

INPLASY PROTOCOL

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Corresponding author:

Kai Yang

a15828075272@163.com

Author Affiliation: 1. Chengdu Medical College, Xindu Avenue, Xindu District, Chengdu (610500), Sichuan, China. 2. Department of Respiratory and Critical Care Medicine, Chengdu Medical College's First Affiliated Hospital, No. 278, Baoguang Avenue, Xindu District, Chengdu (610500), Sichuan, China.

Support: None.

Review Stage at time of this submission: Preliminary searches.

Conflicts of interest:

None declared.

INTRODUCTION

Review question / Objective: This study was conducted to give evidence-based recommendations on the safety of existing

A Bayesian Network Meta-analysis for Comparative Safety Assessment of Favipiravir Interventions in Hospitalized Covid-19 Patients

Yang, K¹; Zeng, J²; Dai, W³; Chen, M⁴; Yang, F⁵.

Review question / Objective: This study was conducted to give evidence-based recommendations on the safety of existing clinically used pharmacological therapy in contrast to favipiravir for COVID-19 patients, Our primary outcomes were adverse events (measured by the total number of patients in each group who experienced an adverse event).

Condition being studied: COVID-19 is a contagious coronavirus-caused illness that produces severe acute respiratory syndrome (SARS-CoV-2). The first known case was detected in Wuhan, China, in December 2019. Since then, the illness has expanded internationally, resulting in an ongoing pandemic; nonetheless, there is a lack of evidence for direct comparison of favipiravir treatment considering the expense and resources available.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 October 2021 and was last updated on 26 October 2021 (registration number INPLASY2021100099).

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METHODS

Participant or population: Hospitalized Covid-19 Patients of all ages.

Intervention: Favipiravir.

Comparator: The control treatment will include any types of interventions and placebo.

Study designs to be included: Only RCT (randomized controlled trials) will be included.

Eligibility criteria: We included double-blind or open-label randomized controlled trials (RCTs) that compared favipiravir to placebo or another active pharmaceutical product at a therapeutic dose for the acute treatment of people of all ages with COVID-19 diagnosed using major standard diagnostic criteria (a positive real-time polymerase chain reaction (RT-PCR) test or typical ground glass appearance on chest CT scan). Furthermore, all traditional antiviral medications and other pharmaceuticals approved by pharmaceutical and medical device regulatory bodies in North America, Europe, and China were included, however, the following dietary supplements and botanical medications were excluded: Favipiravir, Tocilizumab, Favipiravir+Tocilizumab, Lopinavir +Ritonavir, Chloroquine, and Arbidol. Fixed-dose and variable-dose designs were also allowed. The webappendix offers detailed information on review procedures and

search strategy. We chose one week to four months for outcome assessments because we intended to investigate favipiravir's safety for acute treatment in the short term. We used trial data from the time endpoint. We now include a more comprehensive list of six antivirals or placebo, include clinical outcome markers and numerous potential impact modifiers, and use the most powerful statistical technique for network meta-analysis available. This study will enable the prediction of unique therapeutic outcomes, such as early response or specific side effects at various timepoints. Journal articles, conference papers, sponsor publications such as trial summaries, and documents from regulatory reviews and filings were all considered for inclusion. Finally, we removed incomplete randomised trials as well as continuing investigations. The computerized database searches were augmented by manual searches for published, unpublished, and ongoing RCTs in other international trial registers and relevant scientific publications in the region.

Information sources: We searched Pubmed, the Cochrane Central Register of Controlled Trials, the International Clinical Trials Registry Platform, MedRxiv, and ClinicalTrials.gov for relevant RCTs of putative medications drugs for hospitalized patients with COVID-19 from January 10, 2020 to July 10, 2021, with no language restrictions. All relevant pharmaceutical companies and authors were contacted in order to address gaps in the original papers' reporting or to offer fresh data for previously unreported data. In combination with the names of all clinically used antiviral medicines, we used the search terms "Covid-19*" OR "corona virus*" AND "favipiravir*" OR "Avigan*" AND "RCT*" OR "trial*" OR "randomized controlled trials*".

Main outcome(s): Our primary outcomes were adverse events (measured by the total number of patients in each group who experienced an adverse event), ORs were used to calculate effect sizes, and statistical significance was determined if

the 95 percent confidence interval did not include 1 or the p value was less than 0.05.

Quality assessment / Risk of bias analysis:

We assessed the risk of bias using the Cochrane risk of bias (RoB) tool. All included RCTs were reviewed by two independent researchers (W.D and M.C), who rated them as 'low risk,' 'high risk,' or 'unclear risk,' based on the following seven criteria: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias, any disagreements were settled by consensus and arbitration by a panel of researchers from the study team (K.Y, J.Z, W.D, M.C, and F.Y)

Strategy of data synthesis: For data synthesis, researchers used a Bayesian network meta-analysis with a random-effects model, incorporating direct and indirect evidence from trials that looked at several treatments (Favipiravir, Tocilizumab, Favipiravir+Tocilizumab, Lopinavir+Ritonavir, Chloroquine, and control). The free R package 'netmeta' was used to perform a Bayesian strategy based on Makarov chain Monte Carlo simulation. The reference group consisted of patients who received a placebo or standard of treatment. To quantify heterogeneity and inconsistency, Cochran's Q and I² statistical tests were applied. In addition, the Q-statistic was divided into between-design inconsistency and within-design heterogeneity using a design-based decomposition of Cochran's Q. A heat map of ranking probability was created, which is an analog of the surface under the cumulative ranking (SUCRA) value; a greater probability value suggests better treatment. For each conclusion, an overall network plot was also created. The edges show the number of studies that offered direct comparison results between the two therapies, whereas the nodes represent treatment. The thickness of the edges was proportionate to the number of included studies with direct evidence, and the size of the nodes was related to the number of

patients included in the treatment. To visualize all direct and indirect comparisons in this study, a league table was created, and visual inspection of the Brooks–Gelman–Rubin diagnostic ensured model convergence.

Subgroup analysis: None.

Sensitivity analysis: None.

Country(ies) involved: China.

Keywords: COVID-19, favipiravir, network meta-analysis, safety.

Contributions of each author:

Author 1 - Kai Yang.

Email: a15828075272@163.com

Author 2 - Jun Zeng.

Author 3 - Wenjing Dai.

Author 4 - Meifeng Chen.

Author 5 - Fan Yang.

Email: yangfanglung@163.com