Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19: a systematic review and meta-analysis

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Abstract
Several clinical trials have evaluated the efficacy and safety of baricitinib in COVID-19 patients. Recently, there have been reports on critical patients, which are different from previous research results. Studies were searched in PubMed, Embase, and Cochrane Library databases on January 31, 2023. We performed a meta-analysis to estimate the efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19. This study is registered with INPLASY, number 202310086. A total of 3010 patients were included in our analyses. All included studies were randomized controlled trials or prospective study. There was no difference in 14-day mortality between the two groups (OR 0.23 [95% CI 0.03-1.84], I²=72%, P=0.17). In subgroup analyses we found that baricitinib did not seem to improve significantly in 24-day mortality critically ill patients (OR 0.60 [95% CI 0.35-1.02], I²=0%, P=0.06). Fortunately, baricitinib has led to faster recovery and shorter hospital stays for COVID-19 patients. There were no difference in infections and infestations, major adverse cardiovascular events, deep vein thrombosis and pulmonary embolism. Baricitinib is safe. At the same time, we can find that it reduces the mortality of COVID-19 patients, but the prognosis of the critically ill patients is not significantly improved.

Introduction
Many COVID-19 remains an important cause of death in recent years, especially among unvaccinated people with comorbidities or the elderly. A large number of literatures have reported that SARS-CoV-2 infection is often accompanied by excessive inflammation, which may lead to multiple organ dysfunction and even death [1–3]. People are constantly seeking for better drugs to improve patient mortality, including Baricitinib [4]. Barisinib is an oral Janus kinase (JAK) 1/2 inhibitor that was previously approved by the European Medicines Agency (EMA) for several chronic autoimmune diseases [5].

Studies have found that barisinib can reduce inflammatory storms, and serological examination showed that the application of the drug reduced cytokines and biomarkers related to the pathophysiology of COVID-19 in patients [6–8]. Later, World Health Organization (WHO) guidelines recommended the use of baricitinib, a Jak 1,2 inhibitor, for hospitalized COVID-19 patients receiving corticosteroid treatment. However, at that time, the relevant clinical evidence was relatively limited, so WHO recommended initiation of treatment "depending on availability," as well as "clinical and contextual factors"[9].

In the past, five clinical studies [4,6,10–12] have compared the efficacy and safety endpoint of baricitinib and placebo for COVID-19 patients. Although they are all COVID-19 patients, the severity of the groups included in different studies is different. We will analyze the mortality, length of stay and related adverse events of COVID-19 inpatients after the application of baricitinib, and strive to provide certain guidance for clinical practice.

Methods
We carried out the meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[13]. Our protocol has been registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols database (inplasy protocol: INPLASY202310086), and is available in full on inplasy.com (https://inplasy.com/inplasy-2023-1-0086). Ethics approval was not required for our work.

Search strategy
Three independent researchers (Jing Sun, Shufang Wang and Xin Ma) conducted extensive electronic searches for relevant articles published on Jan 30, 2023. The database includes PubMed, Embase and the Cochrane database. Manually select relevant randomized controlled trial. The search strategy of the literature was shown in the supplement (supplement Table S1).

Inclusion and exclusion
EndNote (X9 version) software is selected for document management, two investigators independently evaluated the eligibility of the identified items. The title and summary are filtered for the first time, and qualified articles are reserved for full-text review. Inclusion criteria for studies meeting the following requirements include: (1) Patients of hospitalised adults with COVID-19. (2) Treatment with baricitinib or placebo. (3) Outcomes Indicators: Death from any cause/ Duration of hospitalization/ Median time to recovery/ Infections and infestations/ Major adverse cardiovascular events (MACEs)/ Pulmonary embolism (PE)/ Deep vein thrombosis(DVT), including one. We excluded studies enrolling patients < 18 years old, and there was not enough data to extract, such as the summary of some meetings, literature materials such as review and pharmacological introduction. We contacted the authors if associated data from their studies were required.

Bias & quality assessment
The two researchers independently evaluated, preliminarily selected and checked the literature data according to the unified and standardized method, and included them in the literature in strict accordance with the admission and exclusion criteria, and then collected information. Evaluate the quality of selected articles according to the quality evaluation standard of Cochrane Reviewer Handbook 5.1.0[14].

Data Synthesis And Analysis
Revman5.3 were used for meta-analysis. Data which met homogeneity (P > 0.10 and I² ≤ 50%) through heterogeneity test were meta-analyzed using fixed effect model. If homogeneity (P ≤ 0.10 or I² > 50%) was not met, and heterogeneity cannot be ruled out, random effect model can be used to combine effects[15]. While it should be noted that sensitivity analysis and subgroup analysis should be considered for this type of analysis data. Results were expressed as odds ratio (OR) with a 95% confidence interval (CI) with discontinuous outcomes. For the continuous outcomes, mean differences...
We estimated the mean from median and standard deviations (SD) from IQR using the methods described in the previous studies[16]. A p value < 0.05 was considered statistically significant.

Results

The flow chart (Fig. 1) summarizes the search and study selection process. A total of 242 related literatures were retrieved, of which 73 were excluded due to duplication. 143 studies were also excluded after reading the titles and abstracts. The remaining 26 studies were assessed by reading the full texts. Data from 5 trails evaluating the Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 were included.

The main features of included trials are presented in Table 1. A total of 3010 patients were included in our analyses. All included studies were randomized controlled trials or prospective study. All of the studies were comparing the efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19. The first three of the five studies in Table 1 are for hospitalized patients who have all been diagnosed with COVID-19, and the last two are for critically ill COVID-19 patients who have severe oxygenation disorder or receive mechanical ventilation/extracorporeal membrane oxygenation. No differences were observed in terms of proportion of patients lost to follow up across trials.

<table>
<thead>
<tr>
<th>Num</th>
<th>Author/ Year</th>
<th>Design</th>
<th>Intervention assignments</th>
<th>Participants</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bronte/2020</td>
<td>PS, MC</td>
<td>4mg bid for 2 days, followed by 4mg qd</td>
<td>conventional therapy</td>
<td>14 days or until hospital discharge</td>
</tr>
<tr>
<td>2</td>
<td>Kalil/2021</td>
<td>RCTs, MC</td>
<td>4-mg qd</td>
<td>Placebo</td>
<td>14 days or until hospital discharge</td>
</tr>
<tr>
<td>3</td>
<td>Marconi/2021</td>
<td>RCTs, MC</td>
<td>4-mg qd</td>
<td>Placebo</td>
<td>14 days</td>
</tr>
<tr>
<td>4</td>
<td>Ely/2022</td>
<td>RCTs, MC</td>
<td>4-mg qd</td>
<td>Placebo</td>
<td>14 days</td>
</tr>
<tr>
<td>5</td>
<td>Trøseid/2023</td>
<td>RCTs, MC</td>
<td>4-mg qd</td>
<td>Placebo</td>
<td>14 days</td>
</tr>
</tbody>
</table>

ARDS = Acute respiratory distress syndrome; B/C = baricitinib group/ control group; Bid = twice daily; DVT = deep vein thrombosis; MACEs = Major adverse cardiovascular events; MC = Multicenter; PE = pulmonary embolism; PS = prospective study; Qd = Once a day; RCTs = randomized clinical trials; * Severe or critical COVID-19.

The efficacy outcomes are summarized in Fig. 2A and Fig. 2B (Fig. 2C and Fig. 2D in the Supplement Fig. 2CD). There was no difference in 14-day mortality (A) between the two groups (OR 0.23 [95% CI 0.03–1.84], I²=72%, P = 0.17). Four studies reported 28-day mortality (B) outcomes in which baricitinib improved patient outcomes (OR 0.60 [95% CI 0.47–0.77], I²=0%, P < 0.0001), but in subgroup analyses we saw that baricitinib did not seem to improve significantly in critically ill patients (OR 0.60 [95% CI 0.35–1.02], I²=0%, P = 0.06). Fortunately, baricitinib have led to faster recovery (D) and shorter hospital stays(C) for COVID-19 patients(MD= -1.00 [95% CI -1.12–-0.88], I²=0%, P < 0.0001; MD = -0.80 [95% CI -0.84–-0.76], I²=0%, P < 0.0001). The safety outcomes are summarized in Fig. 3. There were no difference in infections and infestations (a), major adverse cardiovascular events (b), deep vein thrombosis(c) and pulmonary embolism(d). However, these results are based on the results of two randomized controlled trials conducted in patients with critically ill COVID-19.

We use Revman to investigate the influence of a single study on the overall pooled estimate of each predefined outcome. We found that the removal of any one study would not affect the following results. The results of the risk of bias assessment of these trials are summarized in the Supplement Fig. 1. Three studies were considered at low risk for overall risk of bias.

Discussion
This outbreak initially attracted people's attention as an unusual viral pneumonia, and atypical upper respiratory pneumonia has been the main characteristic disease severity of this outbreak so far [17]. Bronchoalveolar lavage fluid was derived from macrophages with high levels of chemokines secreted by severe pneumonia [18]. Postmortem lung tissue analysis of COVID-19 patients with severe pneumonia also found excessive immune cell infiltration [19]. Baricitinib, inhibitors of Janus kinase (JAK)-1 and JAK-2, plays an important role in the regulation of immune response. Our meta-analysis system evaluated its efficacy and safety.

Our article systematically evaluated the efficacy and safety of baricitinib for COVID-19 patients by including 5 high-quality research literatures. It is a meta-analysis with the largest sample size of baricitinib and a high level of evidence. In the analysis of mortality, we adopted 14-day mortality and 28-day mortality. The results showed that baricitinib application improved the 28-day mortality of general inpatients, but did not improve the 14-day mortality of inpatients and 28-day mortality of critically ill patients, which is worth thinking about the application of baricitinib only. However, it is certain that the use of the drug did not increase the occurrence of adverse events in patients, and shortened the length of stay in the inpatient. There have also been studies claiming that the risk/benefit ratio of baricitinib in patients with severe/critical COVID-19 may vary depending on the immune status of SARS-CoV-2, and that potential host factors such as comorbidity, older age and possible immune response [20] may contribute to this difference.

Our study, which pooled existing high-quality studies, has clear advantages, particularly in terms of mortality, and conducted a subgroup analysis of patients who were not at risk, revealing the different effects of the drug in different patients. And the safety of drugs in critically ill patients was analyzed. It provides a strong guiding value for clinic. Of course, this study also has some limitations. The current number of studies is relatively small, and more RCTs are needed to support it in the future.

Conclusions

In terms of safety, baricitinib do not increase the occurrence of adverse reactions (DVT, PE, MACEs, etc.). At the same time, we can find that it reduces the mortality of COVID-19 patients, but the prognosis of the critically ill patients is not significantly improved.

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

All authors approved the final manuscript and the submission to this journal.

Availability of data and materials:

Data sets are available on request from the corresponding author.

Conflict of interest:

Authors state no conflict of interest.

Funding information:

none.

Author contributions:

JS, S-FW and XM searched the scientific literature and drafted the manuscript. Q-QW, Y-JP and YB contributed to data abstract. G-BM, CM and PL contributed to conception, design, data interpretation, manuscript revision for critical intellectual content, and supervision of the study. The authors read and approved the final manuscript.

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References


Figures
Figure 1

The flow chart of the search and study selection process.
Figure 2

a: The efficacy outcomes of 14-day mortality.

b: The efficacy outcomes of 28-day mortality.
Figure 3

The safety outcomes of infections and infestations (a), major adverse cardiovascular events (b), deep vein thrombosis(c) and pulmonary embolism(d).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementTableS1.docx
- SupplementaryFigure1.docx
- SupplementaryFigure2C.png
- SupplementaryFigure2D.png