Anti-interleukin-6 therapies for hospitalized patients with COVID-19: a protocol for a prospective meta-analysis of randomized trials

19 February 2021

On behalf of the World Health Organization (WHO) Rapid Evidence Appraisal for COVID-19 Therapeutics working group of the COVID-19 Clinical Management and Characterization Working Group

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PROSPERO registration number: 230155
Keywords: COVID-19, randomized controlled trial, systematic review, interleukin-6, tocilizumab, sarilumab, mortality, prospective meta-analysis

1. INTRODUCTION

1.1. Rationale

We are in the midst of the COVID-19 pandemic, which has seen numerous randomized clinical trials (RCTs) (referred to as trials in this document) of similar interventions, but with differences in eligibility criteria and design, being conducted simultaneously and globally. The heightened need for rapid reliable information to guide the clinical management of patients with COVID-19 creates a compelling case for prospective meta-analyses (PMA), as PMA can provide timely evidence of efficacy with maximal precision and minimum risk of bias, to inform clinical practice guidelines *(1,2).* The key design feature for PMA is that the study selection criteria, hypotheses and analyses are specified before the results of the studies are known. We recently used this model to evaluate the role of corticosteroids in COVID-19 *(3).*

We present a PMA protocol of anti-interleukin-6 (anti-IL-6) therapy trials recruiting patients hospitalized with COVID-19. It is based on the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 statement *(4).* It will be registered on the PROSPERO international prospective register of systematic reviews, and published online before outcome data are received.

1.2. Objectives

The overall objective of this PMA is to estimate the effect of anti-IL-6 therapy compared with usual care in hospitalized patients with suspected or confirmed COVID-19. The primary comparison is of the class effect of anti-IL-6 therapies. We will also estimate the effects of specific anti-IL-6 therapies.

The primary objective is to estimate the effect of anti-IL-6 therapies compared with usual care or corticosteroids on mortality up to 28 days after randomization. Therefore, treatment comparisons will be:

- anti-IL-6 therapy + usual care (+/- other additional treatment)* versus usual care (+/- placebo) (+/- other additional treatment);*
- anti-IL-6 therapy + usual care versus systemic corticosteroid + usual care.

*provided these are the same for the anti-IL-6 and usual care arms.

The secondary objective is to estimate the overall and individual drug-specific effects of anti-IL-6 therapy compared with usual care or corticosteroids:

- on preventing development of severe COVID-19 illness (see Section 2.4.1);
- within subgroups defined a priori using baseline characteristics (see Section 2.4.2).

2. METHODS

2.1. Search strategy, trial eligibility criteria and invitations to participate

Trials were identified through systematic searching of clinicaltrials.gov, EudraCT and the WHO ISRCTN registry using the term "random" AND “COVID" in the title or abstract, along with terms for all IL-6-antagonists individually (“tocilizumab”; “sarilumab”; “clazakizumab”; “siltuximab”; “olokizumab”) and for the term "Interleukin 6”. Individual searches were then combined. Searches were not restricted by language, trial status (ongoing or completed), publication status, date or language. Additional relevant trials were sought through contact with research and WHO networks, and by full text screening of cited references from relevant published systematic reviews or randomized trials on IL-6 therapies in COVID-19.

Searches were initially carried out on 7 October 2020, and updated on 25 November 2020 and 11 January 2021. Searches will continue to be updated with weekly alerts. Additional eligible trials identified will be invited to participate until the start of data collection for the PMA. No additional trials will be included after outcome data are shared.

Additionally, research and WHO networks were asked for relevant trials. Table 1 shows a summary of trial eligibility criteria. We will include RCTs that recruited hospitalized patients. Note that trials without mortality data will be eligible if they recorded data on secondary outcomes.

Table 1. Trial eligibility criteria summary

Parameter	Inclusion	Exclusion
Population	Hospitalized with suspected or proven COVID-19, including patients admitted and not admitted to critical care at the time of randomization	Non-COVID-19 trials; trials restricted to patients with advanced cancer
Intervention	Anti-IL-6 therapies	Trials in which anti-IL-6 therapies are combined with other active agents
Comparator	Usual care or placebo or systemic corticosteroids	Trials with active comparators other than systemic corticosteroids
Outcome (primary)	All-cause mortality up to 28 days after randomization	
Outcomes (secondary)	See Section 2.4.1	
Study design	Randomized clinical trials (both blinded and open label) including platform trials testing multiple interventions; Phase 2, 3 and 4 trials	Observational cohort studies, including matched cohorts; Phase 1 studies

Invitations offering participation in this PMA will be sent to the Principal Investigators (PIs) of eligible trials by the WHO Chief Scientist on behalf of the WHO COVID-19 Clinical Characterization and Management Working Group. Participation will be based on this protocol. If further eligible trials are identified while the PMA is in progress (but before sharing of outcome data), the PIs of these trials will be sent the protocol and invited to participate. Participation will be confirmed when the trial PI indicates their willingness to participate, subject to the procedures described in this protocol. No additional trials will be included after outcome data are shared.

2.2. Study selection, data items and data synthesis

The supplementary file summarizes details of the trials identified for potential inclusion in this PMA, including their trial registration identifiers and the number of participants. Trial protocols will be compared to make final decisions on those for which data pooling appears justifiable, based on recruitment of sufficiently similar patient groups, treatment with similar anti-IL-6 therapy interventions, and employing similar comparator interventions. All such decisions will be made in advance of sharing of outcome data.

2.3. Risk of bias assessment

We will assess the risk of bias in the overall effect on mortality reported by each trial, based on the Cochrane Risk of Bias Assessment Tool (RoB 2) *(5)*. We will assess the effect of assignment to intervention (the "intention-to-treat" effect) for the primary outcome. Risk of bias assessments will be based on the trial protocols and CONSORT flow charts together with the following information, which will be supplied by each trial:

- methods used to generate the allocation sequence and conceal randomized allocation;
- whether patients and health professionals were blinded to assigned interventions;
- methods used to ensure that patients received their allocated intervention; and
- methods used to measure 28-day mortality.

Risk of bias assessments will be done by at least two individuals independently. Disagreements will be resolved through discussion, with consensus assessments reported.

2.4. Data synthesis

We will collect trial results, not individual participant data. Trial investigators will provide summary tables showing numbers of participants who did and did not experience each outcome according to intervention group, overall and in the following specified subgroups. They will also provide estimated hazard ratios and 95% confidence intervals, for 90-day outcomes.

2.4.1. Outcomes

The primary outcome is all-cause mortality up to 28 days after randomization. Shorter-term mortality (e.g. 21 days) will be acceptable if longer-term mortality is not available.

The secondary outcomes include:

- Other mortality time points from randomization date:
  - in-hospital mortality;
  - 90-day mortality.
- Other outcomes:
  - progression to invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO) or death by 28 days, in those not receiving IMV at randomization;
  - progression to requiring cardiovascular system (CVS) support or death by 28 days in those who did not require CVS support at randomization;
  - progression to renal replacement therapy (RRT) or death by 28 days in those who did not require RRT at randomization. Patients with underlying dialysis dependence or Stage-III or above chronic kidney disease will be excluded from this analysis;
  - duration of IMV up to 28 days (in those receiving IMV at baseline), accounting for survival status by treating patients who died as having 28 days of IMV;
  - length of hospital stay.
- Serious adverse events (SAEs) or serious adverse reactions (SARs) as defined in each trial. Effects in each trial will be reported but no meta-analysis will be conducted.
  - all SAEs or SARs by 28 days;
  - secondary infections by 28 days;
  - secondary infections up to 90 days.

2.4.2. Subgroups

We will estimate intervention effects across trial-level subgroups relating to anti-IL-6 dosing and risk of bias, and across patient-level subgroups relating to disease severity and treatment at randomization, and patient characteristics at the time of randomization. Subgroup effects will be examined for anti-IL-6 therapy overall and, additionally, for specific anti-IL-6 therapies providing that sufficient outcome events are available within subgroups.

Subgroups related to disease severity or treatment at the time of randomization:

- Assigned dose of anti-IL-6 therapy: low (min. to 4 mg/kg tocilizumab or 200 mg sarilumab) vs high (> 4mg/kg; 8 mg/kg or multiple doses [regardless of number of doses received] of tocilizumab or > 400 mg or multiple doses of sarilumab).
- Receipt of systemic corticosteroids. The minimum dose considered as receipt of corticosteroids is defined as ≥ 30 mg prednisone in a calendar day or 4.5 mg dexamethasone or 150 mg hydrocortisone in a calendar day (referred to as lower threshold dose). Corticosteroid subgroups will be compared as follows:
  - meta-analysis restricted to trials that conducted factorial randomization to corticosteroids and anti-IL-6 agents up to June 2020, including examination of evidence for effect modification;
  - corticosteroid treatment at randomization (yes vs no);
  - corticosteroid treatment at randomization (yes vs no) within the four subgroups defined by respiratory support at randomization (see following subgroup).
- Respiratory support (no supplemental oxygen therapy; supplemental oxygen therapy; non-invasive ventilation including high-flow nasal canula [HFNC]; IMV).
- Severity of systemic inflammation at baseline (C-reactive protein [CRP] min./≤ 75 vs 75–150 vs > 150).
- Acute organ support at randomization in the following four groups:
  - patients **not** requiring respiratory support (or requiring respiratory support with supplemental oxygen therapy only) **and not** requiring cardiovascular system (CVS) support (defined as receipt of vasoactive medications);
  - patients **not** requiring respiratory support (or requiring respiratory support with supplemental oxygen therapy only) **and** requiring cardiovascular system (CVS) support (defined as receipt of vasoactive medications);
  - patients requiring respiratory support via non-invasive ventilation (including HFNC) or invasive mechanical ventilation (IMV) **and not** requiring cardiovascular system (CVS) support (defined as receipt of vasoactive medications);
  - patients requiring respiratory support via non-invasive ventilation (including HFNC) or invasive mechanical ventilation (IMV) and requiring cardiovascular system (CVS) support (defined as receipt of vasoactive medications).

Subgroups related to patient characteristics:

- Age (< 70 years vs ≥ 70 years age).
- Sex.
- Race/ethnicity (where available).

Risk of bias

- Low risk of bias, some concerns, high risk of bias. If appropriate, we will present sensitivity analyses:
  - restricted to trial results at low risk of bias; and
  - excluding trial results at high risk of bias.
- Placebo controlled trials vs open label trials.

2.4.3. Other data

Trial investigators will also provide summary information on characteristics of patients at the time of randomization and numbers of patients lost to follow up, which will be tabulated (and provide useful contextual information) but will not be used in analyses.

2.5. Analyses

Characteristics of trials, and of patients recruited to the trials, will be summarized in descriptive tables. The proportion of patients receiving post-randomization corticosteroids and who received second/further doses of anti-IL-6 therapy will be reported.

The primary analyses will be based on inverse-variance weighted meta-analyses of overall and subgroup effects. We will quantify inconsistency in effects between trials heterogeneity using I^2 statistics. We will report precise p-values and will not use a threshold for statistical significance.

We will make two main comparisons:

- anti-IL-6 + usual care/placebo with or without corticosteroids vs usual care/placebo with or without corticosteroids; and
- anti-IL-6 vs corticosteroids.

Factorial trials of anti-IL-6 and corticosteroids will contribute all participants to the first comparison and half their participants to the second comparison.

Random-effects meta-analyses (with restricted maximum likelihood [REML] estimate of heterogeneity *(6)* and Hartung-Knapp adjustment) will be reported as a sensitivity analysis for the primary outcome of overall mortality, in the text of the paper but not in forest plots or results tables *(7,8).* Random-effects meta-analyses estimate the mean treatment effect across trials, based on the assumption that the true treatment effect varies between trials. The confidence interval for this mean reflects both imprecision in estimating the mean and the estimated amount of between-trial variance. The latter is subject to considerable sampling variation when there are not many trials, so the mean treatment effect estimated using random-effects meta-analysis may not be estimated precisely even when treatment effects are estimated with precision within individual trials.

Evidence for subgroup effects will be quantified by ratios of odds ratios comparing effects in the subgroups, and corresponding interaction p-values. Comparisons between subgroups defined by trial characteristics will be made using random-effects meta-regression ("across-trial" approach). Interpretation of meta-regression results will be cautious because of the potential for confounding by other trial characteristics. Comparisons between subgroups defined by patient characteristics (for example, age and sex) will be made following recommendations by Fisher et al. *(9),* by estimating trial-specific ratios of odds ratios comparing intervention effects between subgroups ("within-trial" approach), then combining these. For characteristics that vary between participants in some but not all trials, we will use a within-trial approach restricted to the trials where this is possible, and compare this with an approach in which effects in subgroups are estimated in separate meta-analyses, and ratios of odds ratios derived from the overall effect in each subgroup. Interpretation will be cautious because of the potential for confounding of across-trial comparisons by other trial characteristics.

For 90-day outcomes, estimated log hazard ratios and their standard errors, estimated using Cox regression, will be reported by individual trials and meta-analysed using inverse-variance weighting.

2.6. Certainty of the evidence

We will use the GRADE approach *(10)* to rate the certainty of the evidence for the overall effect of anti-IL-6 therapy across the included trials for the primary outcome *(11).*

3. WHAT WILL AN AGREEMENT TO PARTICIPATE IN THIS PMA ENTAIL?

Trials that agree to participate in this PMA will agree to the following:

- To share their protocol in advance.
- To share summary data in a pre-specified format. These data will be limited to a small number of agreed upon elements, including key aspects of the trial design to inform ROB assessments and GRADE assessments, a CONSORT 2010 flow diagram (see Figure 1), summary trial characteristics (see Table 2), baseline demographics (see Table 3), 2×2 tables (overall and in specified subgroups) for the association of interventions with outcomes, and hazard ratios with 95% confidence intervals for 90-day outcomes. Unblinded pooled data will be analysed according to this protocol.
- To agree to a pre-specified process for reporting results to decision-makers and submitting pooled results for publication.

4. CONSEQUENCES FOR INDIVIDUAL TRIALS

Trial PIs/steering committees (usually with input from their data monitoring committees) will consider whether to suspend ongoing patient enrolment (on the basis of benefit, harm or futility) from the time of the first communication of the results to the trial PI. Subsequent trial management will be at the discretion of each trial PI and their trial steering committee, and is likely to be guided by a number of factors including the consistency of the findings across trials and the perceived relevance to the question addressed in their trial. A trial might opt to continue recruitment if the population, the intervention, or the efficacy signal differed substantively from the overall pooled data. A decision to terminate or continue the trial would be communicated to the appropriate research ethics board and to the study funder, with a detailed rationale for the decision made.

5. REPORTING OF RESULTS

As soon as the analyses are complete, they will be released to:

- Trial PIs, for sharing as appropriate with research ethics boards overseeing each trial.
- Each trial sponsor, who will have 48 hours to review the results and discuss them with the PIs of the other included trials, prior to releasing them.
- The Director-General of the WHO, or designate, for sharing with the relevant guideline development committee.

A paper reporting these findings will be prepared and submitted for publication. The paper will be published using an agreed group title. All members of trial steering committees will be included as authors, together with all individuals involved in conducting the PMA. A writing committee, including one or more representatives from each trial as well as individuals involved in conducting and reporting the PMA, will be established, and its members listed. A list of all contributors to each trial will be provided as supplementary material.

Figure 1. CONSORT 2010 flow diagram (for 28-day mortality)