Adverse Drug Reactions in COVID-19 Patients: Protocol for a Living Systematic Review

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Abstract

The novel coronavirus disease 2019 (COVID-19) is a highly infectious disease with human to human transmission. The COVID-19 may present with mild, moderate, or severe illness. Currently, no proven effective therapies for COVID-19 exist and no vaccine is available. Various pharmacological treatments are currently being tested for patients with COVID-19. The current living systematic review aims to examine the definition, frequency, nature, and severity of the adverse event (AE)/ adverse drug reaction (ADR) occurring in patients with COVID-19 receiving active pharmacological treatment and to compare it against control groups where available. MEDLINE, Embase, Cochrane Central databases will be searched for studies that reported COVID-19 patients receiving treatment for infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with any pharmacological drugs such as but not limited to, chloroquine, hydroxychloroquine, azithromycin, ritonavir, remdesivir, tocilizumab, pirfenidone, etc. Data pertaining to safety parameters like AEs, ADR, serious AEs, serious ADR, treatment non-response, and deterioration of illness will be captured and analysed.

Background And Rationale

1.1 Brief description of the disease

Coronavirus disease (COVID–19) is caused by a new coronavirus (CoV) [1] SARS-CoV–2 [2]. Previous outbreaks of CoVs include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV [2]. Like MERS CoV and SARS-CoV, the SARS-CoV–2 virus is a β coronavirus [1]. The β variant of the coronavirus is able to infect mammal [3]. The novel coronavirus uses the same receptor, angiotensin-converting enzyme 2 as that for SARSCoV [3].

The SARS-CoV–2 mainly spreads through the respiratory tract [3], by droplets, respiratory secretions, and direct contact for a low infective dose [2]. The incubation period is 1–14 days and it is contagious during the latency period [3]. The symptoms of COVID–19 infection appear after an incubation period of approximately 5.2 days [2].

The COVID–19 may present with mild, moderate, or severe illness. The most common symptoms at the onset of COVID–19 illness are fever, cough (dry), fatigue, sore throat, nasal congestion, malaise, headache, muscle pain [1, 2, 4] chills, repeated shaking with chills, muscle pain, loss of taste or smell [1], and shortness of breath [3] other symptoms include sputum production, haemoptysis, diarrhoea, dyspnoea, and lymphopenia [2]. The severe clinical manifestations are severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and septic shock [4]. The elderly population and patients of all ages with underlying conditions are at higher risk [5]. Additionally, they are susceptible to infection and prone to serious outcomes, which may be associated with ARDS and cytokine storm [3].

The possibility of transmission before symptoms develop seems to be infrequent, although it cannot be excluded. Moreover, there are suggestions that individuals who remain asymptomatic could transmit the

virus. The use of public health measures like social distancing, isolation and quarantine currently seems to be the best measures to contain this epidemic until effective vaccines and drugs become available [4].

The global pandemic of COVID–19 began in Wuhan, China, in December 2019, and has spread worldwide since then [6]. As of 05 May 2020, globally a total of 3.44 million confirmed cases (86,108 new) and 239,604 deaths (976 new) have been reported worldwide [7] in more than 200 countries [6].

1.2 Description of the intervention

Currently, no proven effective therapies for COVID–19 exist [6] and no vaccine is available [3]. The current treatments mainly focus on symptomatic and respiratory support [3]. Oxygen therapy represents the major treatment intervention for patients with severe infection. The strategies for addressing respiratory failure, include protective mechanical ventilation and high-flow nasal oxygen or non-invasive ventilation. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock [4]. Rescue treatment with convalescent plasma and immunoglobulin G is delivered to some critical cases based on their conditions [3].

The rapidly expanding knowledge regarding SARS-CoV–2 virology [6] and the previous experience of fighting SARS-CoV and MERS-CoV epidemic [3] has provided a significant number of potential drug targets [6]

As of 1st May–2020, a total of 1,829 clinical trials have been registered with the International Clinical Trials Registry Platform. Of which 626 are randomized trials (excluding Traditional Chinese medicine trials) and 319 of these are currently recruiting [8].

Various pharmacological treatments [9] are currently being tested for patients with COVID–19. Although no antiviral treatment for COVID–19 has been approved, several treatment strategies have been proposed [4]. Primarily, broad-spectrum antiviral drugs like nucleoside analogues and HIV-protease inhibitors that could attenuate virus infection are currently being tested until a specific antiviral becomes available [2]. The most commonly used pharmacological interventions currently being tested for COVID–19 are remdesivir, chloroquine, tocilizumab [4], lopinavir/ritonavir [2, 3, 6, 10] arbidol [3, 6, 10] darunavir [6, 10], favipiravir [6].

1.3 How the intervention might work

Many pharmacological interventions are being tried for the treatment of COVID–19 patients, here we have provided an example for one such promising agent currently being test in COVID–19 patients. Further intervention may be described in the review as appropriate.

Remdesivir (GS–5734) is one of the promising therapies currently being tested in COVID–19 patients [6]. Remdesivir is a nucleoside analogue prodrug [3] and shows broad-spectrum antiviral activity against several Ribonucleic Acid (RNA) viruses [3, 10]. It is an inhibitor of RNA polymerase with in vitro activity against multiple RNA viruses, including Ebola. It could be effective for both prophylaxis and therapy of HCoVs infections [4].

Pre-clinical studies experiments indicated that remdesivir can effectively reduce the viral load in lung tissue of mice infected with MERS-CoV, improve lung function, and alleviate pathological damage to lung tissue. This drug was positively tested in a rhesus macaque model of MERS-CoV infection [4]. It has potent in vitro activity against SARSCoV–2 and is currently being tested in ongoing randomized trials [6].

On 1st May–2020, remdesivir has been approved by the US Food and Drug Administration for emergency use in the treatment of hospitalized COVID–19 patients [11].

1.4 Why it is important to do this review

The elderly population and patients with underlying disease are at high risk of severe illness from COVID–19 [5]. The elderly patients are susceptible to greater frequency of decreased hepatic, renal, or cardiac function, and often have a concomitant disease or are on other drug therapy. All these conditions make COVID–19 patients more prone to experience adverse events (AEs) especially when various existing and novel pharmacological agent currently being tested in this population. For instance, consider the example of remdesivir; its pharmacokinetic is yet to be evaluated in patients with renal and hepatic impairment, in paediatric patients, and in the elderly patients (>65 years of age). Additionally, no adequate and well-controlled studies reporting the use of remdesivir in pregnant women have been conducted [12]. The limited clinical data and previous compassionate use of remdesivir make it imperative to assess AEs in COVID–19.

Additionally, in patients with COVID19, adverse effects may be exacerbated by combination therapy or viral infection because approximately 20% to 30% of patients have elevated transaminases at presentation with COVID–19. Also, one of the limitations of using repurposed agents is the tendency of these agents to cause acute toxicity. This is of utmost concern in patients at high risk for toxicity and in situations where AEs may preclude entry into clinical trials [6].

Objectives

This systematic review aims to examine the definition, frequency, nature, and severity of AEs/adverse drug reactions (ADRs) reported in patients with COVID–19 receiving active pharmacological agent for the treatment of COVID–19 and to compare it against control groups where available.

Methodology

Eligibility criteria

We will include case studies, case series, cross-sectional studies, cohort studies, before-after studies as well as randomized controls (RCTs) trials reporting ADR or serious ADR in patients receiving treatment for COVID–19. We will include studies reported as full-text and those published as abstract. We will only include studies that were published in English. Unpublished data will be excluded.

Characteristics of participants (P)

We will include participants with a confirmed diagnosis of COVID–19 by a polymerase chain reaction (PCR), point-of-care immunodiagnostic tests, or other appropriate tests as reported in the primary research articles. We will exclude studies if the population did not reflect the general population of interest, such as studies that included patients with other viral infections (e.g. SARS-CoV or MERS-CoV).

Characteristics of interventions (I)

We will include studies that reported COVID–19 patients receiving treatment for infection caused by SARS-CoV–2 with any pharmacological drugs such as but not limited to, chloroquine, hydroxychloroquine, azithromycin, ritonavir, remdesivir, tocilizumab, pirfenidone, etc.

Characteristics of comparators (C)

Comparators can be any pharmacological agents or placebo.

Characteristics of outcome measures (O)

We will include the studies reporting the safety outcomes that are measured post-treatment and at follow-up in COVID–19 patients receiving treatment. The treatment non-response will be captured based on the criteria reported in the primary studies. The included studies may report any/all of the below outcomes.

- Adverse drug reaction (ADR): As per the WHO definition, a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.
- Serious ADR: A serious adverse event or reaction is any untoward medical occurrence that at any dose:
- results in death
- is life-threatening
- requires inpatient hospitalisation or results in prolongation of existing hospitalisation

- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a medically important event or reaction
- Treatment non-response (number of participants with a lack of clinically meaningful [positive] change after treatment)
- Deterioration of illness (number of participants with clinically meaningful [negative] change after treatment).

Information sources and search procedure

We will search MEDLINE and Embase database using the Ovid search platform. We will use adverse effects - focussed special Ovid filters. Ovid filters will be “AND” combined with the COVID–19 search terms to limit searches. We will not use any study design search filters and restrict the search to human and last one year [13]. We will also search the Cochrane COVID–19 study register. We will also search Clinicaltrial.gov to identify the ongoing studies in patients with COVID–19.

Electronic source and search strategy

Ovid search strategy for MEDLINE and Embase.

#	Searches
1	(coronavir* or coronovirus* or "corona virus" or "virus corona" or "corono virus" or "virus corono" or hcov* or "covid-19" or covid19* or "covid 19" or "2019-nCoV" or cv19* or "cv-19" or "cv 19" or "n-cov" or ncov* or "sars-cov-2" or (wuhan* and (virus or viruses or viral)) or (covid* and (virus or viruses or viral)) or "sars-cov" or "sars cov" or "sars-coronavirus" or "severe acute respiratory syndrome" or "mers-cov" or "mers cov" or "middle east respiratory syndrome" or "middle-east respiratory syndrome").mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]
2	exp "drug-related side effects and adverse reactions"/ or adverse.ti,ab,kf. or side effect?.ti,ab,kf. or adverse effects.fs. or exp drug overdose/ or overdos*.ti,ab,kf. or exp drug misuse/ or misus*.ti,ab,kf. or exp substance-related disorders/ or abus*.ti,ab,kf. or exp pregnancy/ or pregnan*.ti,ab,kf. or exp pregnancy complications/ or exp lactation/ or exp lactation disorders/ or exp breast feeding/ or (exp milk, human/ and exp secretion/) or exp fertility/ or exp infertility/ or exp reproduction/ or exp fetus/ or exp embryonic structures/ or terat*.ti,ab,kf. or drug efficacy.ti,ab,kf. or therapeutic efficacy.ti,ab,kf. or drug withdrawal.ti,ab,kf. or exp medication errors/ or exp death/ or death*.ti,ab,kf. or fatal*.ti,ab,kf. or exp drug interactions/ or exp carcinogens/ or carcinogen*.ti,ab,kf. or mutagen*.ti,ab,kf. or exp "off-label use"/ or exp occupational exposure/ or toxicity.fs. or toxic*.ti,ab,kf. or pharmacotox*.ti,ab,kf. or neurotox*.ti,ab,kf. or cardiotox*.ti,ab,kf. or nephrotox*.ti,ab,kf. or immunotox*.ti,ab,kf. or hepatotox*.ti,ab,kf. or cytotox*.ti,ab,kf. or immunocytotox*.ti,ab,kf. or intoxicat*.ti,ab,kf. or exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or drug treatment failure.ti,ab,kf. or drug toxicity.ti,ab,kf. or exp case report/ or case report?.ti,ab,kf. or exp environmental exposure/ or treatment contraindication.ti,ab,kf. or exp contraindications, drug/ or exp "wounds and injuries"/ or suicid*.ti,ab,kf. or exp poisoning/ or poisoning.fs. or exp drug tolerance/ or exp treatment failure/ or exp drug resistance/ or exp substance-related disorders/
3	1 and 2
4	limit 3 to human
5	limit 4 to last year
6	remove duplicates from 5

Searching other sources

We will search google scholar and perform hand searching to screen the bibliography of the included studies.

Study selection

We will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Additional file 1) [14] for conducting the review. Two authors will independently screen the title and abstract retrieved from the searches independently. The study judged eligible by at least one author would be retrieved in full text and screened for eligibility. The fulltext screen will also be conducted by two authors and a third author would be consulted in case of disagreement.

Living systematic review approach

We plan to update and run the database searches every six months from the date of the baseline review search. The search strategy and methods will also be reviewed every six months and will be updated according to the new evidence that is expected to arrive in the future. The searches will be run manually for Embase and MEDLINE using the Ovid interface and screened for the eligible articles by two independent reviews. Any new study providing evidence eligible for inclusion will be identified and incorporated in the review updates henceforth. We anticipate that most of the studies included for the first few updates to be observational and non-randomized in design; however, our inclusion criteria include RCTs and we anticipate that more eligible RCTs will be available as the research progress in this fast-moving scenario.

Assessment of risk of bias

The risk of bias will be assessed using Risk of Bias in Non-randomised studies of intervention (ROBINS-I) [15]. The domains that will be assessed are: bias due to confounding, bias in the selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions (effect of assignment to intervention), bias due to missing data, bias in the measurement of outcomes and bias in the selection of the reported result. We will judge each domain as low risk, moderate risk, serious risk, critical risk, or no information, and evaluate individual bias items as described in ROBINS-I guidance. The confounders that would be considered in judging risk of bias are age, comorbidity, co-interventions and severity of the condition. We will develop a summary of findings tables and rate the overall certainty of evidence as high, moderate, low or very low depending on the grading of the individual domains.

Assessment of certainty of evidence

We will use Grading of Recommendations Assessment, Development and Evaluation working group methodology (GRADE Working Group) [16, 17] for judging certainty of evidence taking into consideration of domains of bias, consistency, directness, precision and reporting bias.

Data extraction

We will collect the data on a pre-developed excel sheet piloted using at least one of the included studies. The following study characteristics will be extracted and will be checked for accuracy by at least one independent author against the primary source.

Identification features

- Record number (to uniquely identify study)

- Author
- Article title
- Citation
- Type of publication (e.g. journal article, conference abstract)
- Country of origin
- Source of funding

Study characteristics

- Aim/objectives of the study
- Study design
- Study inclusion and exclusion criteria
- Recruitment procedures used (e.g. details of randomization, blinding in case of RCTs)
- Total duration of the study
- Number of study centres and location

Participant characteristics

- Characteristics of participants at the beginning of the study e.g.
- Age
- Gender
- Ethnicity
- Socio-economic status
- Disease characteristics, the severity of the condition
- Co-morbidities
- Diagnostic criteria (TR-PCR test, antibody test, etc.)
- Number of participants in the intervention and control group (for RCTs)

Intervention and setting

- Setting in which the intervention is delivered
- Description of the intervention(s) and control(s) (e.g. dose, route of administration, care provider, etc.)
- Description of co-interventions

Safety Outcome data/results

- ADR/Serious ADR (number of participants with treatment-emergent reactions, adverse treatment reactions or side effects, malpractice reactions, etc.)

- Treatment non-responders (number of participants with a lack of clinically meaningful [positive] change after treatment etc.)
- Deterioration of condition (number of participants with clinically meaningful [negative] change after treatment etc.)

Methods for future updates

We will review the scope and methods of this review approximately yearly considering the potential changes in the topic area, and the availability of new evidence being generated in this area. As the evidence will start getting accumulated, we plan to split the review in multiple reviews based on drug class or single pharmaceutical agent, depending on the availability of substantial evidence.

Statistical analysis

We will perform qualitative and quantitative evidence syntheses as per the availability and appropriateness of the data. For the meta-analysis, we plan to pool Serious ADR/Serious AE outcomes from studies with similar characteristics either using a fixed-effect or a random-effects model as found appropriate based on between-study heterogeneity [18]. Along with assessing the statistical heterogeneity using I^2 statistics, we will also consider the clinical heterogeneity between the studies. We will use the fixed-effect model if no evidence of significant heterogeneity of either type is present. If data permits, we will express the comparative results as the percentage of participants experiencing an ADR with drug and comparator. The statistical differences will be presented using risk ration (RRs), numbers needed to treat to prevent an event (NNTp) or numbers needed to treat for an additional harmful outcome (NNH), based on data availability. We will use STATA version 16 (STATA Corp., Texas, USA) and Review Manager 5 (RevMan 5.3) (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for the meta-analysis of the outcomes.

However, considering the current evidence base, we anticipated the included trials to demonstrate a high level of clinical homogeneity. A large number of studies are anticipated to be of observational study design, such as case reports, case-series thus making pooling of the data inappropriate. In such cases where we cannot pool data, we will present effect estimates from each study in tables and summarise the results in text. For each update, we will assess the risk of bias, extract data and incorporate it in the synthesis from the newly identified studies that meet inclusion criteria. We will update the ‘What’s New’ section of the review at every six-month update to indicate the status of the search results.

When reporting date in tabular form, we plan to present the results grouped as per the treatments received and further sub-grouped as per the type of ADR/Serious ADR reported. When appropriate we will present the data grouped as per the age group as well (i.e. ADR/Serious ADR reported in children, adults, and elderly patients).

Abbreviations

ADRs Adverse drug reactions

AEs Adverse events

ARDS acute respiratory distress syndrome

CoV Corona virus

GRADE Grading of Recommendations Assessment, Development and Evaluation working group methodology

MERS Middle East respiratory syndrome

NNTp Numbers needed to treat to prevent an event

PCR Polymerase chain reaction

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

REVMAN Review Manager

RCT Randomised control trial

ROBINS-I Risk of Bias in Non-randomised studies of intervention

RNA Ribonucleic Acid

SARS Severe acute respiratory syndrome

Declarations

Ethical approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of supporting data

Not applicable

Competing interests

The authors declare no competing interests in preparing this manuscript.

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Authors' Contributions

AS, SH, and DAM: Conceived and established the main concept. AS and SH developed search strategy. AS, SH, DAM, wrote the protocol with substantial contributions and support from NS, BA.

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