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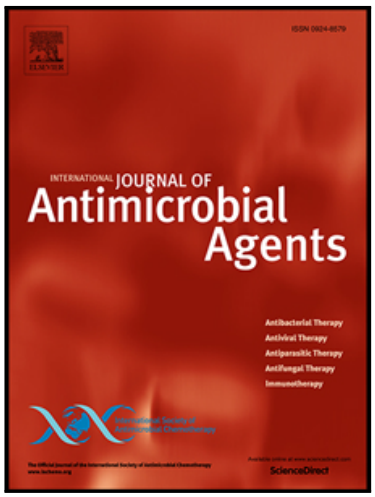

BARICITINIB - A JANUASE KINASE INHIBITOR - NOT AN IDEAL OPTION FOR MANAGEMENT OF COVID 19

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Highlights

- Several studies suggested Baricitinib as a potential drug for the management of COVID 19 infection through drug repurposing strategies because of its ability to act on AT2 cells and AAK1 mediated endocytosis.
- Baricitinib, a Januase Kinase Inhibitor, have known to cause Lymphocytopenia, Neutropenia and Viral Reactivation.
- Reported Epidemiological studies have shown that COVID 19 patients have a lesser absolute lymphocyte count closer to the threshold value.
- Moreover, incidence of Co-infection for COVID 19 patients is one of the leading causes of Mortality. Baricitinib may enhance the incidence of Co-infection.
- Hence, Baricitinib may not be an ideal option for Management of COVID 19.

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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 AP-2 associated protein Kinase 1 associated endocytosis.

The most important human receptor for the SARS S glycoprotein in human is the angiotensin converting enzyme 2.[1] Novel corona virus has a similar glycoprotein which may also target angiotensin-converting enzyme 2. Angiotensin converting enzyme 2 is predominantly available in the lower respiratory tract especially in the lung AT 2 alveolar epithelial cells.[2] This AT2 cells are prone to viral infections like SARS corona virus.[3] These cells might help in the possible viral reproduction and transmission through endocytosis.[4] AP-2 associated protein Kinase 1 (AAK1) is potential promoter of this endocytosis helping the viral assembly in the intracellular matrix.[5] Cyclin G associated kinase is another regulator of this endocytosis.[6] Baricitinib is another drug that can be a potential option for the management of this novel corona viruses. Baricitinib inhibits both AP 2 associated protein Kinase 1 as well as the Cyclin G associated Kinase. Thereby preventing the endocytosis it can reduce the viral assembly. Baricitinib is an inhibitor of Janus Kinase JAK 1 and JAK 2 and therefore it might help in managing the inflammation.[7] Several studies suggested the use of Baricitinib for treating COVID 19.[3,8]

Studies have suggested that Baricitinib cannot be initiated in patients with absolute neutrophil count less than $1x10^9$ cells/L. Similarly, it cannot be initiated in patients with an absolute lymphocyte count less than $0.5x10^9$ cells/L.[9] In the epidemiological studies being carried out the values of the selected patients are closer to the threshold levels in the baseline. [10,11,12,13,14](Table 1). An epidemiologic study reported that absolute lymphocyte count in the non-survivors is $0{\cdot}6$ x10^9 cells/L (Inter-quartile range : $0{\cdot}5$–$0{\cdot}8$ x10^9 cells/L).[14](Table 2). Similarly another study carried out by Huang D *et al* reported that absolute lymphocyte count

in patients receiving ICU Care is 0·4 x10^9 cells/L (Inter-quartile range : 0·2–0·8 x10^9 cells/L).[12] The risk of lymphocytopenia may affect the disease progression of COVID 19. Incidence of anaemia is predicted with Baricitinib therapy.[15] 26% incidence of anaemia is reported in the non-survivors due to COVID 19 infection.[14] Initiation of Baricitinib therapy may further reduce these counts.[9]

Elevations of Creatine Kinase was observed in patients with Baricitinib therapy.[15] Although the median value of creatine kinase is reported to be in the normal range (<175U/L), it is greatly increased in the critically ill patients and non survivors. [10,11,12,13,14] 46% of ICU patients have reported elevated creatine kinase levels.[12] In one critically ill patient the creatine kinase levels were as high as 493 U/L.[12] Elevated Creatine Kinase levels pose a risk for the initiation of baricitinib therapy.

Limited data is available on the potential effects of Baricitinib in the elderly population of 75 years and above.[15] Fei Zhou *et al* reports that mortality is higher in the elderly patients.[14]

Studies have reported 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 this novel corona virus infection.[10] There is also a risk of re-activation of latent infections. The patients will be at the risk of Tuberculosis as well as Hepatitis B.[16]

Studies have concluded Baricitinib therapy has constituted for the reactivation of Varicella Zoster, Herpes Simplex and Epstein Barr Virus strains.[17] Fei Zhou *et al* reports that 50% patients who succumbed to COVID 19 experienced secondary infections.[14]

Baricitinib as predicted earlier may not be an ideal drug of choice for COVID 19. Available therapeutic options must be explored in order to prevent the mortality in these cases.

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References:

1. Gruber CC, Steinkellner G. Wuhan coronavirus 2019-nCoV—what we can find out on a structural bioinformatics level. Jan 23, 2020. https://innophore.com/2019-ncov/ (accessed Feb 10, 2020).
2. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; published online Jan 30. https://doi. org/10.1016/S0140-6736(20)30251-8.
3. Richardson, P., Griffin, I., Tucker, C., Smith, D., Oechsle, O., Phelan, A. and Stebbing, J. (2020). Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *The Lancet*.
4. Pu SY, Xiao F, Schor S, et al. Feasibility and biological rationale of repurposing sunitinib and erlotinib for dengue treatment. Antiviral Res 2018, 155: 67–75.
5. Sorrell F, Szklarz M, Abdul Areez KR, et al. Family-wide structural analysis of human numb-associated protein kinases. Structure 2016; 24: 401–11.
6. Mesa RA (June 2010). "Ruxolitinib, a selective JAK1 and JAK2 inhibitor for the treatment of myeloproliferative neoplasms and psoriasis". *IDrugs*. **13** (6): 394–403.
7. Channappanavar, R., Fett, C., Mack, M., Ten Eyck, P., Meyerholz, D. and Perlman, S. (2017). Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. *The Journal of Immunology*, 198(10), pp.4046-4053.

8. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D et al. COVID-19: combining antiviral and anti-inflammatory treatments. The Lancet Infectious Diseases. 2020
9. Chaplin S. Baricitinib: a new oral treatment for rheumatoid arthritis. Prescriber. 2017;28(6):44-46.
10. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020 Feb 7 doi:10.1001/jama.2020. 1585.
11. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13. doi:10.1016/ S0140-6736(20)30211-7.
12. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497– 506. doi:10.1016/S0140-6736(20)30183-5.
13. Ng M, Lee E, Yang J, Yang F, Li X, Wang H et al. Imaging Profile of the COVID-19 Infection: Radiologic Findings and Literature Review. Radiology: Cardiothoracic Imaging. 2020;2(1):e200034.
14. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020
15. Ema.europa.eu. 2020 [cited 20 March 2020]. Available from: https://www.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_en.pdf

16. Mehta SK, Crucian B, Pierson DL, Sams C, Stowe RP. Monitoring immune system function and reactivation of latent viruses in the Artificial Gravity Pilot Study. J Gravit Physiol. 2007 Jul;14(1): 21-5.

17. Harigai M, Winthrop K, Takeuchi T, Hsieh T, Chen Y, Smolen J et al. Evaluation of hepatitis B virus in clinical trials of baricitinib in rheumatoid arthritis. RMD Open. 2020;6(1):e001095.

Table 1: Published Biochemical Data of COVID 19 patients

Parameter	Reference Range	Wang D *et al* [10]	Chen N *et al* [11]	Huang D *et al* [12]	Ng *et al* [13]	Fei 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 (Inter-Quartile Range). NA- Not Available

Table 2: Published Biochemical Data of ICU care COVID 19 patients and Non Survivors

Parameter	Reference Range	Wang D *et al* [10] (n=138)	Huang D *et al* [12] (n=41)	Fei Zhou *et al* [14] (n=191)
ICU Care / Non Survivors		ICU Care	ICU Care	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 [No.of Patients (%)]	-	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 [No.of Patients (%)]	-	NA	6/13 (46%)	11/52 (21%)[#]

Values are Median (Inter-Quartile Range). NA- Not Available. [#]Data not available for 2 patients