INPLASY

Adverse effects of Monoclonal Antibodies in COVID-19 patients: A Systematic Review and Meta-analysis of Observational Studies

INPLASY202470053
doi: 10.37766/inplasy2024.7.0053
Received: 12 July 2024
Published: 12 July 2024

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ADMINISTRATIVE INFORMATION

Support - IMU University (formerly known as International Medical University).

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202470053

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 July 2024 and was last updated on 12 July 2024.

INTRODUCTION

Review question / Objective To investigate the safety (adverse effects) of monoclonal antibodies (mAbs) in COVID-19 patients reported in observational studies.

Rationale The first case of the COVID-19 pandemic was first reported in December 2019. Up until 23rd April 2024, there were a total of 704,753,890 cases of COVID-19 positive cases worldwide with a global mortality of 7,010,681 cases. All ages are prone to COVID-19 infection. However, the risk of severity and mortality is increased in patients with comorbidities such as diabetes mellitus, malignancy, or obesity etc. During the pandemic, the World Health Organization (WHO) developed up-to-date technical clinical management guidelines for COVID-19-infected patients based on ongoing new evidence generated by the international community of healthcare researchers. Based on the randomised clinical trials, case reports and living systematic reviews, WHO guideline modified the guidelines and added or excluded some treatments during the pandemic. The COVID-19 treatment guidelines include antiviral agents, monoclonal antibodies (mAbs), Janus Kinase (JAK) inhibitors, and corticosteroids and the treatment regimens differ depending on the severity.

Among these, the mAbs have emerged as particularly promising agents for COVID-19 management. Recommended mAbs for COVID-19 infection include casirivimab/imdevimab, sotrovimab, tocilizumab, bamlanivimab and sarilumab.

Casirivimab/imdevimab act on the two distinct receptor binding sites of SARS-CoV-2 spike glycoprotein, and subsequently prevent the virus from infecting host cells. These drugs received first approval in Japan in July 2021 for the treatment of COVID-19 infection.

The most reported adverse drug event was injection-site reactions immediately after

subcutaneous injection, while other adverse drug events included nausea, rash, dizziness, and chills. Tocilizumab and sarilumab are both interleukin-6 (IL-6) receptor blockers which have immunomodulatory effects that may be particularly significant in patients with COVID-19 who have inflammatory and malfunctioning immune systems.

Condition being studied Understanding the potential adverse effects and possible drug-drug interactions is a crucial factor in treatment success. There were many published kinds of literature including interventional studies and observational studies that reported adverse effects of monoclonal antibodies used during the pandemic time of COVID-19. After nearly four years of the pandemic, and the use of mAbs, observational studies which studied the adverse effects of mAbs are invaluable to investigating the long-term side effects of mAbs, especially for COVID-19-infected patients with different ages, gender, comorbidity, and severity.
To the best of our knowledge, serious and non-serious as well as organ system-specific adverse effects such as haemorrhage, hepatoxicity, and renal toxicity of COVID-19 treatments including monoclonal antibodies on long-term reported in observational studies as evidence-based reports still have a gap.
We will include any reported adverse effects of the approved antivirals on monoclonal antibodies (e.g., casirivimab/imdevimab, sotrovimab, tocilizumab, sarilumab) on specific time points i.e. short term and long term and specific time-points. Hence, the objective of our review is to investigate the frequencies of serious and non-serious adverse events of monoclonal therapies reported in observational studies.

METHODS

Participant or population Participants with PCR-approved COVID-19 infection, any age, gender regardless of severity.

Intervention Monoclonal antibodies aimed for treatment of COVID-19 infections (casirivimab/imdevimab, sotrovimab, tocilizumab, bamlanivimab and sarilumab).

Comparator Alternative COVID-19 treatment regimens, or usual care standard of care or placebo.

Study designs to be included Observational studies (case-control, cohort, retrospective & prospective).

Eligibility criteria Studies published in the 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 to Dec 2024. We will search the following databases to identify relevant clinical trials: Ovid MEDLINE The Cochrane CENTRAL PubMed
We will also search the following COVID-19 study resourcesCOVID-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) Studies must report at least one of the outcomes:

1. The proportion of people with one or more serious adverse events: ((we will consider an event as severe/serious if the trial authors clearly stated that it was due to the experimental or control intervention and have defined it as a 'serious adverse event' or if it fulfilled the definition of the International Conference on Harmonization (ICH) guidelines for serious adverse events (ICH 2003; ICH-GCP 2016), that is, any event that leads to death; is life-threatening; requires hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability; congenital birth or anomaly; and any important medical event which may have jeopardised the patient or requires intervention to prevent it.)

2. The proportion of people with one or more adverse events is considered non-serious. We will consider all other adverse events as non-serious (European Medicines Agency 1995)

3. Organ system-specific adverse events (e.g. hepatoxicity, renal toxicity, infusion reactions, allergic reactions, bone marrow toxicity).

Additional outcome(s) 4. Health-related quality of life: any validated assessment scale, completed by the participants if it is reported in the included studies.

Data management The two investigators will do data extraction independently using COVIDENCE

web-based systematic review tool. Any discrepancies will be reached to a consensus by the third investigator.

Quality assessment / Risk of bias analysis Two investigators will independently extract the data for analysis. Newcastle-Ottawa Scale (NOS) tool will be used for the methodological qualities of the included studies. Data analysis will be done with Rev Man Web (web-based software).

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. 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 Sub-group analysis will be done depending on COVID-19 severity, age, gender or co-morbidity 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 be considered a low heterogeneity, 50% as 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 publication bias. Data analysis The GRADE approach will be used for the overall quality of evidence.

Language restriction English only.

Country(ies) involved Malaysia.

Keywords COVID-19, adverse effect, monoclonal antibodies; case-control, cohort; observational study; casirivimab/imdevimab; sotrovimab; tocilizumab; bamlanivimabsarilumab.

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