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Letter to Editor

Baricitinib in COVID-19; a letter to editor on recent findings

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Implication for health policy/practice/research/medical education

Baricitinib as a selective Janus kinase (JAK) 1 and 2 inhibitors, is currently being used as an alternative drug in the treatment of patients with refractory rheumatoid arthritis Baricitinib act through two possible mechanisms to prevent COVID-19 and cytokine storms, first by hampering SARS-CoV2 entry into cells via binding AP2-associated protein kinase 1 (AAK1), and secondly through reducing cytokines and chemokines release by inhibiting JAK 1 and 2.

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Abnormal immune reactions are among the possible causes of death in patients with coronavirus disease 2019 (COVID-19). Therefore, the combination of immunomodulatory with antiviral drugs may be an effective therapy in the hyper-inflammatory phase of COVID-19 (1). However, side effects of immunomodulatory agents limit the usefulness of these drugs for COVID-19 treatment.

Baricitinib (Olumiant), a selective Janus kinase (JAK) 1 and 2 inhibitors, is currently being used as an alternative drug in the treatment of patients with refractory rheumatoid arthritis (RA) (2). Baricitinib act through two possible mechanisms to prevent COVID-19 and cytokine storms; a) hampering severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into cells via binding AP2-associated protein kinase 1 (AAK1), b) reducing cytokines and chemokines release by inhibiting JAK 1 and 2 (3).

Previous studies showed a positive effect of baricitinib either alone or in combination with other antiviral drugs in patients with COVID-19. A randomized, double-blind, controlled trial revealed that the use of 4mg daily baricitinib reduces 28-days mortality from 13% to 8%, and reduces 60-days mortality from 15% to 10% (4). Treatment with baricitinib was associated with decreased 30-days mortality in patients aged more than 70 years with moderate to severe COVID-19 by 18.5% (5). Moreover, patients treated with baricitinib plus dexamethasone had significantly lower mortality compared to patients who received dexamethasone only (6). Besides, this addition of baricitinib to corticosteroids results in greater improvement of respiratory function in patients with COVID-19 (7).

Although baricitinib may play a significant role in COVID-19 treatment clinicians should be aware of its adverse effects including infection, thrombosis, and hepatobiliary disorders. As guidelines panel for COVID-19 treatment does not recommend baricitinib routinely due to its safety issues.

One of the main causes of complication and death in COVID-19 patients is a secondary infection due to immunosuppression (1). Corticosteroids are approved drugs that can protect against autoimmune reactions. Meanwhile, infection due to immunosuppression caused by these drugs is seen (8). Another immunomodulatory approach is using baricitinib (JAK inhibitor), but there are infection-related concerns about this drug too. A clinical trial by Beigel et al revealed that secondary infections after using baricitinib are lower than the placebo group, suggesting that not only baricitinib is not as immunosuppressive as other drugs like dexamethasone, it may play a protective role against secondary infections (9). Another study by Marconi et al showed that adding baricitinib to steroids for COVID-19 treatment might be safe (4).

JAK inhibitors like baricitinib can produce reactive metabolites that consider hepatotoxic (10). Hence, liver injury due to baricitinib is expected. The previous research about baricitinib and liver injury has shown elevation in the serum aminotransferases, which often was self-limited even without dose adjustment (11). In pre-license and post-marketing drug evaluation studies, there was no

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association between this drug and hepatotoxicity (11). Recently a combination of baricitinib and other drugs like corticosteroids and remdesivir is administered in COVID-19 patients. The study by Peng et al reported a considerable amount of hepatobiliary problems after baricitinib prescription in COVID-19 patients (12). It is the first post-marketing evidence of liver injury due to baricitinib. Considering aminotransferase raises is common in severe COVID-19 patients and sometimes these patients present jaundice and remdesivir is related to serum aminotransferase elevation, liver injury due to baricitinib in COVID-19 patients, needs more investigation.

Authors' contribution

Conceptualization: MRR and GGD; Methodology: MMR; Validation: MRR and GGD; Formal Analysis: MRR and GGD; Research: MRR and GGD; Resources: MRR and GGD; Data Curation: MRR and GGD; Writing—Original Draft Preparation: MRR and GGD; Writing—Reviewing and Editing: HVR and HRJ; Visualization: MRR and GGD; Supervision: MRR and GGD; Project Management: MRR and GGD.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

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References

1. Alijotas-Reig J, Esteve-Valverde E, Belizna C, Selva-O'Callaghan A, Pardos-Gea J, Quintana A, et al. Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: A comprehensive review. Autoimmun Rev. 2020;19:102569. doi: 10.1016/j.autrev.2020.102569.
2. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Baricitinib in Patients with Refractory Rheumatoid Arthritis. N Engl J Med. 2016;374:1243-52. doi:10.1056/NEJMoa1507247.
3. Zhang X, Zhang Y, Qiao W, Zhang J, Qi Z. Baricitinib, a drug with potential effect to prevent SARS-COV-2 from entering target cells and control cytokine storm induced by COVID-19. Int Immunopharmacol. 2020;86:106749. doi: 10.1016/j.intimp.2020.106749.
4. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al; COV-BARRIER Study Group. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med. 2021:S2213-260000331-3. doi: 10.1016/S2213-2600(21)00331-3.
5. Abizanda P, Calbo Mayo JM, Mas Romero M, Cortés Zamora EB, Tabernero Sahuquillo MT, Romero Rizos L, et al. Baricitinib reduces 30-day mortality in older adults with moderate-to-severe COVID-19 pneumonia. J Am Geriatr Soc. 2021;69:2752-2758. doi: 10.1111/jgs.17357.
6. Pérez-Alba E, Nuzzolo-Shihadeh L, Aguirre-García GM, Espinosa-Mora J, Lecona-Garcia JD, Flores-Pérez RO, et al. Baricitinib plus dexamethasone compared to dexamethasone for the treatment of severe COVID-19 pneumonia: A retrospective analysis. Journal of Microbiology, Immunology and Infection. 2021;54:787-93. doi: 10.1016/j.jmii.2021.05.009.
7. Rodriguez-Garcia JL, Sanchez-Nievas G, Arevalo-Serrano J, Garcia-Gomez C, Jimenez-Vizuete JM, Martinez-Alfaro E. Baricitinib improves respiratory function in patients treated with corticosteroids for SARS-CoV-2 pneumonia: an observational cohort study. Rheumatology. 2021;60:399-407. doi: 10.1093/rheumatology/keaa587.
8. Youssef J, Novosad SA, Winthrop KL. Infection Risk and Safety of Corticosteroid Use. Rheum Dis Clin North Am. 2016;42:157-76. doi: 10.1016/j.rdc.2015.08.004.
9. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020;383:1813-1826. doi: 10.1056/NEJMoa2007764.
10. Ai H, Chen W, Zhang L, Huang L, Yin Z, Hu H, et al. Predicting Drug-Induced Liver Injury Using Ensemble Learning Methods and Molecular Fingerprints. Toxicol Sci. 2018;165:100-107. doi: 10.1093/toxsci/kfy121.
11. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548012/ Updated 2021 May 11.
12. Peng L, Xiao K, Ottaviani S, Stebbing J, Wang YJ. A real-world disproportionality analysis of FDA Adverse Event Reporting System (FAERS) events for baricitinib. Expert Opin Drug Saf. 2020;19:1505-11. doi: 10.1080/14740338.2020.1799975.