



Thomas Handoyo, Gianina Dinda Pamungkas, Nur Farhanah

BARICITINIB AS TREATMENT OPTION FOR CORONA VIRUS DISEASE-19: A LITERATURE REVIEW

Thomas Handoyo¹, Gianina Dinda Pamungkas², Nur Farhanah¹

¹Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

²Research Assistant, Dr. Kariadi Hospital, Semarang, Indonesia

*Corresponding Author : E-mail : nurfarhanahams@gmail.com

ABSTRACT

Background : Treatment of COVID-19 using IL-6 inhibitors, including Sarilumab or Tocilizumab, significantly decreased mortality risk. Though, Remdesivir therapy gave benefits, morbidity and mortality remained high. Baricitinib, a JAK inhibitor, can inhibit the IL-6 activation pathway and has the potential effect of inhibiting disease progression from becoming severe. **Objective** : This study aimed to evaluate the use of Baricitinib for COVID-19 patients. **Methods** : This study was conducted by searching for observational and randomized controlled trial studies through online databases, “PubMed” and “Google Scholar”. Studies included must evaluate Baricitinib effectivity as therapy for hospitalized COVID-19 patients. This study included 11 studies (9 observational and 2 randomized controlled trials). Patients included had moderate-to-severe symptoms of COVID-19. **Results** : Standard dose of Baricitinib was administered at 4 mg daily dose. Length of therapy varied between 5-14 days, or up to patients’ discharge. Baricitinib therapy in included studies was administered with intravenous Remdesivir, Steroid, Tocilizumab, or other complementary therapies. The mortality rate within 7-day of hospitalization with Baricitinib was 4.4%. Requirement of invasive mechanical ventilation rate after Baricitinib administration was approximately 4%. Laboratory parameters were significantly improving after Baricitinib administration: IL-6, CRP, ferritin, and D-dimer. In a randomized controlled trial, serious adverse events occurred more often in the placebo-treated compared to the Baricitinib-treated group. **Conclusion** : Baricitinib as therapy for COVID-19 patients can decrease the progression, morbidity, and mortality of the disease. Further studies are needed to evaluate the benefit of Baricitinib as the main therapy for COVID-19.

Keywords : Baricitinib, COVID-19, IL-6, treatment

INTRODUCTION

Corona Virus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS CoV-2) infection, has become a pandemic. World Health Organization (WHO) reported that until November 7, 2021, there were more than 249 million confirmed cases, with more than 5 million deaths.^{1,2} Acute respiratory distress syndrome (ARDS) caused 39% of mortality in COVID-19 patients and 40% of deaths among COVID-19 who were administered to the intensive care unit (ICU).^{3,4} Hyperinflammation, caused by cytokine storm, was the underlying pathogenesis of ARDS. Cytokine storm was caused by the overproduction of proinflammatory cytokines, such as interleukin (IL) -6, IL-7, and IL-8. Previously, SARS CoV infection also showed inflammatory response at upper respiratory tract, which was inducted and influenced by IL-6. A similar finding was found in critical COVID-19 patients, which had high IL-6 level.^{5,6}

Treatment of COVID-19 using IL-6 inhibitors, including Sarilumab or Tocilizumab, significantly decreased mortality risk. However, there was no difference between outcome upon hospital discharge,

length of stay, or requirement of mechanical ventilation.⁷ Though, Remdesivir therapy gave benefits, morbidity and mortality remained high.⁸ Baricitinib is a JAK inhibitor which use as autoimmune disease therapy. Inhibition at the JAK pathway can inhibit the IL-6 activation pathway and potentially inhibit disease progression from becoming severe. ⁹ Food and Drug Administration (FDA) had published authority for Baricitinib as therapy for COVID-19 patients who need oxygen supplementation.¹⁰ This study aimed to evaluate the use of Baricitinib for COVID-19 patients.

METHODS

This study was conducted by searching for observational and randomized controlled trial studies published from 2019 - November 2021 through online databases, “PubMed” and “Google Scholar”. Keywords were “Baricitinib”, “COVID-19”, “SARS-CoV2”, or a combination of both.

Studies included must evaluate Baricitinib effectivity as therapy for hospitalized COVID-19 patients. The inclusion criteria were (1) COVID-19 patients included in the studies must be confirmed with RT-PCR, (2) Publications were cohort,



Thomas Handoyo, Gianina Dinda Pamungkas, Nur Farhanah

retrospective cohorts, or randomized controlled trials, (3) Outcomes were clinical outcomes (requirement for ventilation, length of stay, and mortality), laboratory outcome, or adverse events outcome. Studies were excluded if they were not published in Bahasa Indonesia or English and could not be accessed as full-text.

This study included 11 studies, consisting of 9 observational studies and 2 randomized controlled trial studies. All patients had moderate-to-severe symptoms of COVID-19. Studies included were summarized in Table 1.

Table. 1 Included studies

Author (year)	Study	Treatment	Output
Gomez, et al. (2021) ¹¹	Retrospective cohort	Baricitinib and other standard therapies	There were better laboratory outcomes of IL-6 (-50.7 pg/mL); CRP (-86.4 mg/L); ferritin (-159.0 ng/mL); and D-dimer (-347 ng/mL)
Abizanda, et al. (2021) ¹²	Retrospective cohort	Baricitinib and other standard therapies	Older patients, aged > 70 years old, who were treated with Baricitinib had a 30-days mortality risk reduction of 18.5%, while < 70 years old groups had a reduction of 8.1%.
Thoms, et al. (2021) ¹³	Retrospective cohort	Baricitinib, Remdesivir, and Dexamethasone	The mortality rate with 7-days of hospitalization and the requirement of invasive mechanical ventilation after Baricitinib therapy were 4.4% and 4%.
Izumo, et al. (2021) ¹⁴	Cohort	Baricitinib, Remdesivir, and Dexamethasone	Length of stay, time-to-recovery, invasive mechanical ventilation duration, and oxygen supplement therapy were 11 days, 9 days, 6 days, and 5 days. Adverse events reported were ventilator-associated pneumonia and herpes zoster infection, as 2% of cases
Alba, et al. (2021) ¹⁵	Retrospective cohort	Baricitinib + Dexamethasone vs. Dexamethasone and other standard therapies	Additional Baricitinib to dexamethasone had a hazard risk 0.5 (p<0.01) for mortality, and the requirement of invasive mechanic ventilation was lower compared to dexamethasone monotherapy (15.6% vs. 15 %; p=0.94)
Kalil, et al. (2020) ¹⁶	Randomized-controlled trial	Baricitinib vs Placebo and Remdesivir	The recovery ratio of patients who received high-flow oxygen therapy or non-invasive ventilation support was 1.51. The baricitinib group had an infection rate significantly lower than the placebo group (5.9% vs 11.2%; p=0.003). Infections that occurred were Herpes Simplex Virus, Herpes Zoster Virus, and Tuberculosis. There were no differences between thromboembolic events (3% vs 3%) and cardiovascular events (1% vs 1%).
Marconi, et al. (2021) ¹⁷	Randomized-controlled trial	Baricitinib vs Placebo and Remdesivir	28-days and 60-days mortality rate were significantly lower in Baricitinib treatment compared to placebo (HR= 0.57; p=0.0018 and HR= 0.62; p=0.005) In a randomized controlled trial, serious adverse events occurred more often in placebo treatment compared to the Baricitinib treated group (15% vs. 18%). Mortality due to serious adverse events was found to be more frequent in the placebo group (2 % vs 4%). Serious infections were reported as 9% in the Baricitinib group and 10% in the placebo groups
Hasan, et al. (2021) ¹⁸	Cohort	Baricitinib high dose vs standard dose with Remdesivir and Dexamethasone	High dose Baricitinib had a lower requirement of ICU and intubation compared to the standard dose (17.25 vs. 9%; p<0.05 and 11.2% vs. 4.1% p >0.05) High dose and standard dose of Baricitinib was found to have no difference in bacterial, fungal, or other opportunistic infections
Hasan, et al. (2021) ¹⁹	Cohort	Baricitinib loading dose vs. without loading dose and Remdesivir and Dexamethasone	Baricitinib administration both using loading dose and without loading dose did not give any difference of the 30-days mortality rate (5% vs. 5%) Administration using loading dose also reduced the requirement of ICU (29.4 vs. 10%; p<0.05) and faster oxygen saturation recovery of >94% in room air also in respiratory rate (3 vs. 4 days and 5 vs. 8 days).
Rosas, et al. (2020) ²⁰	Retrospective cohort	Baricitinib vs. Tocilizumab vs. both combination	Mortality of patients receiving Baricitinib as combination with Tocilizumab was lower than monotherapy of both drugs (18% vs 20% vs 33%). Baricitinib-treated patients required ICU less than both Tocilizumab monotherapy and combination of Tocilizumab-Baricitinib groups (0% vs. 65% vs. 27%).
Garcia, et al. (2020) ²¹	Cohort	Baricitinib + corticosteroid vs. corticosteroid other standard of care	Oxygen support was less needed in Baricitinib-treated patients at hospital discharge and 1 month after (OR= 0.18<0.001 and OR=0.31, p=0.024) Baricitinib and dexamethasone combination reduced D-Dimer greater than dexamethasone monotherapy (-497ng/mL vs. -269 ng/mL; p=0.019)



Thomas Handoyo, Gianina Dinda Pamungkas, Nur Farhanah

RESULTS

Baricitinib Administration

There were 2 schemes of Baricitinib administration upon included studies. A standard dose of Baricitinib was administered at 4 mg daily dose. Older patients or patients with glomerular filtration rate < 30 mL/min/1.73 m² were given at 2 mg daily dose.¹¹⁻¹⁷ Some studies use a higher dose of Baricitinib 8 mg daily or as a loading dose 8 mg on the first day.^{18,19} Length of therapy varied between 5-14 days. There were studies that gave Baricitinib up to patients' discharge.¹¹⁻¹⁹

Baricitinib therapy in included studies was administered with intravenous Remdesivir at a 200 mg loading dose followed by a daily 100 mg dose for maximum 10 days. Steroids used were Dexamethasone 6-10 mg daily injection or methylprednisolone pulse dose for 4 days followed with 30 mg daily prednisone and tapering off up to 7-10 days. There was a study that used Tocilizumab as a comparative and combination therapy with 400-600 mg daily dose. Other complement therapies were convalescent plasma, Lopinavir/ritonavir, Drunavir/cobicistat, Fanciclovir, Hydroxychloroquine, and/or Colchicine.¹¹⁻²¹

Clinical outcome

The mortality rate within 7-day of hospitalization with Baricitinib was 4.4%.¹³ A randomized-controlled trial found 28-days and 60-days mortality rate were significantly lower in Baricitinib treatment compared to placebo (HR= 0.57; $p=0.0018$ and HR= 0.62; $p=0.005$).¹⁷ Older patients aged > 70 years old, who were treated with Baricitinib had a 30-days mortality risk reduction by 18.5%, while < 70 years old groups had a reduction of 8.1%.¹² Thirty-day mortality rate was significantly higher in patients that were given standard Baricitinib dose compared to high Baricitinib dose (6% vs 3.3%; $p<0.01$).¹⁸ While, Baricitinib administration, both using loading dose and without loading dose, did not give any difference in 30-day mortality rate (5% vs. 5%).¹⁹ Baricitinib as additional dexamethasone therapy had a hazard risk of 0.5 ($p<0.01$).¹⁵ Mortality of patients receiving Baricitinib in combination with Tocilizumab was lower than monotherapy of both drugs (18% vs. 20% vs. 33%).²⁰ The most common cause of death was a septic shock (44%),

followed by neurological complications (12%) and renal insufficiency (4%).¹⁵

The median time-to-recover of Baricitinib treated COVID-19 patients was 12 days, with a median length of stay in ICU being 13 days.¹¹ Recovery ratio of patients who received high-flow oxygen therapy or non-invasive ventilation support was 1.51. While, progression from administration to requirement of high-flow oxygen support, invasive mechanic ventilation, or death were lower in Baricitinib treated patients (OR 0.85).^{16,17} Requirement of invasive mechanical ventilation rate after Baricitinib administration was approximately 4%.¹³ High dose Baricitinib had a lower requirement of ICU and intubation compared to the standard dose (17.25 vs. 9%; $p<0.05$ and 11.2% vs. 4.1% $p>0.05$).¹⁸

Administration using loading dose also reduced the requirement of ICU (29.4 vs. 10%; $p<0.05$) and faster oxygen saturation recovery of $>94\%$ in room air also in respiratory rate (3 vs. 4 days and 5 vs. 8 days).¹⁹ Baricitinib treated patients required ICU less than both Tocilizumab monotherapy and combination of Tocilizumab-Baricitinib groups (0% vs. 65% vs. 27%).²⁰ Baricitinib as additional therapy to dexamethasone reduced requirement of invasive mechanical ventilation compared to the dexamethasone-only group (15.6% vs. 15 %; $p=0.94$).¹⁵ Oxygen support were less needed in Baricitinib-treated patients at hospital discharge and 1 month after (OR= 0.18 <0.001 and OR=0.31, $p=0.024$).²¹

Laboratory Outcome

Laboratory parameters were significantly getting better after Baricitinib administration: IL-6 (-50.7 pg/mL); CRP (-86.4 mg/L); ferritin (-159.0 ng/mL); and D-dimer (-347 ng/mL).¹¹ Baricitinib and dexamethasone combination reduced D-Dimer greater than dexamethasone monotherapy (-497ng/mL vs. -269 ng/mL; $p=0.019$).²¹

Adverse events

In a randomized controlled trial, serious adverse events occurred more often in placebo-treated compared to the Baricitinib treated group (15% vs. 18%). Mortality due to serious adverse events were found to be more frequent in the placebo group (2 % vs. 4%). Serious infections were reported as 9% in the Baricitinib group and 10% in



Thomas Handoyo, Gianina Dinda Pamungkas, Nur Farhanah

the placebo groups.¹⁷ Another randomized controlled trial study reported the Baricitinib group had infection rate significantly lower than the placebo group (5.9% vs 11.2%; $p=0.003$). Infections that occurred were Herpes Simplex Virus, Herpes Zoster Virus, and Tuberculosis. There were no differences between thromboembolic events (3% vs. 3%) and cardiovascular events (1% vs. 1%).¹⁶ Both high dose and standard dose of Baricitinib were found to have no difference in bacterial, fungal, or other opportunistic infections.¹⁸

DISCUSSION

Pathogen-associated molecule pattern (PAMP) in SARS-CoV2 infection had not been known. However, it is predicted that SARS-CoV 2 entered human cells through the ACE2 receptor after recognizing of genetic material, single stranded RNA. This event can activate the IRF3/7 factor and NF- κ B pathways to produce inflammatory cytokines and interferon (IFN)-1. The production of IFN-1 as a protective response to viral infection was inhibited by structural protein M, protein N, open reading frame 3a (ORF3a), and ORF6 within the SARS-CoV2 structure. It caused pro-inflammatory cytokines to become dominant. Immune responses within respiratory tracts will then produce IL-1, IL-6, IL-8, IL-12, and TNF- α . Those cytokines cause adaptive and innate immune cells to be activated and other inflammatory cytokines' existence to be maintained. Moreover, myelopoiesis and granulopoiesis become more active and have a role in lung epithelial damage which induce ARDS. Overproduction of systemic proinflammatory cytokines induces coagulation and vascular homeostasis, contributing to DIC.²²⁻²⁴

The severity of COVID-19 has a correlation to the IL-6-JAK-STAT3 axis. There are 2 activation pathways that caused by IL-6, membrane-bound (mIL-6R) pathway, and soluble form (sIL-6R) pathway. The mIL-6R pathway is found only in immune cells and creates a complex with gp130 protein in order to activate JAK/STAT3, Akt/mTOR, and MAPK pathways. Activation of those pathways had pleiotropic effect in immune cells, which manifested as Th17, T cells and B cells CD8+ differentiation, and increased neutrophil migration. In contrast, sIL-6R pathways can happen within almost all cells and have an activation pathway of JAK/STAT3. Activation in sIL-6R pathway, will

induce secretion of IL-6 itself, IL-8, MCP-1, vascular endothelial growth factor (VEGF), and decrease the production of E-cadherin within endothelial. Increment of MCP-1 is an atherogenesis compound that induce cardiovascular symptoms. Increment in VEGF and decrement of E-cadherin can be caused decrement in vascular permeability and induce hypotension and pulmonary dysfunction. IFN- γ and IL-2 can also cause activation of JAK pathway within COVID-1. However, this activation and its effects had not been known in the progression of COVID-19.²²⁻²⁴

Baricitinib is a type 1 and type 2 JAK inhibitor. Those types of JAK receptors are activators of several cytokines, such as IL-6, IL-10, G-CSF, IFN- α , and IFN- γ . Inhibition of JAK system in COVID-19 can influence the pathogenesis, which has been described previously, which may prevent cardiovascular events, hypotension, and pulmonary dysfunction. Baricitinib can also reduce the infectivity of SARS-CoV 2 by inhibiting endocytosis which is mediated by AP-2 -associated protein kinase-1 (AAK1) and cyclin G-associated kinase (GAK) mediate clathrin-dependent at ACE-2 receptor. Alteration within AAK1 causes interruption of adaptor protein (AP) phosphorylation which has a role in viral substance invagination into trans-Golgi. Therefore, the viral life cycle can be altered.²²⁻²⁵

Previously, Baricitinib was used for rheumatoid arthritis patients did not show a response to methotrexate. Baricitinib is administered orally at a daily dose of 4 mg.²⁶ Studies included in this review used Baricitinib with an oral route in various doses of 4-8 mg daily. Baricitinib dose is reduced in patients with a glomerular filtration rate of < 30 mL/minute/1.73 m² to be 1-2 mg daily. This is caused by the main elimination of Baricitinib in kidney filtration and active secretion. Baricitinib's half-life can reach 19 hours in patients with end-stage renal disease.²⁷ Both higher doses and loading doses of Baricitinib correlated faster respiratory function recovery. A cost-effectiveness study, Baricitinib administration as an additional therapy for COVID-19 patients had good cost-effectiveness for both hospital and payer.²⁸

Therapy with Baricitinib for moderate-to-severe COVID-19 patients who were hospitalized, shows decrement of mortality rate even after 60-day. This finding was also found for patients aged more



Thomas Handoyo, Gianina Dinda Pamungkas, Nur Farhanah

than 70 years old. Reduction of length of stay, requirement of mechanic ventilation, inflammation parameter, and coagulation was found in Baricitinib-treated patients. However, upon this study being conducted, Baricitinib was still used as additional therapy to standard of care therapy, including Remdesivir and corticosteroid. Therefore, further studies are needed to confirm Baricitinib as the main therapy for COVID-19 patients.

CONCLUSION

Baricitinib as therapy for COVID-19 patients can decrease the progression, morbidity, and mortality of the disease. Further studies are needed to evaluate the benefit of Baricitinib as the main therapy for COVID-19.

CONFLICTS OF INTEREST

The authors declare no conflict of interest in this article.

FUNDING

No specific funding was provided for this review.

AUTHOR CONTRIBUTIONS

Author contributions to this review are as follows: conceptualization, collecting literature, and writing draft : Nur Farhanah; supervision, review : Thomas Handoyo; editing : Gianina Dinda Pamungkas.

REFERENCES

1. WHO. COVID-19 weekly epidemiological update. World Heal Organ [Internet]. 2021;(58):1–23. Available from: <https://www.who.int/publications/m/item/covid-19-weekly-epidemiological-update>
2. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* [Internet]. 2021;19(3):141–54. Available from: <http://dx.doi.org/10.1038/s41579-020-00459-7>
3. Tzotzos SJ, Fischer B, Fischer H, Zeitlinger M. Incidence of ARDS and outcomes in hospitalized patients with COVID-19: A global literature survey. *Crit Care*. 2020;24(1):1–4.
4. Hasan SS, Capstick T, Ahmed R, Kow CS, Mazhar F, Merchant H a., et al. Mortality in COVID-19 patients with acute respiratory distress syndrome and corticosteroids use: a systematic review and meta-analysis. *Expert Rev Respir Med* [Internet]. 2020;14(11):1149–63. Available from: <https://doi.org/10.1080/17476348.2020.1804365>
5. Saji R, Nishii M, Sakai K, Miyakawa K, Yamaoka Y, Ban T, et al. Combining IL-6 and SARS-CoV-2 RNAemia based risk stratification for fatal outcomes of COVID-19. *PLoS One* [Internet]. 2021;16(8 August):1–13. Available from: <http://dx.doi.org/10.1371/journal.pone.0256022>
6. Torres Acosta MA, Singer BD. Pathogenesis of COVID-19-induced ARDS: Implications for an ageing population. *Eur Respir J* [Internet]. 2020;56(3). Available from: <http://dx.doi.org/10.1183/13993003.02049-2020>
7. Taslim R, Ongko V, Bijak R. Interleukin-6 (IL-6) inhibitors as therapeutic agents for coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *J Infeccion Public Heal*. 2020;14(January):1001–9.
8. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* [Internet]. 2020;395(10229):1033–4. Available from: [http://dx.doi.org/10.1016/S0140-6736\(20\)30628-0](http://dx.doi.org/10.1016/S0140-6736(20)30628-0)
9. Bronte V, Ugel S, Tinazzi E, Vella A, de Sanctis F, Canè S, et al. Baricitinib restrains the immune dysregulation in patients with severe COVID-19. *J Clin Invest*. 2020;130(12):6409–16.
10. US Food and Drug Administration (FDA). Baricitinib Letter of Authorization Revised July 28 2021. 2021;564:1–9. Available from: [https://www.fda.gov/media/143822/download#:~:text=Baricitinib \(Olumiant\) is approved by,the treatment of COVID-19.](https://www.fda.gov/media/143822/download#:~:text=Baricitinib (Olumiant) is approved by,the treatment of COVID-19.)
11. Iglesias Gómez R, Méndez R, Palanques-Pastor T, Ballesta-López O, Borrás Almenar C, Megías Vericat JE, et al. Baricitinib against severe COVID-19: Effectiveness and safety in hospitalised pretreated patients. *Eur J Hosp Pharm*. 2021;(April 2020):1–5.
12. Abizanda P, Calbo Mayo JM, Mas Romero M, Cortés Zamora EB, Tabernero Sahuquillo MT, Romero Rizo L, et al. Baricitinib reduces 30-day mortality in older adults with moderate-to-severe COVID-19 pneumonia. *J Am Geriatr Soc*.



Thomas Handoyo, Gianina Dinda Pamungkas, Nur Farhanah

- 2021;69(10):2752–8.
13. Thoms BL, Gosselin J, Libman B, Littenberg B, Budd R. Efficacy of Combination Therapy With The JAK Inhibitor Baricitinib In The Treatment of COVID-19. *Res Sq [Internet]*. 2021;19:1–22. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/34518834> %0A<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC8437315>
 14. Izumo T, Kuse N, Awano N, Tone M, Sakamoto K, Takada K, et al. Clinical impact of combination therapy with baricitinib, remdesivir, and dexametason in patients with severe COVID-19. *Respir Investig*. 2020;59(January):799–803.
 15. Pe E, Aguirre-garcía GM, Lecona-garcía JD, Flores-pe RO, Leo N. Baricitinib plus dexametason compared to dexametason for the treatment of severe COVID-19 pneumonia: A retrospective analysis. *J Microbiol Immunol Infect*. 2020;54(January):787–93.
 16. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med*. 2021;384(9):795–807.
 17. Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, et al. 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 Me*. 2020;(January):19–21.
 18. Hasan MJ, Rabbani R, Anam AM, Huq SMR, Polash MMI, Nessa SST, et al. Impact of high dose of baricitinib in severe COVID-19 pneumonia: a prospective cohort study in Bangladesh. *BMC Infect Dis*. 2021;21(1):1–9.
 19. Hasan MJ, Rabbani R, Anam AM, Huq SMR. Additional baricitinib loading dose improves clinical outcome in COVID-19. *Open Med*. 2021;16(1):041–6.
 20. Rosas J, Liano FP, Canot ML, Brea JMC, Beser AR, Rabasa JTA, et al. Experience With the Use of Baricitinib and Tocilizumab Monotherapy or Combined, in Patients With Interstitial Pneumonia Secondary to Coronavirus COVID19: A Real-World Study. *Reum Clin*. 2020;(January):1–7.
 21. Rodriguez-Garcia JL, Sanchez-Nievas G, Arevalo-Serrano J, Garcia-Gomez C, Jimenez-Vizuet JM, Martinez-Alfaro E. Baricitinib improves respiratory function in patients treated with corticosteroids for SARS-CoV-2 pneumonia: An observational cohort study. *Rheumatol (United Kingdom)*. 2021;60(1):399–407.
 22. Yang L, Xie X, Tu Z, Fu J, Xu D, Zhou Y. The signal pathways and treatment of cytokine storm in COVID-19. *Signal Transduct Target Ther [Internet]*. 2021;6(1):1–20. Available from: <http://dx.doi.org/10.1038/s41392-021-00679-0>
 23. Qi F, Qian S, Zhang S, Zhang Z. Baricitinib, a drug with potential effect to prevent SARS-COV-2 from entering target cells and control cytokine storm induced by COVID-19. *Biochem Biophys Res Commun*. 2020;(January):135–40.
 24. Seif F, Aazami H, Khoshmirsafa M, Kamali M, Mohsenzadegan M, Pornour M, et al. JAK Inhibition as a New Treatment Strategy for Patients with COVID-19. *Int Arch Allergy Immunol*. 2020;181(6):467–75.
 25. M. Salazar, J. Barochiner WE el. E. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Ann Oncol [Internet]*. 2020;(January):2–5. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7254017/pdf/main.pdf>
 26. Fakhouri W, Wang X, de la Torre I, Nicolay C. A network meta-analysis to compare effectiveness of baricitinib and other treatments in rheumatoid arthritis patients with inadequate response to methotrexate. *J Heal Econ Outcomes Res*. 2020;7(1):10–23.
 27. Jorgensen SCJ, Tse CLY, Burry L, Dresser LD. Baricitinib: A Review of Pharmacology, Safety, and Emerging Clinical Experience in COVID-19. *Pharmacotherapy*. 2020;40(8):843–56.
 28. Ohsfeldt R, Kelton K, Klein T, Belger M, Mc PL, Spiro T, et al. Cost-Effectiveness of Baricitinib Compared With Standard of Care: A Modeling Study in Hospitalized Patients With COVID-19 in the United States. *Clin Ther*. 2020;(January):1–21.