



A review study of targeting of AAK1 and JAK1/2 using baricitinib in COVID-19 infected human cells

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ABSTRACT

The outbreak of a current public health coronavirus 2019 disease is a causative agent of a serious acute respiratory syndrome and even death. COVID-19 has exposed to multi-suggested pharmaceutical agents to control this global disease. Baricitinib, a well-known antirheumatic agent, was one of them. This article reviews the likely pros and cons of baricitinib in attenuation of COVID-19 based on the mechanism of drug action as well as its pharmacokinetics. The inhibitory effect of baricitinib on receptor mediated endocytosis promoter, AKK1, and on JAK-STAT signaling pathway is beneficial in inhibition of both viral assembling and inflammation. Also, its pharmacokinetic has encouraged the physicians toward the drug selection for COVID-19 treatment. On the other hand, most of baricitinib side effects are dose-dependent. In conclusion, targeting of AAK1 and JAK1/2 using baricitinib has predicted to be potential and effective with minimal side effects in management

COVID-19 infected patients for a short therapeutic dosing period. Laboratory monitoring should be considered for some parameters. However, experimental trials are mandatory for a long-term treatment with a lower dose of baricitinib to evaluate its effectiveness and safety in patients with moderate COVID-19 infection.

Keywords: Adaptor-associated protein kinase-1; baricitinib; COVID-19; cytokines; Janus Kinases.

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INTRODUCTION

The present coronavirus disease 2019 is a leading cause of a serious acute respiratory syndrome which has been announced as a pandemic on March 11, 2020 by the World Health Organization. This novel virus has the ability to infect respiratory, gastrointestinal, and central nervous systems⁽¹⁾ of both human and animals. Further, coronavirus disease is a highly contagious with a 2% mortality rate. In spite of utilization of mechanical respiratory help, certain supplemental vitamins, and other drugs there is still lack of a particular COVID-19 treatment.

Baricitinib is an oral selective Janus Kinase (JAK 1) and (JAK2) inhibitor^(2, 3). It has been acquired approval in more than forty countries

for moderate to severe active rheumatoid arthritis as a mono- or combined therapy. Some previous studies have been suggested the application of baricitinib for patients infected with COVID-19^(4, 5). Herein, it has been reviewed the databases published in PubMed and Google Scholar using "baricitinib" and "COVID-19" as a search keywords for collection of the required references from inception till June 30, 2020.

What are the objectives of this review?

This review is needed in order to establish the benefits and harms of clinically relevant outcomes of baricitinib in people infected with novel coronavirus COVID-19.

COVID-19 pathogenesis

Coronavirus 2019 enters host respiratory epithelial cells through receptor-mediated endocytosis mechanism using a protein expressed on its own spike, a surface viral glycoprotein, to bind to the host angiotensin converting enzyme 2 (ACE-2) receptor, a cell membrane bound aminopeptidase receptor which expressed fundamentally in mature lung type II alveolar cells⁽⁶⁾ and further in oral cavity mucosa⁽⁷⁾.

Additionally it is expressed by heart, proximal tubular cells of kidneys, and blood vessels. This binding has been followed by cleavage the spike (S) protein, an essential step for lung injury in patients with COVID-19, by the action of lysosomal proteases resulting in signal peptide release which assist the entry of the virus into the cell⁽⁸⁾. Notably, type II alveolar epithelial cells might assist both viral reproduction and transmission through endocytosis⁽⁹⁾. Importantly, adaptor-associated protein kinase-1 "AP-2 associated protein kinase-1" (AAK 1) acts as a promotor for receptor mediated endocytosis helping in assembly of the virus particles in the intracellular matrix⁽¹⁰⁾. Furthermore, cyclin G associated kinase serves as another endocytosis regulator.

Why baricitinib?

Baricitinib was selected as one of the suggested agents for COVID-19 treatments and was

predicted to diminish the viral ability to infect host respiratory cells due to its inhibitory action on AAK1 associated endocytosis with high binding affinity, also it has binding ability to cyclin G-associated kinase (GAK), another regulator of endocytosis. Thus, the viral entry into host cells may be hindered and lead in turn to interruption of the viral assembly (figure 4.1). Additionally, baricitinib is a selective JAK1 and JAK2 inhibitor therefore it might assist in managing the inflammation⁽¹¹⁾ which is a natural immune response from which the COVID-19 patients had been undergone.

From the view of pharmacokinetics, baricitinib absorption is rapid after oral administration and the absorption extent does not influenced by the presence of food⁽¹²⁾. Also, its peak plasma concentrations happen within 1.5 hours of dosing⁽¹²⁾, with once-day by day dosing related to its long terminal half-life (fourteen hours)⁽¹³⁾. Moreover, the little interactions with the drug transporter and cytochrome enzymes⁽⁵⁾ enabling it to be combined with another suggested agents for COVID-19 to lessen viral infectivity.

Consequently, modes of baricitinib action and its pharmacokinetics rationalize the reasons behind its suggestion to be a potential choice in COVID-19 treatment.

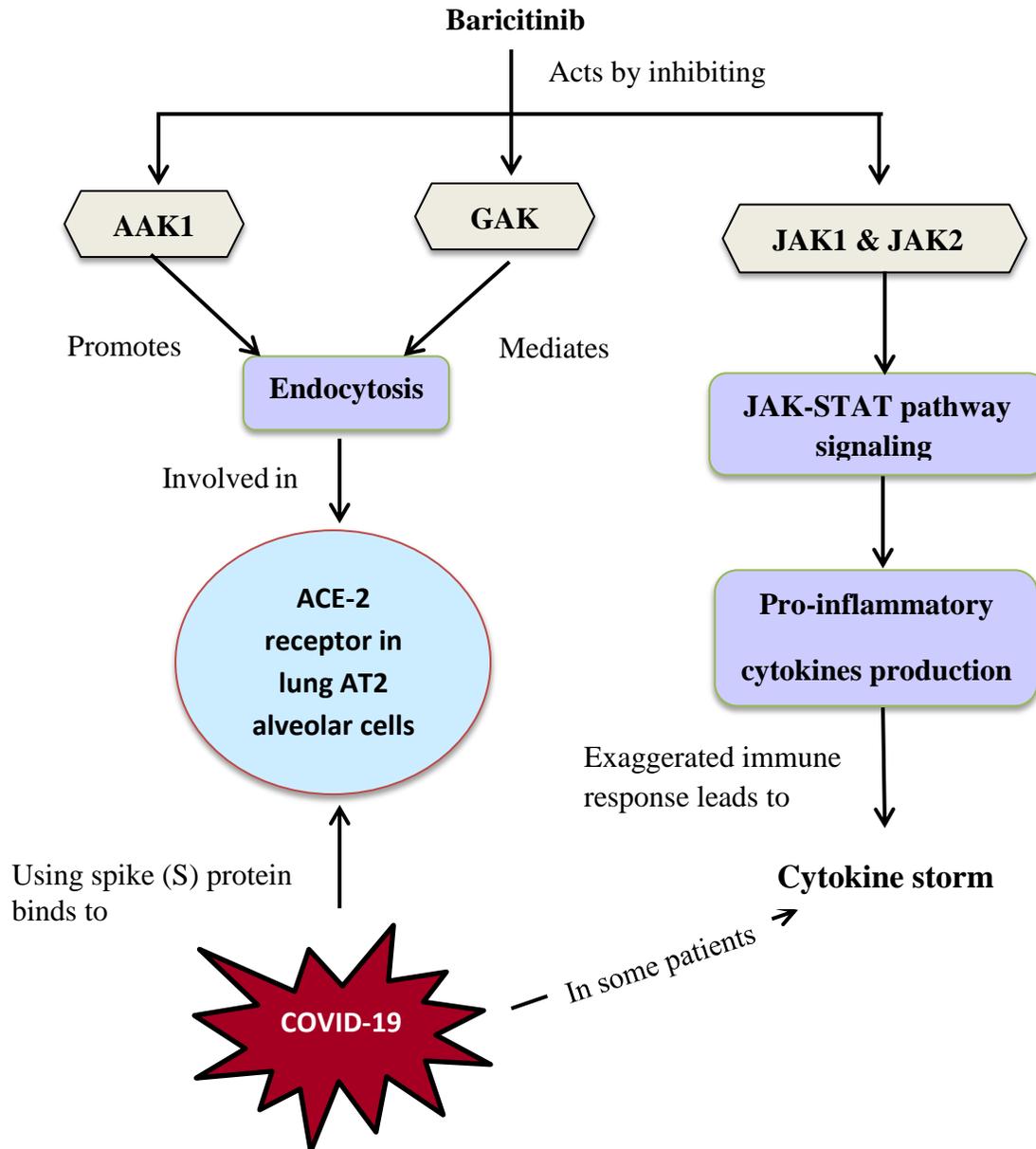


Figure 4.1: Explanation of possible modes of action of baricitinib in COVID-19. AAK1= AP-2 associated protein kinase-1; ACE2= angiotensin converting enzyme 2; GAK= cyclin G-associated kinase; JAK= Janus Kinase; STAT= signal transducer and activator of transcription proteins. Modified Richardson *et al.*, 2020 graph 5U

Pros and cons of baricitinib in patients with COVID-19

Baricitinib is proposed to be beneficial for COVID-19 patients in blocking viral passage into the host lung cells and ultimately

blocking viral assembly at therapeutic doses for rheumatoid arthritis treatment through its high affinity for AAK1 inhibition and possibly for GAK binding. Additionally, application of baricitinib might be successful

strategy in managing of inflammation that resulting in cytokine storm, a clinically severe phase of novel coronavirus disease, which is joined by elevated levels of intracellular signaling involving abundance levels of interleukine-6 (IL-6) and interferons α and β through JAK-STAT pathway.

From one hand, it is reported that baricitinib therapy is associated with a potential risk of reactivation of varicella zoster, herpes simplex, and Epstein Barr virus strains⁽¹⁴⁾ which is believed to be involved in the outcome of hindrance of JAK-STAT pathway. It is additionally detailed that half of the patients who surrendered to COVID-19 experienced secondary infections⁽¹⁵⁾. From the other hand, it is found that the incidence of herpes zoster and other serious infections was small and near to that of placebo when used for more than fifty two weeks' dosing. Notably, these infections were reported to be more in patients who used 4 mg baricitinib dose than who administered the lower dose.

Furthermore, baricitinib dose is needed to be adjusted when creatinine clearance is somewhere in range of 30 and 60 mL/minute, and it is not recommended for administration if creatinine clearance is under 30 mL/minute.

Baricitinib also causes elevation in creatine kinase level where forty six percent of ICU patients have revealed raised creatinine kinase levels⁽¹⁶⁾. However, the probability of abnormally high level of creatine kinase was dose-dependent and it is more with 4 mg (1.5 %) in comparison with that of 2 mg (0.8%). Further, most of these cases were transient and did not need for withdrawal of medication.

Moreover, it has been recommended that baricitinib cannot be started in patients with absolute neutrophil count under 1×10^9 cells/L where it is revealed, within the first month of therapy, that the mean absolute neutrophil count reduced but it become stable thereafter⁽¹⁷⁾.

It has been found that there is increment in the mean absolute lymphocyte count in the first month of baricitinib administration but this count has been returned to baseline level with prolongation of therapy. Interestingly, lymphocyte count alterations showed to be within normal range in most patients⁽¹⁷⁾.

Baricitinib therapy associated with initial decrease in the concentrations of hemoglobin but this reduction has been revealed to be transient.

A marked increase in parameters related to lipids has been considered with this medication, particularly with higher dose

(4mg) but this abnormal change in lipid parameters has been at plateau at week 12⁽¹⁸⁾ and then returned to be stable⁽¹⁹⁾.

Additionally, according to the animal studies, utilization of baricitinib is contraindicated in pregnancy as animal studies have exhibited embryotoxicity⁽²⁰⁾.

The recent retrospective, observational, multicenter, longitudinal study in an one hundred and thirteen hospitalized patients provided a motivated results and concluded that baricitinib is an effective and safe therapy in moderate COVID-19 pneumonia patients⁽²¹⁾. Furthermore, the outcomes of utilization of baricitinib therapy in Northern Italy patients with mild-moderate COVID-19 has been reported that there is a rapid reduction in plasma levels of interleukin-6 and C-reactive protein along with improvement in clinical, viral, and radiological measurements^(22,23).

Therapeutic dosing and course of baricitinib

The therapeutic dosing of baricitinib using either 2 mg or 4 mg is once daily. The dose is adequate to inhibit AAK1 and JAK1/2 which leads to a dual action including the inhibition of the viral entry and the inflammation characteristic of COVID-19 patients. It is proposed that 7-14 days (short period) might

be used will not produce reactivation of any latent infections, such as herpes infection or tuberculosis.

CONCLUSION

Targeting of AAK1 and JAK1/2 using baricitinib together with its invaluable pharmacokinetic properties has predicted to be potential and effective in management moderate COVID-19 infected patients. In spite of the insignificant side effects when use baricitinib for over 7-14 days, the laboratory parameters should be considered including hemoglobin level, lipids, and both absolute neutrophil and lymphocyte count during treatment. Regarding dose dependent side effects, it is predicted that the lower dose (2mg) of baricitinib is preferred for COVID-19 patients. However, experimental trials are mandatory for a long-term treatment with a lower dose of baricitinib to evaluate its effectiveness and safety in patients with moderate COVID-19 infection.

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Conflict of interests: the author declares that there is no conflict of interests.

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