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Review Article (Fast Track COVID-19)

Effectiveness and Safety of Baricitinib as a Covid-19 Drug Candidate: A Systematic Review

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Abstract
Baricitinib is an approved selective JAK1/JAK2 inhibitor that can potentially inhibit IL-6 as the primary driver of COVID-19-related cytokine storm syndrome. Therefore, this study aimed to assess the effectiveness and safety of baricitinib therapy in COVID-19 patients. It was reported following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search for eligible articles reporting the efficacy and safety of baricitinib on COVID-19 patients, published up to May 2021, was conducted using PubMed and Embase. The research protocol was registered at PROSPERO (CDR42021235282), and data were presented in a metasynthetic (descriptive) manner. Out of 878 identified articles, seven were eligible and consisted of three randomized clinical trials, one quasi-experimental study, two before-after (pre-post) studies, and one cross-sectional study. The articles suggested that baricitinib could improve the clinical conditions of COVID-19 patients indicated by negative PCR test results, improve breathing quality, and decrease: ICU requirements, length of hospital stay, as well as the risk of death. The trial studies showed that this inhibitor works better with a loading dose of 8 mg, continued with 4 mg daily. Baricitinib could also produce synergistic effects with standard therapy such as corticosteroid and remdesivir. Therefore, it is a promising candidate therapy for COVID-19 patients, but since the number and methodological quality of the studies are low, further and better research is needed to ascertain its potential use on COVID-19.

Keywords: Baricitinib, COVID-19, JAK1/2 inhibitor

Efektivitas dan Keamanan Baricitinib sebagai Kandidat Obat Covid-19: Tinjauan Sistematis

Abstrak
Baricitinib adalah inhibitor selektif JAK1 JAK2 yang dapat menghambat IL-6 sebagai pemicu utama terjadinya sindrom badai sitokin terkait COVID-19. Tinjauan sistematis ini dilakukan untuk menilai efektivitas dan keamanan terapi baricitinib pada pasien COVID-19. Kami melaporkan penelitian ini dengan mengikuti pedoman *Preferred Reporting Items for Systematic Review and Meta-Analyses* (PRISMA). Kami menggunakan mesin pencari *PubMed* dan *Embase* untuk mencari artikel yang melaporkan efektivitas dan keamanan baricitinib pada pasien COVID-19, yang diterbitkan hingga Mei 2021. Protokol penelitian ini telah terdaftar di PROSPERO (CDR42021235282). Data disajikan secara metasintetik (deskriptif). Di antara 878 artikel yang teridentifikasi, ada tujuh artikel yang memenuhi syarat yang terdiri dari tiga artikel uji klinis acak terkendali, satu studi kuasi-eksperimental, dua studi sebelum-sesudah (pra-pasca) dan satu studi *cross-sectional*. Semua artikel menyatakan bahwa baricitinib dapat memperbaiki kondisi klinis pasien COVID-19 yang ditunjukkan dengan hasil tes PCR negatif, meningkatkan kualitas pernapasan, dan menurunkan: kebutuhan ICU, lama rawat inap, dan resiko kematian. Baricitinib tidak menyebabkan efek samping yang serius. Hasil uji klinis menunjukkan bahwa baricitinib bekerja lebih baik dengan pemberian *loading dose* 8 mg lalu dilanjutkan dengan baricitinib 4 mg setiap hari dibandingkan tanpa *loading dose* baricitinib. Baricitinib juga menghasilkan efek sinergistik jika dikombinasikan dengan terapi standar seperti kortikosteroid dan remdesivir. Oleh karena itu, dapat disimpulkan bahwa baricitinib adalah kandidat terapi yang menjanjikan untuk pasien COVID-19. Namun, karena jumlah dan kualitas metodologi penelitiannya rendah, penelitian lebih lanjut dan lebih baik secara metodologi masih dibutuhkan untuk memastikan potensi penggunaan baricitinib pada COVID-19.

Kata kunci: Baricitinib, COVID-19, inhibitor JAK1/2

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Introduction

At the end of 2019, the world is being diverted by the presence of a new type of corona virus, the so-called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the emergence of Coronavirus Disease-2019 (COVID-19).[1] This virus was originated in China, precisely in the city of Wuhan. This virus is spreading so fast to all countries in the world and on March 11, 2020, World Health Organization (WHO) declared COVID-19 as a pandemic.[2]

On January 12, 2022, there were 313,638,451 positive cases of COVID-19 in the world. A total of 261,575,434 patients have been declared cured and 5,520,187 patients have died. The United States ranks first with a total of 63,312,876 cases and Indonesia is ranked 18th in the world.[3] Based on data from the Ministry of Health of the Republic of Indonesia, the number of COVID-19 cases in Indonesia until January 12, 2022 reached 4,268,097 positive cases. The number of patients recovered was 4,116,962 cases and those who died were 144,150 cases.[4]

In COVID-19 patients, Cytokine Storm Syndrome, characterized by elevated Interleukin (IL)-6, is common. The Cytokine Storm Syndrome is associated with the emergence of severe clinical conditions such as acute respiratory distress syndrome, impaired tissue perfusion, and eventually death due to dysfunctions of several organs.[5]

Baricitinib is a drug of choice for treating moderate to severe rheumatoid arthritis because it has immunosuppressive effects. Currently, it is one of the drug candidates being researched as an option in the management of COVID-19. Baricitinib acts by inhibiting JAK1/JAK2 intracellularly and altering proinflammatory signals from several cytokines such as IL-6, IL-23, IL-10, IL-12. Therefore, this medicine is expected to block and/or relieve the Cytokine Storm Syndrome.[6] Currently, baricitinib is recommended to be co-administered with corticosteroids for severe or critical COVID-19 patients.[3]

Bronte et al. (2020) reported that baricitinib can reduce IL-6 levels as well as may decrease serum IL-1, and Tumor necrosis factor-alpha (TNF-α). It was also described that it produces rapid recovery of T and B cell frequencies and increases antibodies, thereby reducing the clinical need for oxygen therapy.[7]

However, to date, there have been no reports of the effectiveness and safety of baricitinib in COVID-19 pneumonia patients. Therefore, the purpose of this study was to review systematically the relevant literature reporting the effectiveness and safety of baricitinib as a COVID-19 drug candidate.

Methods

This systematic review is compiled and reported based on the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline.[8] PubMed and Embase were used to search eligible articles reporting the efficacy and safety of baricitinib on COVID-19 patients, published up to May 2021. The study protocol can be found on PROSPERO (www.crd.york.ac.uk) with the registration number of CRD4202123 5282.[9]

Inclusion and exclusion criteria

This systematic review was intended to include experimental as well as observational (analytical or descriptive studies) studies reporting the effectiveness and safety of baricitinib on adult (≥18 years old) COVID-19 patients. The infection should be confirmed by using the gold standard molecular test, real-time quantitative PCR. We also applied no language restriction in the process of article selection.

We excluded case-reports and case-series as well as non-original studies such as

reviews, correspondence, letters, editorials, or conference proceedings with a collection of abstracts only. Studies in the forms of modeling *in silico*, *in vitro*, *ex vivo*, and *in vivo* were also excluded.

Databases and searching strategy

PubMed and Embase were used to search for appropriate articles that have been published up to May 8, 2021. We used COVID-19 and baricitinib related keywords combined with the boolean operators (OR, AND). Full lists of searching queries can be found in the Supplementary Material 1.

Selection article

The retrieved articles were sent to Rayyan®-QCRI (Qatar Computing Research Institute).[10] The software helps to remove duplication and provides some tools for article selection. The article screenings were conducted by two reviewers (YSR and AA) independently. In case of disagreement, the third reviewer was involved (MAB). There were two steps of the screening process i.e. titles and abstracts screening and then continued with full-text screening. The percentage of agreement between reviewers in both screening processes was calculated and then translated to reliability Cohen's kappa (κ) statistic. The Kappa Cohen scores range from –1 to +1. A score of 1 will be obtained when a perfect agreement is reached. On the other hand, if there is no match or purely coincidental, the proportion of conformity will be equal to 0.[11]

Data items and collection process

Data on the identity of articles (authors, country, year of publication), study design, characteristics of patients (age, gender, severity of COVID-19), drug information (drug dose, route of administration, comedication), and parameters of efficacy and safety of baricitinib were collected.[12] Data collection process was performed by YSR and re-checked by AA.

Risk of bias assessment

Each selected article will be assessed for its methodological quality. This assessment was carried out by two reviewers (YSR and MAB). Critical appraisal tools from The Joanna Briggs Institute (JBI) were used to appraise the quality of articles with study design in the form of RCT and quasi-experimental studies.[13] For the cross-sectional studies, we used the Specialist Unit For Review Evidence (SURE) form.[14] Meanwhile, to judge the quality of a Before-After Study with no control group, we used assessment tool from The National Heart, Lung, and Blood Institute.[15] The list of questions can be found in the Supplementary Materials 2.

Data analysis and presentation data

Data analysis was carried out descriptively and grouped based on the study design.

Results

We found 181 articles in PubMed and 850 articles in Embase discussing COVID-19 and baricitinib (Figure 1). A total of 153 duplicate articles were removed. There were 878 articles available for the Title and Abstract screening (TIAB screening), however 862 articles were excluded as they did not meet the inclusion criteria such as wrong study designs, non-original studies or wrong topics. The percentage of agreement between the two reviewers for the first stage of screening is 100% with a kappa value of 1.0 which is in the very good category.

There were 16 articles entering the second stage of screening (full-text screening). A total of 11 articles was excluded and there were five eligible articles. Furthermore, we found 2 articles from the reference tracking. The percentage of agreement between the two reviewers for the second stage of screening is 100% with a kappa value of 1.0 (very good category).

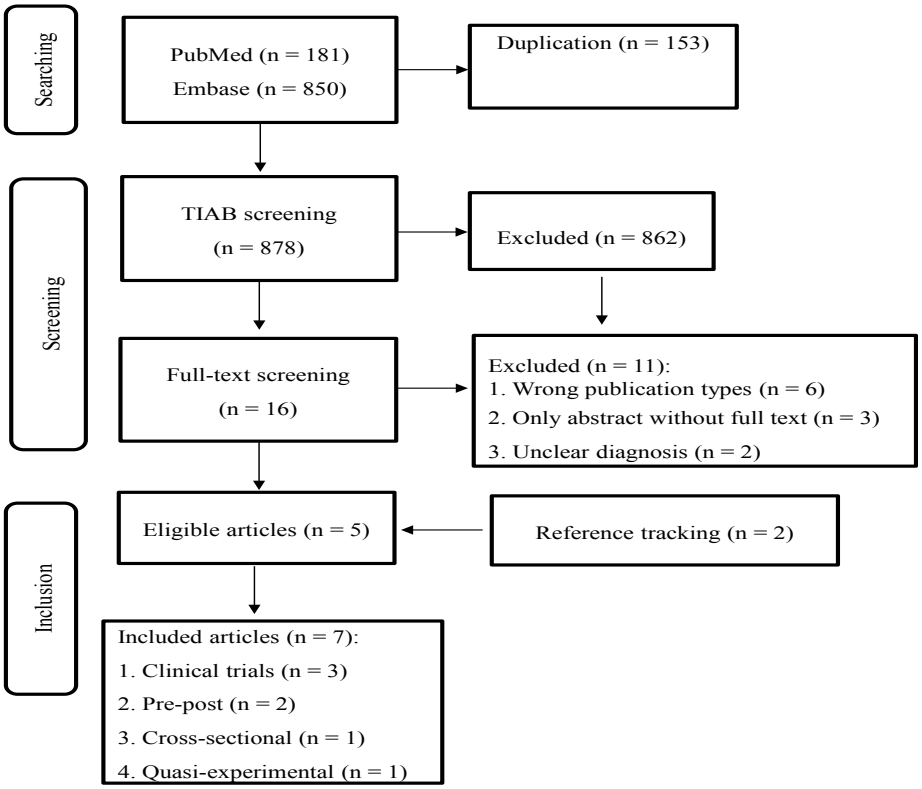

Figure 1 Flow Chart of Study Selection

The final included articles were seven consisting of three clinical trials, one a quasi-experimental study, two before-after (pre-post) studies, and the remaining one was a cross-sectional study. Characteristics and the results of each selected study were presented in the Table 1 and described as follows:

Clinical trials

The first clinical trial study involved 37 hospitalized COVID-19 patients. Patients were randomly divided into two groups i.e. treatment group (20 people) and control group (17 people). The treatment group received a loading dose of 8 mg followed by 4 mg per day for two weeks. Meanwhile, the control group did not receive a loading dose. In addition to baricitinib, the patient was also treated with dexamethasone (10–20 mg daily) intravenously on the first day. Giving a loading dose of 8 mg per day produced a faster clinical improvements, increased respiratory function, decreased ICU requirements, and length of hospital stay.[16]

The second and third clinical trials were multicenter studies involving more than a thousand participants.[17,18] Both studies compared the efficacy of baricitinib to placebo. However, the second study included patients which were mostly treated by corticosteroids (about 80%) and only less than 20% of them receiving remdesivir (in which >90% of them also receiving corticosteroid). Meanwhile, the third trial involved all patients treated with remdesivir and the use of corticosteroid was only restricted for special condition such as renal disease, asthma, septic shock, and acute respiratory distress syndrome.

The second trial indicated that the use of baricitinib could effectively reduce the risk of death among hospitalized COVID-19 patients.[17] The results of the third trial also

Table 1 Characteristics and Results of Each Selected Study

Reference	Country	Study Design	Dose	Route of Administration	Types and Doses of Other Drugs	Participant	Number of Participant(s)	Age (in years)	Sex (male, %)	Results
Hasan et al., 2021	Bangladesh.	Randomized controlled trial.	**Intervention:** 4 mg and 8 mg loading dose. **Control:** 4 mg without loading dose.	Oral	Dexametason 10–20 mg per day.	Patients hospitalized due to COVID-19.	**Intervention:** 20. **Control:** 17.	**Intervention** Median (IQR): 59 (49.8–69). **Control** Median (IQR): 52 (50.5–62).	**Intervention:** 80%. **Control:** 7 6%.	Giving a loading dose of 8 mg showed a faster recovery of respiratory function, a decrease in the need for ICU and length of hospital stay compared to the group without a loading dose.
Marconi et al., 2021	Multicentres: Argentina. Brazil, India, Japan, South Korea, Mexico, and Russia.	Randomized, double-blind, placebo-controlled, parallel-group, phase 3 trials.	**Intervention:** 4 mg/day. If patients had a kidney problem, the dose is 2 mg/day.	Oral	Corticosteroid, remdesivir or combination of them.	Patient hospitalized due to COVID-19.	**Intervention:** 764. **Control:** 761.	**Intervention** Mean (SD): 57.8 (14.3). **Control** Mean (SD): 57.5 (13.8).	**Intervention:** 64%. **Control:** 62%.	Baricitinib produced 5 and 4.9 percentage points in all-cause mortality at 28 days and 60 days, respectively.
Kalil et al., 2021	Multicentres: the US, the UK, Singapore, South Korea, Mexico, Japan, Spain, Denmark.	Randomized, double-blind placebo-controlled trial.	**Intervention:** 4 mg/day. **Control:** Placebo	Oral	Remdesivir 200 mg loading dose on day 1, followed by a 100 mg maintenance dose administered daily on days 2 until 10 i.v.	Patient hospitalized due to COVID-19.	**Intervention:** 515. **Control:** 518.	**Intervention** Mean (SD): 55.0 (15.4). **Control** Mean (SD): 55.8 (16.0).	**Intervention:** 61.9%. **Control:** 64.3%.	Baricitinib plus remdesivir produced faster and better clinical improvement than remdesivir alone.

Table 1 (Cont.) Characteristics and Results of Each Selected Study

Reference	Country	Study Design	Dose	Route of Administration	Types and Doses of Other Drugs	Participant	Number of Participant(s)	Age (in years)	Sex (male, %)	Results
Bronte et al., 2020	Italy.	Quasi-experimental study.	**Intervention:** 1) 4 mg twice a day for two days, followed by 4 mg per day for 7 days. 2) 2 mg low doses twice a day for 2 days, followed by 2 mg per day for patients more than 75 years. **Control:** No baricitinib	Oral	Hydroxychloroquine, antiviral therapy (lopinavir/ritonavir) as a single agent or in combination (hydroxychloroquine and antiviral therapy), prophylactic antibiotics, anticoagulants.	Patients hospitalized for pneumonia due to COVID-19.	**Intervention:** 20. **Control:** 56.	**Intervention** Median (IQR): 68 (64.5–78.5). **Control** Median (IQR): 77.5 (62–87.5).	**Intervention:** 35%. **Control:** 55%.	Baricitinib reduced the number of deaths and produced a faster clinical improvement significantly than the control group.
Gómez et al., 2021	Spanish.	Before-after (Pre and post-study) with no control group,	4 mg daily for 5 to 7 days, given orally.	Oral	Chloroquine/ hydroxychloroquine, corticosteroids, tocilizumab, convalescent plasma, lopinavir/ ritonavir, darunavir/ cobicistat, famciclovir, colchicine.	Patients hospitalized due to severe COVID-19.	43	Mean (IQR): 70 (54–79).	70%	There was clinical improvement, no relevant adverse events and 100% patient survival.
Titanji et al., 2020	Georgia.	Before-after (Pre and post-study) with no control group,	2–4 mg baricitinib per day.	Oral	Hydroxychloroquine, levofloxacin, vancomycin, azithromycin.	Patient treated at hospital because COVID-19 moderate to severe.	15	Mean: 62 (Range: 36–87).	100%	Combination of baricitinib and hydroxychloroquine gave clinical improvement, 12 of 15 patients recovered.
Rosas et al., 2020	Spanish.	Cross sectional descriptive study.	**Intervention:** 2 mg or 4 mg per day. **Control:** No baricitinib and tocilizumab	Oral	Ramdesivir, lopinavir/ritonavir, interferon β 1b, hydroxychloroquine, azithromycin, corticosteroids, tocilizumab.	Patients hospitalized due to severe COVID-19.	**Intervention:** 12. **Control:** 17.	**Intervention** Mean (SD): 67.8 (13.6).. **Control** Mean (SD): 73.8 (14.8).	**Intervention:** 75%. **Control:** 65%.	Therapy with baricitinib and tocilizumab did not cause serious side effects in COVID-19 patients.

support the positive effects of baricitinib. It was reported that patients treated with baricitinib (in combination with remdesivir) achieved clinical improvement faster than those who were treated by remdesivir only especially for patients with non-invasive mechanical ventilation.[18]

Quasi-experimental study

Bronte et al. conducted a study on 76 patients hospitalized with COVID-19 related pneumonia in a quasi-experimental study design. There were 20 patients as a case group (receiving baricitinib therapy) and 56 patients as a control group (not receiving baricitinib therapy). All patients received hydroxychloroquine treatment regimen or lopinavir/ritonavir as a single agent or in combination (hydroxychloroquine and lopinavir/ritonavir). Supportive therapies were given, such as prophylactic antibiotics and anticoagulants, depending on the medical doctor's discretion. The results showed a faster clinical improvement with fewer deaths in the case group than the control group.[7]

Before-after (pre-post) studies

A first pre-post study consisted of 43 patients hospitalized for severe COVID-19. Patients were treated with 4 mg baricitinib daily with a median of 6 days, of which 80% were also treated with corticosteroid. After being treated with baricitinib, patients had good clinical condition without having significant side effects, and more importantly no mortality was observed.[19]

The last article with pre-post study type reported 15 male COVID-19 patients with moderate to critical clinical condition. Patients received baricitinib therapy at a dose of 2–4 mg per day and hydroxychloroquine with a dose of 200–400 mg per day given orally or through a nasogastric tube. A dose reduction of baricitinib to 2 mg per day was given to renal patients with abnormal GFR value (30–60 mL/min/m^2). The combination of baricitinib and hydroxychloroquine resulted in clinical improvements of 80% of the patients.[20]

Cross-sectional study

Rosas et al. reported 60 hospitalized COVID-19 patients treated with baricitinib (12 patients) or tocilizumab (20 patients) or combination of baricitinib and tocilizumab (11 patients) or without baricitinib and tocilizumab (17 patients). Among patients having baricitinib therapy (23 patients), 13% of them was admitted to the ICU. Meanwhile, among patient with tocilizumab therapy (31 patients), 47% of them needed ICU care. No patient with a single baricitinib therapy was admitted to the ICU. However, there was 60% of single tocilizumab users admitted to the ICU. In term of mortality, there were comparable numbers between all of groups. There are no relevant side effects associated with the administration of baricitinib or tocilizumab.[21]

Quality assessment of the eligible articles

The methodological quality of the first clinical trial is low since there were unclear information about the randomization, allocation concealment, and blinding. However, the other two trials had a good quality. From the results of the methodological assessment of the quasi-experimental study, we found that the characteristics of patients with and without baricitinib are not comparable. For the before-after (pre-post) studies, the sample size is limited and no information about blinding of outcome assesor. Meanwhile, for the cross-sectional study, we found that the article did not explain how the size of the study is determined and information about the selection of eligible participants is not complete (Table 2).

Discussion

There were seven eligible articles found from 878 identified articles. All the articles suggested

Table 2 Critical Appraisals of Each Eligible Article

Critical Appraisal Tools	References	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13
JBI Critical Appraisal Checklist for RCT	Hasan et al., 2021	Unclear	Unclear	No	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Marconi et al., 2021	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Kalil et al., 2021	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
JBI Critical Appraisal Checklist For Quasi-Experimental Study	Bronte et al., 2020	Yes	No	No	Yes	Unclear	Yes	Yes	Yes	Yes	_	_	_	_
NHLBI Critical Appraisal Checklist For Before-After (Pre-Post) Studies With No Control Group	Gomez et al., 2021	Yes	Yes	Yes	Yes	No	Yes	Yes	Not reported	Not applicable	Yes	Not applicable	Not applicable	_
	Titanji, et al., 2020	Yes	Yes	Yes	Yes	No	Yes	Yes	Not reported	Not applicable	Yes	Not applicable	Not applicable	_
SURE Critical Appraisal Checklist For Cross Sectional Descriptive Study	Rosas et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	_

that baricitinib can improve the clinical condition of COVID-19 patients indicated by negative PCR test results, improving breathing quality, decreased ICU requirements, decreased length of hospital stay as well as the risk of death. Moreover, baricitinib administration does not cause serious side effects.

From the clinical trials, it was reported that the administration of 8 mg baricitinib (loading dose) on the first day, then added with a maintenance dose of 4 mg on day 2 to day 14 produced a better clinical improvements, than without baricitinib loading dose (4 mg daily).[22] Baricitinib also produced synergistic effects with standard therapy such as corticosteroid or remdesivir or combination of them.[17,18] Moreover, the combination is also reportedly safe.[17,18]

Baricitinib might have two dual actions i.e. as an immunomodulator that interferes with the cytokine release and as an antiviral that prevents viral endocytosis. Inhibition of AAK1 and GAK can prevent virus entry into host cells. Baricitinib is an immunomodulatory agent that works by selective and reversible inhibition of JAK1/2. JAK is an enzyme that can transduce signals mediated by various cytokines involved in inflammation and immunity. Signal transduction of JAK1/2 begins with the binding of IL-6 to its receptor and is also involved in signal transduction of other cytokines such as TNF- and IL-10. Therefore, baricitinib has an important role in reducing systemic inflammation and lung damage.[19]

Virus enters the pneumocyte via endocytosis. This occurs through the binding process of the S1 protein on the surface of SARS-CoV-2 through the ACE2 receptors found on the cell surface of some organs, such as the lungs. ACE2 receptor regulators including (AAK1) and GAK mediate clathrin-dependent endocytosis.[23] Baricitinib might work by inhibiting the passage and intracellular assembly of SARS-CoV-2 into target cells through impaired AAK1 signaling. Baricitinib may also reduce inflammation in ARDS patients.[23]

Another potent immunosuppressor that has been also studied as an alternative therapy for COVID-19 is tocilizumab. Both tocilizumab and baricitinib inhibit IL-6. However, the use of baricitinib monotherapy and tocilizumab monotherapy gave different results in terms of the percentage of ICU admissions. Rosas et al. reported that patients receiving baricitinib therapy did not require ICU treatment, in contrast to patients treated with tocilizumab who still required ICU care. Yet, combination therapy of baricitinib and tocilizumab shortens hospitalization time, compared to baricitinib alone. This may reinforce the idea of early use of baricitinib to prevent the need for an ICU care. Both of tocilizumab and baricitinib do not cause serious side effects.[24]

Another study comparing the use of baricitinib and tocilizumab therapy in hospitalized moderate to severe COVID-19 patients indicates that baricitinib administration was correlated with a reduction in the use of assisted mechanical ventilation (AMV). As much as 45% of tocilizumab users required AMV and there was only 20% of baricitinib users needed AMV. The use of baricitinib was also correlated with a lower mortality than the use of tocilizumab. There was 45% of tocilizumab user died. Meanwhile, there was only 37% of baricitinib users died. Furthermore, tocilizumab did not reduce the length of hospital stay (remained hospitalized for more than 10 days) but patients treated with baricitinib have shorter hospital stays (had a hospitalized stay of fewer than 10 days).[22]

Furthermore, the combination of baricitinib and lopinavir or ritonavir for the treatment of COVID-19 has a strong potential because of baricitinib with the relevant cytochrome drug-metabolizing enzymes has minimal interaction. Comedication of baricitinib with lopnavir/ritonavir can reduce viral infectivity,

aberrant host inflammatory response and viral replication.[16] Cantini et al. reported the clinical benefit and safety of using baricitinib in combination with lopinavir-ritonavir (case group) compared to patients taking standard therapy for COVID-19 treatment (lopinavir-ritonavir and hydroxychloroquine/control group). Participants were divided into two groups, i.e. case group (12 participants) and comparison group (12 participants). The 12 patients in the case group experienced better improvement in respiratory function, clinical symptoms, and clinical laboratory parameters. Patients with baricitinib and lopinavir-ritonavir combination also did not need ICU care and 80% of them were discharged from the hospital during two weeks of treatment. Meanwhile, almost 60% of patients with standard therapy needed ICU transfer and only one of them was discharged after two weeks of therapy.[23]

From the risk of bias assessment, there were two RCTs which have a good methodological quality. However, the other articles have some important shortcomings in their methodology and therefore, influence their quality. Currently, there are 25 clinical trials underway in various countries which are expected to provide better scientific evidence and support the use of baricitinib as a candidate for COVID-19 drugs.[24]

This study is a systematic review that has the highest position in the scientific evidence hierarchy because of its methodological strength in which the article search, screening, and data extraction process were carried out systematically. We performed methodological quality assessments for each eligible study. However, this study has also some limitations. We only describe the results descriptively, without any statistical analysis, because of the heterogeneity of the study designs, treatments, and outcomes. We recommend to do an updated systematic-review regarding this topic regularly by including the studies with a high-evidence level (RCTs) only with comparable treatments and outcomes to enable a meta-analysis of the effect estimates. Finally, the current evidence of the baricitinib use on COVID-19 patients is still limited and the quality of the evidence is low. Therefore, further clinical study is needed to warrant the effectiveness and safety of baricitinib in COVID-19.

Conclusions

From the limited study, it can be concluded that baricitinib seems to be a potential candidate therapy for COVID-19 patients. However, since the number and methodological quality of the studies are low, we still need more and better studies to ascertain the promising effect of baricitinib on COVID-19.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the study, authorship, and/or publication of this article.

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Supplementary Material 1 Results of Library Searches on PubMed and Embase

Database	Keyword	Searching Strategy	Number of Articles Identified
PubMed	COVID-19	("COVID-19"[MeSH Terms] OR "SARS-CoV-2"[MeSH Terms] OR "COVID-19 drug treatment"[Supplementary Concept] OR ("COVID-19 infections"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR "2019 ncov"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "2019 novel coronavirus disease"[Title/Abstract] OR "COVID-19 pandemic"[Title/Abstract] OR "SARS-CoV-2 infection"[Title/Abstract] OR "COVID-19 virus disease"[Title/Abstract] OR "2019 novel coronavirus infection"[Title/Abstract] OR "2019-nCoV infection"[Title/Abstract] OR "coronavirus disease 2019"[Title/Abstract] OR "coronavirus disease-19"[Title/Abstract] OR "2019-nCoV disease"[Title/Abstract]))	128,925
	Baricitinib	("baricitinib"[Supplementary Concept] OR "Janus Kinase Inhibitors"[MeSH Terms] OR "olumiant"[Title/Abstract] OR "baricitinib"[Title/Abstract] OR "janus kinase inhibit*"[Title/Abstract])	1,693
	COVID-19 AND Baricitinib	("COVID-19"[MeSH Terms] OR "SARS-CoV-2"[MeSH Terms] OR "COVID-19 drug treatment"[Supplementary Concept] OR ("COVID-19 infections"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR "2019 ncov"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "2019 novel coronavirus disease"[Title/Abstract] OR "COVID-19 pandemic"[Title/Abstract] OR "SARS-CoV-2 infection"[Title/Abstract] OR "COVID-19 virus disease"[Title/Abstract] OR "2019 novel coronavirus infection"[Title/Abstract] OR "2019-nCoV infection"[Title/Abstract] OR "coronavirus disease 2019"[Title/Abstract] OR "coronavirus disease-19"[Title/Abstract] OR "2019-nCoV disease"[Title/Abstract])) AND ("baricitinib"[Supplementary Concept] OR "Janus Kinase Inhibitors"[MeSH Terms] OR "olumiant"[Title/Abstract] OR "baricitinib"[Title/Abstract] OR "janus kinase inhibit*"[Title/Abstract])	181
Embase	COVID-19	(('coronavirus disease 2019'/exp OR 'severe acute respiratory syndrome coronavirus 2'/exp) OR ('anti-sars-cov-2 agent'/exp OR 'sars-related coronavirus'/exp OR 'sars cov 2':ab,ti OR 'covid 19':ab,ti OR '2019 ncov':ab,ti OR covid19:ab,ti OR 'severe acute respiratory syndrome coronavirus 2':ab,ti OR '2019 novel coronavirus disease':ab,ti OR 'covid-19 pandemic':ab,ti OR 'sars-cov-2 infection':ab,ti OR 'covid-19 virus disease':ab,ti OR '2019 novel coronavirus infection':ab,ti OR '2019-ncov infection':ab,ti OR 'coronavirus disease 2019':ab,ti OR 'coronavirus disease-19':ab,ti OR '2019-ncov disease':ab,ti OR 'covid-19 pneumonia'))	135,199
	Baricitinib	(('baricitinib'/exp OR 'janus kinase inhibitor'/exp) OR (baricitinib:ab,ti OR 'janus kinase inhibit*':ab,ti OR olumiant:ab,ti))	18,014
	COVID-19 AND Baricitinib	(('coronavirus disease 2019'/exp OR 'severe acute respiratory syndrome coronavirus 2'/exp) OR ('anti-sars-cov-2 agent'/exp OR 'sars-related coronavirus'/exp OR 'sars cov 2':ab,ti OR 'covid 19':ab,ti OR '2019 ncov':ab,ti OR covid19:ab,ti OR 'severe acute respiratory syndrome coronavirus 2':ab,ti OR '2019 novel coronavirus disease':ab,ti OR 'covid-19 pandemic':ab,ti OR 'sars-cov-2 infection':ab,ti OR 'covid-19 virus disease':ab,ti OR '2019 novel coronavirus infection':ab,ti OR '2019-ncov infection':ab,ti OR 'coronavirus disease 2019':ab,ti OR 'coronavirus disease-19':ab,ti OR '2019-ncov disease':ab,ti OR 'covid-19 pneumonia')) AND ((('baricitinib'/exp OR 'janus kinase inhibitor'/exp) OR (baricitinib:ab,ti OR 'janus kinase inhibit*':ab,ti OR olumiant:ab,ti))	878

Supplementary Material 2 Bias Assessment of Each Eligible Studies: (1) 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.

No.	Criteria	Yes	No	Unclear	NA
1	Was true randomization used for assignment of participants to treatment groups?	√			
2	Was allocation to treatment groups concealed?			√	
3	Were treatment groups similar at the baseline?	√			
4	Were participants blind to treatment assignment?			√	
5	Were those delivering treatment blind to treatment assignment?			√	
6	Were outcomes assessors blind to treatment assignment?			√	
7	Were treatment groups treated identically other than the intervention of interest?	√			
8	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	√			
9	Were participants analyzed in the groups to which they were randomized?	√			
10	Were outcomes measured in the same way for treatment groups?	√			
11	Were outcomes measured in a reliable way?	√			
12	Was appropriate statistical analysis used?	√			
13	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	√			

Supplementary Material 2 (Cont.) Bias Assessment of Each Eligible Studies: (2) Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, 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 Med. 2021;9(12):1407–18.

No.	Criteria	Yes	No	Unclear	NA
1	Was true randomization used for assignment of participants to treatment groups?	√			
2	Was allocation to treatment groups concealed?	√			
3	Were treatment groups similar at the baseline?	√			
4	Were participants blind to treatment assignment?	√			
5	Were those delivering treatment blind to treatment assignment?	√			
6	Were outcomes assessors blind to treatment assignment?		√		
7	Were treatment groups treated identically other than the intervention of interest?	√			
8	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	√			
9	Were participants analyzed in the groups to which they were randomized?	√			
10	Were outcomes measured in the same way for treatment groups?	√			
11	Were outcomes measured in a reliable way?	√			
12	Was appropriate statistical analysis used?	√			
13	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	√			

Supplementary Material 2 (Cont.) Bias Assessment of Each Eligible Studies: (3) Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolf CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med. 2021;384(9):795-807.

No.	Criteria	Yes	No	Unclear	NA
1	Was true randomization used for assignment of participants to treatment groups?	√			
2	Was allocation to treatment groups concealed?	√			
3	Were treatment groups similar at the baseline?	√			
4	Were participants blind to treatment assignment?	√			
5	Were those delivering treatment blind to treatment assignment?	√			
6	Were outcomes assessors blind to treatment assignment?		√		
7	Were treatment groups treated identically other than the intervention of interest?	√			
8	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	√			
9	Were participants analyzed in the groups to which they were randomized?	√			
10	Were outcomes measured in the same way for treatment groups?	√			
11	Were outcomes measured in a reliable way?	√			
12	Was appropriate statistical analysis used?	√			
13	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	√			

Supplementary Material 2 (Cont.) Bias Assessment of Each Eligible Studies: (4) 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.

No.	Criteria	Yes	No	Unclear	NA
1	Is it clear in the study what is the ‘cause’ and what is the ‘effect’ (i.e. there is no confusion about which variable comes first)?	√			
2	Were the participants included in any comparisons similar?		√		
3	Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?		√		
4	Was there a control group?	√			
5	Were there multiple measurements of the outcome both pre and post the intervention/exposure?			√	
6	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	√			
7	Were the outcomes of participants included in any comparisons measured in the same way?	√			
8	Were outcomes measured in a reliable way?	√			
9	Was appropriate statistical analysis used?	√			

Supplementary Material 2 (Cont.) Bias Assessment of Each Eligible Studies: (5) Titanji BK, Farley MM, Mehta A, Connor-Schuler R, Moanna A, Cribbs SK, et al. Use of baricitinib in patients with moderate to severe coronavirus disease 2019. Clin Infect Dis. 2021;72(7):1247–50.

No.	Criteria	Yes	No	Other (CD,NR,NA)*
1	Was the study question or objective clearly stated?	Yes		
2	Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes		
3	Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes		
4	Were all eligible participants that met the prespecified entry criteria enrolled?	Yes		
5	Was the sample size sufficiently large to provide confidence in the findings?		No	
6	Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes		
7	Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes		
8	Were the people assessing the outcomes blinded to the participants' exposures/interventions?			NR
9	Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?			NA (retrospective study)
10	Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes		
11	Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?			NA
12	If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			NA

Supplementary Material 2 (Cont.) Bias Assessment of Each Eligible Studies: (6) Gómez RI, Méndez R, Palanques-Pastor T, Ballesta-López O, Almenar CB, Vericat JEM, et al. Baricitinib against severe COVID-19: Effectiveness and safety in hospitalised pretreated patients. Eur J Hosp Pharm. 2022;29(e1):e41–45.

No.	Criteria	Yes	No	Other (CD,NR,NA)*
1	Was the study question or objective clearly stated?	Yes		
2	Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes		
3	Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes		
4	Were all eligible participants that met the prespecified entry criteria enrolled?	Yes		
5	Was the sample size sufficiently large to provide confidence in the findings?		No	
6	Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes		
7	Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes		
8	Were the people assessing the outcomes blinded to the participants' exposures/interventions?			NR
9	Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?			NA (retrospective study)
10	Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes		
11	Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?			NA
12	If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			NA

Supplementary Material 2 (Cont.) Bias Assessment of Each Eligible Studies: (7) Rosas J, Liaño FP, Cantó ML, Barea 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. Reumatol Clin. 2020;18(3):150–6.

Citation: Rosas, 2020. Are there other companion papers from the same study?		
No.	**Criteria**	**Yes/Can't tell/No**
1	Is the study design clearly stated?	Yes
2	Does the study address a clearly focused question? Consider: Population; Exposure (defined and accurately measured?); Outcomes.	Yes
3	Are the setting, locations and relevant dates provided? Consider: recruitment period; exposure; data collection.	Yes
4	Were participants fairly selected? Consider: eligibility criteria; sources & selection of participants.	Yes
5	Are participant characteristics provided? Consider if: sufficient details; a table is included.	Yes
6	Are the measures of exposures & outcomes appropriate? Consider if the methods of assessment are valid & reliable.	Yes
7	Is there a description of how the study size was arrived at?	No
8	Are the statistical methods well described? Consider: How missing data was handled; were potential sources of bias (confounding factors) considered/controlled for.	Yes
9	Is information provided on participant eligibility? Consider if following provided: number potentially eligible, confirmed eligible, entered into study.	No
10	Are the results well described? Consider if: effect sizes, confidence intervals/standard deviations provided; the conclusions are the same in the abstract and the full text.	Yes
11	Is any sponsorship/conflict of interest reported?	Yes
12	Finally... Did the authors identify any limitations and, if so, are they captured above?	Yes