INPLASY PROTOCOL

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TMPRSS2 inhibitors for the treatment of COVID-19 in adults: a systematic review and meta-analysis of nafamostat and camostat mesylate randomised clinical trials

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Review question / Objective: **The primary objective of the systematic review and meta-analysis is to determine whether TMPRSS2 inhibition with nafamostat or camostat mesylate is associated with a reduced risk of 30-day all-cause mortality in hospitalised and non-hospitalised adults with COVID-19.**
Condition being studied: **Coronavirus disease 2019 (COVID-19). COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. Most people infected with the virus will experience mild to moderate respiratory illness and recover without requiring special treatment. However, some will become seriously ill and require medical attention. Older people and those with underlying medical conditions like cardiovascular disease, diabetes, chronic respiratory disease, or cancer are more likely to develop serious illness. Anyone can get sick with COVID-19 and become seriously ill or die at any age.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 February 2023 and was last updated on 28 February 2023 (registration number INPLASY202320120).

INTRODUCTION

Review question / Objective: **The primary objective of the systematic review and meta-analysis is to determine whether TMPRSS2 inhibition with nafamostat or camostat mesylate is associated with a reduced risk of 30-day all-cause mortality in hospitalised and non-hospitalised adults with COVID-19.**

Rationale: **The lack of effective treatments for the coronavirus disease 2019 (COVID-19) led to numerous attempts to repurpose drugs. Nafamostat and camostat mesylate are synthetic serine**

protease inhibitors licensed in Japan and Korea for indications unrelated to COVID-19. Mechanistically, both drugs block the cellular enzyme transmembrane protease serine 2 (TMPRSS2), responsible for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike protein priming, which facilitates membrane fusion and entry to the host cell surface. In vitro, both nafamostat and camostat have been tested against SARS-CoV-2 and demonstrated high potency.
The clinical efficacy and safety of nafamostat and camostat remains uncertain. There are few randomised clinical trial publications with a variety of conclusions. The available results to date should be summarised and assessed through a meta-analysis to reach an evidence-based conclusion.

Condition being studied: Coronavirus disease 2019 (COVID-19). COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. Most people infected with the virus will experience mild to moderate respiratory illness and recover without requiring special treatment. However, some will become seriously ill and require medical attention. Older people and those with underlying medical conditions like cardiovascular disease, diabetes, chronic respiratory disease, or cancer are more likely to develop serious illness. Anyone can get sick with COVID-19 and become seriously ill or die at any age.

METHODS

Search strategy: "COVID-19" AND "treatment" AND "clinical trial" AND "nafamostat" OR "CKD-314" OR "nafabeltan" OR "camostat" OR "DWJ1248".

Participant or population: Adults with COVID-19 enrolled in randomised clinical trials will be eligible.

Intervention: Nafamostat or camostat mesylate for the treatment of COVID-19 in adults.

Comparator: Standard of care or placebo.

Study designs to be included: Only randomised clinical trials will be included.

Eligibility criteria: This review will be limited to randomised clinical trials of nafamostat or camostat vs standard of care or placebo for the treatment of COVID-19 in adults. There will be no exclusions made for language.

Information sources: A comprehensive literature search will be conducted in PubMed and Cochrane databases. The medRxiv Health Sciences source will also be searched to identify preprints of preliminary reports. Additionally, registers of ongoing clinical studies will be screened.

Main outcome(s): 30-day all-cause mortality.

Additional outcome(s): Time to recovery, adverse events, and serious adverse events.

Data management: The extracted information will include study status, sponsor, author and year of publication, study location, trial identifiers, objective, participants, sample size, intervention, comparison, clinical and safety outcomes, and conclusions. Data will be managed in an Excel workbook.

Quality assessment / Risk of bias analysis: Risk of bias assessment will be performed using the revised Cochrane RoB 2 tool for individually randomised trials, which evaluates five domains:
1) bias arising from the randomisation process;
2) bias due to deviations from intended interventions;
3) bias due to missing outcome data;
4) bias in measurement of the outcomes;
5) bias in selection of the reported result.

Strategy of data synthesis: We anticipate there will be limited scope for meta-analysis due to the range of different outcomes measured across the small number of existing trials. However, where studies have used the same intervention and comparator, with the same outcome

measure, results will be pooled using a random-effects meta-analysis. Summaries of intervention effects will be provided for each study by calculating risk ratios for dichotomous outcomes or mean differences for continuous outcomes. Heterogeneity will be assessed using the Chi-squared test and the I-squared statistic. Analyses will be performed using the computer program Review Manager 5.4.1 (The Cochrane Collaboration, 2020).

Subgroup analysis: Nafamostat and camostat will be analysed separately due to significant differences in drug potency and the continuous intravenous infusion required for nafamostat. Camostat will be assessed separately in hospitalised and non-hospitalised patients because of the heterogeneity in outcomes associated between both groups where a greater mortality risk is present in hospitalised patients.

Sensitivity analysis: No sensitivity analysis will be conducted.

Language restriction: No language restrictions will be used.

Country(ies) involved: Australia and New Zealand.

Keywords: Nafamostat, camostat, COVID-19, mortality, clinical trials.

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Conflicts of interest: The following authors Susan C. Morpeth, Balasubramanian Venkatesh, Thomas E. Hills, Joshua Davis, Robert K. Mahar, Grace McPhee, Mark Jones, James Totterdell, Steven Y.C. Tong and Jason A. Roberts are members of the Australasian COVID-19 Trial (ASCOT), which is studying nafamostat as an antiviral treatment for non-critically ill, hospitalised COVID-19 patients.
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