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Favipiravir for treating patients with novel coronavirus (COVID-19): protocol for a systematic review and meta-analysis of randomised clinical trials

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ABSTRACT

Introduction An outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was reported in Wuhan, China, in mid-December 2019, and declared a pandemic by the WHO on 11 March 2020. Due to the unknown nature of the disease and the lack of specific drugs, several potential treatments were used for patients. This systematic review and meta-analysis will evaluate studies of the effects of favipiravir in COVID-19 pneumonia.

Methods and analysis We will search electronic databases including LitCovid hub, PubMed, Scopus, ISI Web of Sciences, Cochrane and Embase using keywords related to COVID-19 and favipiravir. We will search the reference lists of all included studies and reviews. We will also search for clinical trial registries, such as ClinicalTrials.gov, for the ongoing clinical trials. All randomised clinical trials investigating the safety and efficacy of favipiravir compared with other control groups for the treatment of patients with confirmed infection with SARS-CoV-2 will be included. Patients' survival at the end of the treatment as well as the follow-up will be the primary outcome of the treatment, followed by the time and rate of the patient with a negative COVID-19 test. The desired secondary outcome will consist of a decreased rate of symptoms, proportion of intensive care unit (ICU) transfers, length of the hospital stay, ICU treatments, the quality of life and additional adverse events. Data synthesis will be conducted using CMA V.2. Two independent investigators will be screening titles, abstracts and full texts of included studies, based on eligibility criteria. These investigators will then independently extract the data and appraise the quality of said studies. All potential discrepancies will be resolved through consultation with the third reviewer. Statistical heterogeneity will be assessed using a standard I^2 test. A funnel plot, Egger's test and Begg's test will be used for detecting asymmetry to explore possible publication bias.

Ethics and dissemination All findings of this systematic review and meta-analysis will help identify the safety and efficacy of favipiravir for patients with COVID-19. Given that the design of the study is a systematic review, there is no need to follow the code of ethics protocol. The results of this study will be published in a reputable journal.

PROSPERO registration number CRD42020180032.

Strengths and limitations of this study

- In the protocol, all stages of the study will be conducted by two reviewers independently and supervised by a third reviewer.
- This systematic review may produce the first meta-analysis that provides evidence regarding the safety and effectiveness of favipiravir on patients with COVID-19.
- The small number of studies published in this field when writing a protocol can be one of the most important limitations.

INTRODUCTION

An outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was reported in Wuhan, China, in mid-December 2019, and declared a pandemic by the WHO on 11 March 2020.[1 2] Novel coronavirus 2019, named COVID-19 by WHO, is characterised by several symptoms including fever, cough and shortness of breath. The effects of this disease are much more severe with men, the elderly and people with other chronic health conditions, such as cardiovascular disease, diabetes, chronic respiratory disease and hypertension.[3 4] As of 14 April 2020, nearly 2 000 000 people have been diagnosed with COVID-19 and about 120 000 deaths have been reported worldwide.[5]

It is important to find effective treatment options as the disease progresses and has potential effects on global health.[6] In addition to other drugs such as lopinavir, ritonavir, ribavirin and chloroquine phosphate, which are used to treat this disease, the use of favipiravir is also being initiated in many clinical trials.[7 8] Favipiravir, a purine nucleic acid analogue and a virus RNA-dependent RNA polymerase (RdRp) inhibitor, is an antiviral medication that was approved in 2014 by the Japan Pharmaceuticals and Medical Devices Agency for the treatment of influenza A virus

infection. It is also being studied to treat several other viral infections including COVID-19.[9 10]

While the use of favipiravir drug is being applied for treatment of patients with COVID-19, uncertainty remains about its safety and effectiveness. Little was known about the drug at the time of writing this protocol.[11] However, studies have been recorded in some clinical trial registries that have not yet been published.[12 13] Therefore, we aim to systematically review the available literature of the application of favipiravir in patients with COVID-19 to examine the empirical evidence of the effects of this drug for COVID-19-related pneumonia. We intend to provide rigorous evidence for clinical practice in treating patients with COVID-19.

METHODS AND ANALYSIS

Protocol and registration

This protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) on 5 February 2020. We report this protocol following the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols statement (online supplementary appendix 1).[14] This systematic review and meta-analysis will also be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[15]

Eligibility criteria

All randomised clinical trials (study design) which addressed the safety and efficacy of favipiravir (intervention) in comparison to other control groups (comparison) for treatment of patients with confirmed infection with SARS-CoV-2 (population) will be included. There will be no restrictions concerning gender, age, ethnicity, blinding, follow-up or publication status. All publications in English and Farsi will be included. Survival of patients at the end of treatment and follow-up will be the primary outcome, followed by the time and rate of the patient with a negative test for the COVID-19. Additional outcomes will consist of a decreased rate of symptoms, proportion transferred to the intensive care unit (ICU), length of stay in the hospital, ICU length of stay, quality of life and adverse events (outcomes). Articles with unavailable full text in English or Farsi language or whose full text is not accessible will be excluded from the study. The studies with insufficient or incomplete data will not be incorporated.

Information sources and search strategy

Two independent reviewers (MAZ and SH) will search the electronic databases including LitCovid hub/PubMed,[16] Scopus, ISI Web of Sciences, Cochrane, Embase and Scientific Information Database[17] using keywords combination (Medical Subject Headings term and free term), such as '2019 nCoV' OR 2019nCoV OR '2019 novel coronavirus' OR COVID-19 OR 'new coronavirus' OR 'novel coronavirus' OR 'SARS CoV-2' OR (Wuhan AND coronavirus) OR 'SARS-CoV' OR '2019-nCoV' OR 'SARS-CoV-2' and Favipiravir OR Avigan. We will search the reference lists of all included studies, reviews and clinical trial registries for an ongoing clinical trial (see online supplementary appendix 2 for the final proposed PubMed search strategy).

Study records

Once the records have been imported to EndNote X7 software and all duplicates have been removed, two reviewers (SH and DGN) will independently screen the titles, abstracts and full texts of included studies based on predefined eligibility criteria to identify studies concerning safety and efficacy of favipiravir among patients with COVID-19. A kappa (κ) statistic will be used to calculate the extent of interobserver agreement on the independent inclusion of articles. All potential discrepancies will be resolved on consultation with a third reviewer (MAZ).

Data extraction and data items

Two reviewers (SH and DGN) will independently extract data from included studies using a prepiloted data extraction form. We will pilot this form using at least three examples of included studies, and if there is a 90% and above agreement, it will be approved. The data extraction form includes the following items: author's name, year of publication, study design, study sample, country of origin, mean age of participants, gender, the severity of diseases, comorbidities, type of intervention and dose, control group, follow-up, randomisation, blinding, allocation concealment, primary and secondary outcomes and adverse events. All potential discrepancies will be resolved by consultation with a third reviewer (MAZ).

Risk of bias in individual studies

Two reviewers (SH and DGN) will independently assess the risk of bias among the included studies. We will assess the risk of bias of the included studies using Cochrane Collaboration criteria including seven items of selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias and other forms of bias. Any discrepancies will be resolved on consultation with a third reviewer (MAZ).

Data synthesis

Statistical analyses will be carried out using the CMA V.2. We will conduct analyses employing risk ratios and mean differences with 95% CIs for dichotomous continuous data, respectively. Statistical heterogeneity will be tested using Cochran's Q statistic and quantified using the I^2 statistic. If possible, we will perform subgroup analyses based on dose, follow-up time, level of disease, gender, ethnicity and age group. The Mantel-Haenszel method and the DerSimonian and Laird inverse variance method will be used for dichotomous outcomes and continuous outcomes, respectively. The fix or random effects model will be used to pool the data based on the level of

heterogeneity and the number of studies in each unit of analyses. A funnel plot, Egger's test and Begg's test will be used for detecting asymmetry to explore possible publication bias.

PATIENT AND PUBLIC INVOLVEMENT

We will not collect primary data, and therefore ethical approval will not be required.

ETHICS AND DISSEMINATION

The onset of COVID-19 and its subsequent pandemic situation is becoming a substantial global health emergency.[18] This systematic review and meta-analysis will be carried out to investigate the world's relevant literature on safety and effectiveness of favipiravir in the treatment of patients with COVID-19. Favipiravir, a purine nucleic acid analogue and a potent RdRp inhibitor, played an important role in the treatment of influenza and Ebola in recent years.[9] Several drugs such as chloroquine, Arbidol, remdesivir and favipiravir are currently undergoing clinical studies to test their efficacy and safety in the treatment of COVID-19 in many countries such as Iran, Japan and China. [7 8] To date, there is no gold standard for the treatment of COVID-19 as the evidence is poor.[19] The findings of this systematic review and meta-analysis will help evaluate the potential safety and effectiveness of favipiravir compared with other drugs. We hope the knowledge gained from this research will also assist physicians in selecting better treatment options and developing a guideline in this field. Given that the design of the study is a systematic review, there is no need to get a code of ethics. The results of this study will be published in reputable journals.

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Contributors MAZ designed the review. MAZ and SH conducted the database searches. SH and DGN screened the included studies, piloted the data extraction form, extracted the data and were involved in quality appraisal. MAZ and SH performed the meta-analysis. MAZ and SH wrote the manuscript draft. All authors read, revised and approved the final manuscript.

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