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A systematic review and meta-analysis of adverse events of WHO approved COVID-19 treatment regimens

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ADMINISTRATIVE INFORMATION

Support - International Medical University.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 August 2023 and was last updated on 06 August 2023.

INTRODUCTION

Review question / Objective To evaluate the safety of WHO-approved treatment regimens for COVID-19 infection.

Rationale The serious and non-serious adverse events of the WHO-recommended treatment regimens for COVID-19 infections should be reported on a long-term basis and so far, this area is a gap in the literature except in meta-analysis of individual treatment regimens. We will not include hydroxychloroquine, lopinavir/ritonavir, and convalescent plasma which are strongly recommended against the use or recommended not to use category by WHO. We will include any reported adverse effects of the approved antivirals (nirmatrelvir-remdesivir, molnupiravir); monoclonal antibodies (casirivimab/imdevimab, sotrovimab,tocilizumab, sarilumab); immunosuppressants (baricitinib, ruxolitinib and tofacitinib) and systematic corticosteroids. Hence, the current systematic review and meta-analysis aimed to assess the frequencies of serious and non-serious adverse events reported in treatment groups and controlled groups of clinical trials.

Condition being studied The pandemic of COVID-19 started with its first reported case in December 2019. As of May 2022, there were more than 521 millionconfirmed cases globally with a global death of 6.2 million. Individuals of all ages are prone to COVID-19 infection with theprobability of severe consequences in elderly patients and those with comorbidities such as diabetes mellitus and loweredimmunity. World health organization (WHO) develops the most up-to-date technical clinical management guidance for COVID-19-infected patients based on ongoing assessment of new evidence generated by the international community and firstresponders.
As of May 2022, there are seventeen (17) recommendations in the WHO living guideline with two new recommendations, related tonirmatrelvir-ritonavir. There are a few studies that reviewed the side effects of COVID-19 treatments, on vitamin D, Zinc, remdesivir, hydroxychloroquine and chloroquine, azithromycin, amantadine, aspirin,

etc., but some of the treatments are outdated and not recommended anymore. A narrative study published by Chiu et al included 30 case reports, 3 case series and 10 randomized trials.

METHODS

Participant or population People with PCR-approved COVID-19 infection, any age, gender.

Intervention Any intervention of WHO-approved COVID-19 treatment regimens (approved antivirals (nirmatrelvir- remdesivir, molnupiravir); monoclonal antibodies (casirivimab/imdevimab, sotrovimab,tocilizumab, sarilumab); immunosuppressants (baricitinib, ruxolitinib and tofacitinib) and systematic corticosteroids).

Comparator Alternative WHO-approved treatment regimens or placebo.

Study designs to be included Randomized controlled trials.

Eligibility criteria Studies published in English language only will be included. Studies must report at least one outcome related to serious adverse events, non-serious adverse events and health-related quality of life..

Information sources An extensive electronic search of the multiple databases will be done to identify relevant studies available from inception toAug 2023. We will search the following databases to identify relevant clinical trials:
MEDLINE
The Cochrane Library
PubMed
We will also search the following clinical trials registries:
ClinicalTrials.gov (http://www.clinicaltrials.gov/)
WHO International Clinical Trials Registry Platform(http://apps.who.int/trialsearch/Default.aspx)
EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/)
COVID-19 resources
World Health Organization (WHO) - Global Literature on Coronavirus Disease
Oxford COVID-19 Evidence Service
A manual search will be performed in the reference lists of the relevant studies. To do so, appropriate MeSH terms with suitable Boolean operators will be used.

Main outcome(s) The proportion of people with one or more serious adverse events: we will consider an event assevere/serious if the trial authors clearly stated that it was due to the experimental or control intervention andhave defined it as a 'serious adverse event' or if it fulfilled the definition of the International Conference onHarmonization (ICH) guidelines for serious adverse events (ICH 2003; ICH-GCP 2016), that is, any event thatleads to death; is life-threatening; requires hospitalisation or prolongation of existing hospitalisation; resultsin persistent or significant disability; congenital birth or anomaly; and any important medical event which mayhave jeopardised the patient or requires intervention to prevent it. We will consider all other adverse events asnon-serious (European Medicines Agency 1995)The proportion of people with one or more adverse events is considered non-serious.
Health-related quality of life: any validated assessment scale, completed by the trial participants.

Quality assessment / Risk of bias analysis The methodological quality of the studies will be assessed using the Cochrane risk of bias tool. Methodological quality assessment will be conducted by the two independent investigators and any discrepancy will be solved by a discussion with the third investigator.

Strategy of data synthesis The safety of different therapeutic agents will be compared by pairwise meta-analysis. Relative risk and 95% confidence level will be measured for dichotomous outcomes and mean difference, or standard mean difference will be measured for continuous outcomes. Heterogeneity will be assessed using the χ^2 test and the I^2 statistic. The I2 value of 25% will be considered a low heterogeneity, 50% as moderate heterogeneity, and more than75% as a high heterogeneity. A two-tailed P value of less than 0.05 will be considered statistically significant. A funnel plot will be done to detect publication bias.
Data extraction and analysis will be conducted independently by the two investigators. A consensus will be reached in case of discrepancy by discussing it with the third investigator.
Adverse events will be reported based on the severity (serious or non-serious), based on organ system (e.g., cardiovascular, or respiratory) or grading (grade 1 – mild, asymptomatic, or mild symptoms) or grade 5 (death related to AE).
Data entry and analysis will be done with Review Manager Web, and Covidence software.

Subgroup analysis Subgroup analysis will be done according to age, gender, disease severity, and/or comorbidities if data permits.

Sensitivity analysis Heterogeneity will be assessed using the χ^2 test and the I^2 statistic. The I2 value of 25% will consider as low heterogeneity, 50% as the moderate heterogeneity, and more than 75% as a high heterogeneity. A two-tailed P value of less than 0.05 will be considered statistically significant. A funnel plot will be done to detect the publication bias.

Language restriction English only.

Country(ies) involved Malaysia.

Keywords COVID-19, adverse effect, WHO guideline, randomized clinical trial.

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