 11.8%/5 %, $p>0.05$) compared with no loading dose.

However, a more distinct benefit was seen in the use of a higher dose with 8 mg per day, which was seen in a study by Hasan dkk. (2021). The study found the dose of 8 mg per day stabilized oxygen saturation more rapidly (5 vs 8, $p<0.05$), reduced the need for critical care and intubation (17.2 %/9%, $p<0.05$; 11.2%/4.1%, $p>0.05$), and reduced mortality and re-hospitalization (6% /.33%,$p<0.01$;1.9%/7.6%, $p>0.05$) compared with patients receiving 4 mg daily. But it should be noted that with the use of higher doses, the risk of patients experiencing adverse events will also be higher. The study found that patients taking 8 mg daily were associated with significantly more thrombocytosis and mouth sores than patients taking 4 mg daily (9.8%/2.6% and 2.4%/0.8%), although there were no occurrences of opportunistic infections, both bacterial and fungal due to the use of baricitinib after 14 days of use.

4. CONCLUSION

The addition of baricitinib in COVID-19 patients to standard treatment of antiviral therapy resulted in a beneficial outcome for the patients, including improvement of lung function, oxygen saturation, recovery rate, and mortality. Contrary to the concern of adverse event incidence with the use of baricitinib, research showed that the adverse event was similar and even lower than the placebo. In general, the administration of baricitinib 4 mg daily may result in a patient benefit, but the use of either a higher dose or a loading dose resulted in a better outcome. Based on the result of this review, we conclude baricitinib is both effective and safe for COVID-19 patients. A loading dose or a higher dose can be recommended for patients with caution and consideration of higher possibility in the incidence of adverse events.

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