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Janus kinase inhibitor baricitinib is not an ideal option for management of COVID-19

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ABSTRACT

The Wuhan outbreak of novel Corona virus infection has been the global focus since December 2019. This infection has become a global pandemic. It is highly important to understand the virology of the pathogen and to explore the therapeutic options for management of this pandemic. Drug repurposing strategies are being considered for management of COVID 19. Among the identified drugs, Baricitinib has become a keen interest for researchers because of its ability to inhibit the viral assembly by the prevention of Clarithrin associated endocytosis. We tried to explore the reasons on why Baricitinib is not an ideal option for COVID 19.

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Drug repurposing strategies are being considered for the management of novel coronavirus disease 2019 (COVID-19). The janus kinase (JAK) inhibitor, baricitinib has gained considerable research interest because it can inhibit viral assembly by preventing AP-2 associated protein kinase 1 (AAK1)-mediated endocytosis.

The most important human receptor for the severe acute respiratory syndrome (SARS) S glycoprotein is the angiotensin-converting enzyme 2 (ACE2) [1]. Novel coronavirus has a similar glycoprotein that may also target this enzyme. ACE2 is predominantly found in the lower respiratory tract, particularly in the lung AT2 alveolar epithelial cells [2], which are prone to viral infections like SARS coronavirus [3]. These AT2 alveolar epithelial cells might contribute to viral reproduction and transmission through endocytosis [4]. AAK1 is a potential promoter of this endocytosis, thus enhancing viral assembly in the intracellular matrix [5]. Cyclin G-associated kinase is another regulator of this endocytosis [6].

Baricitinib is a potential option for the management of disease caused by novel coronaviruses. Baricitinib inhibits both AAK1 and cyclin G-associated kinase, thereby preventing endocytosis and reducing viral assembly. Baricitinib inhibits JAK1 and JAK2 and therefore may help manage inflammation [7]. Several studies suggested the use of baricitinib for treating COVID-19 [3,8].

Study results indicate that baricitinib cannot be initiated in patients with an absolute neutrophil count less than 1×10^9 cells/L, or in patients with an absolute lymphocyte count less than 0.5×10^9 cells/L [9]. Epidemiological studies show the values of the selected patients are closer to the threshold levels at baseline (Table 1) [10–14]. In one epidemiological study, absolute lymphocyte count in non-survivors was reported to be $0 \cdot 6 \times 10^9$ cells/L (interquartile range: $0 \cdot 5$–$0 \cdot 8 \times 10^9$ cells/L) (Table 2) [14]. Similarly, another study carried out by Huang et al. reported that absolute lymphocyte count in infected patients in ICU was $0 \cdot 4 \times 10^9$ cells/L (interquartile range: $0 \cdot 2$–$0 \cdot 8 \times 10^9$ cells/L) [12]. The risk of lymphocytopenia may affect the progression of COVID-19. A 26% incidence of anaemia has been reported in non-survivors of COVID-19 infection [14]. Baricitinib therapy is predicted to be associated with incidence of anaemia [15]; therefore, initiation of baricitinib therapy in patients with COVID-19 may further increase anaemia incidence [9].

Elevated creatine kinase has been observed in patients receiving baricitinib therapy [15]. Although the median value of creatine kinase is reported to be in the normal range (<175 U/L) in patients with COVID-19, it is greatly increased in critically ill patients and non-survivors of this disease [10–14]. A total of 46% of patients with COVID-19 in ICU have been reported to have elevated creatine kinase levels [12]. In one critically ill COVID-19 patient, creatine kinase levels were as high as 493 U/L [12]. Elevated creatine kinase levels pose a risk for the initiation of baricitinib therapy.

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Table 1
Published biochemical data of COVID-19 patients.

Parameter	Reference range	Wang et al [10]	Chen et al [11]	Huang et al [12]	Ng et al [13]	Zhou et al [14]
No. of patients	-	99	138	41	21	191
Absolute neutrophil count (x10^9 cells/L)	2.0-7.4	3.0 (2.0-4.9)	5.0 (3.3-8.1)	5.0 (3.0-8.9)	3.33 (3-3.91)	NA
Absolute lymphocyte count (x10^9 cells/L)	1.1-3.6	0.8 (0.6-1.1)	0.9 (0.5)	0.8 (0.6-1.1)	1.29 (0.7-1.65)	1 · 0 (0 · 6-1 · 3)
Creatine kinase (U/L)	<170	102 (62- 252)	85.0 (51-184)	132.0 (62-219)	78.0 (69-137)	21 · 5 (13 · 0-72 · 4)

Values are median (interquartile range). NA - Not Available

Table 2
Published biochemical data of COVID-19 patients in ICU and non-survivors.

Parameter	Reference range	Wang et al [10] (n=138)	Huang et al [12] (n=41)	Zhou et al [14] (n=191)
ICU/non-survivors	-	ICU	ICU	Non-survivors
No. of patients	-	36	13	54
Absolute lymphocyte count (x 10^9 cells/L)	1.1-3.6	0.8 (0.5-0.9)	0 · 4 (0 · 2-0 · 8)	0 · 6 (0 · 5-0 · 8)
No. of patients (%) with lymphocytopenia	-	NA	11 (85%)	41 (76%)
Creatine kinase (U/L)	<170	102 (62-252)	132 · 0 (82 · 0-493 · 0)	39 · 0 (19 · 5-151 · 0)
No. of patients (%) with elevated creatine kinase	-	NA	6/13 (46%)	11/52 (21%)[#]

Values are median (interquartile range). NA - Not Available. [#]Data not available for 2 patients

Limited data are available on the potential effects of baricitinib in the elderly population aged at least 75 years [15]. Zhou et al. reported that mortality is higher in elderly infected patients [14]. Furthermore, studies have shown increased incidence of respiratory tract infections (16.3%) and incidence of infective diseases (29-42%). Co-infection is one of the most common threats in the management of COVID-19 [10]. There is also a risk of re-activation of latent infections. Infected patients will also be at risk of tuberculosis and hepatitis B [16]. Researchers have concluded that baricitinib therapy can reactivate varicella-zoster, herpes simplex and Epstein-Barr virus strains [17]. Zhou et al. reported that 50% of patients with COVID-19 experienced secondary infections [14].

Baricitinib may not be an ideal drug of choice for management of COVID-19. Available therapeutic options must be explored to prevent mortality in patients with this disease.

Declarations

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Ethical Approval Not required.

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