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Tocilizumab in COVID-19- A meta-analysis, trial sequential analysis, and meta-regression of randomized controlled trials

Timothy Arthur Chandos Snow FFICM[1] ORCID ID: 0000-0002-8395-7857

Naveed Saleem MD[1] ORCID ID: 0000-0003-2963-6996

Gareth Ambler PhD[2] ORCID ID: 0000-0002-5322-7327

Eleni Nastouli FRCPath[3,4] ORCID ID: 0000-0002-1684-2013

Mervyn Singer FRCP[1] ORCID ID: 0000-0002-1042-6350

Nishkantha Arulkumaran PhD[1] ORCID ID 0000-0001-7942-8007

[1] Bloomsbury Institute of Intensive Care Medicine, University College London, London, UK

[2] Department of Statistical Science, University College London, London, UK

[3] Department of Clinical Virology, University College London Hospital, London, UK

[4] Department of Infection, Immunity and Inflammation UCL Great Ormond Street Institute of Child Health, London, UK

Address for correspondence:

Dr Tim Snow

Bloomsbury Institute of Intensive Care Medicine

University College London

Gower St, London WC1E 6BT, United Kingdom

Email: timothy.snow@doctors.net.uk

Tel: +44 208 383 2214

Fax: +44 208 383 2062

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Abstract

Purpose: Interleukin-6 (IL-6) levels discriminate between patients with mild and severe COVID-19, making IL-6 inhibition an attractive therapeutic strategy. We conducted a systematic review, meta-analysis, trials sequential analysis (TSA) and meta regression of randomized control trials to ascertain the benefit of interleukin-6 blockade with tocilizumab for COVID-19.

Methods: We included randomized controlled trials (RCTs) allocating patients with COVID-19 to tocilizumab. Our control group included standard care or placebo. Trials co-administering other pharmacological interventions for COVID-19 were not excluded. Primary outcome was 28-30 day mortality. Secondary outcomes included progression to severe disease defined as need for mechanical ventilation, intensive care unit (ICU) admission, or a composite.

Results: We identified 10 RCTs using tocilizumab, nine of which reported primary outcome data (mortality), recruiting 6493 patients with 3358 (52·2%) allocated to tocilizumab. Tocilizumab may be associated with an improvement in mortality (24·4% vs. 29·0%; OR 0·87 [0·74 - 1·01]; p = 0·07; I^2 = 10%; TSA adjusted CI 0·66 – 1·14). Meta regression suggested a relationship between treatment effect and mortality risk, with benefit at higher levels of risk (logOR vs %risk beta = -0·018 [-0·037 – -0·002]; p = 0·07). Tocilizumab did reduce the need for mechanical ventilation and was associated with a benefit in the composite secondary outcome but did not reduce ICU admission.

Conclusions: For hospitalized COVID-19 patients, there is some evidence that tocilizumab use may be associated with a short-term mortality benefit, but further high-quality data is required. Its benefits may also lie in reducing the need for mechanical ventilation.

Registration: PROSPERO registration CRD42021231300

Key words: COVID-19; Immunologic Factors; Interleukin-6; Meta-analysis

Take home message

There is some evidence that the use of tocilizumab may be associated with a short-term mortality benefit in patients with COVID-19. Amongst patients not requiring advanced respiratory support, it may also reduce disease progression to requiring mechanical ventilation. However, most trials are at high risk of bias and further high-quality data is required.

Introduction

Patients with COVID-19 demonstrate a heterogeneous clinical course ranging from mildly symptomatic disease through to acute respiratory distress syndrome (ARDS) and death.[1] Hospital mortality in patients admitted to US hospitals during the first pandemic was 9.6%.[2] Short- and long-term morbidity associated with COVID-19 are also significant.[3]

The beneficial effect of dexamethasone on mortality among critically ill patients with COVID-19 highlights the role of an excessive host inflammatory response in the progression of mild disease to critical illness and death.[4] In addition to corticosteroids, multiple other immunomodulatory drugs have been proposed as therapeutic candidates.[5]

Interleukin-6 (IL-6) is a key regulator of CRP production and fever, biomarkers of the severity of COVID-19.[6] IL-6 levels also discriminate between patients with mild and severe disease,[7] making IL-6 inhibition an attractive therapeutic strategy. However, the absolute levels of IL-6 in patients with COVID-19 are significantly lower than those seen in other systemic inflammatory disorders such as bacterial sepsis,[8] raising questions about the potential benefit of IL-6 blockade as a viable therapeutic strategy in COVID-19.

We conducted a systematic review, meta-analysis, and trials sequential analysis (TSA) to ascertain the benefit of tocilizumab, the most commonly used IL-6 antagonist in COVID-19.

Methods

The protocol for this review was registered with the International prospective register of systematic reviews (PROSPERO registration number: CRD42021231300) and is reported according to PRISMA guidelines (**Online Resource**).[9]

Information sources and search strategy

A systematic search of PubMed, Embase, Cochrane Library, and MedRxiv using a controlled vocabulary (MeSH) and keywords. Date and language restrictions were not applied. The last search update was on 7th March 2021. The Boolean search strategy was as follows: ((Tocilizumab OR Sarilumab OR Interleukin 6 OR IL-6) AND (COVID-19 OR SARS-CoV-2) AND ((Clinical trial) OR Randomized OR Trial OR RCT)).

Research papers and review articles were also hand-searched for further relevant trials. Where data on the primary outcome were not available from the manuscript, the corresponding author was contacted for this information.

Eligibility criteria

Inclusion and exclusion criteria were determined *a priori*. All trials comparing patients who received tocilizumab interleukin-6 blockade in patients with COVID-19 were considered. To avoid potential confounding, where sicker patients were more likely to receive tocilizumab, we only included randomized control trials. We included patients being treated with other COVID-19 therapies (co-interventions), as part of other trials, with the control group defined as those not receiving IL-6 antagonists. Details of co-interventions are provided in the **Supplementary Data**. Trials enrolling pediatric patients (<18 years were excluded).

Trial selection

Two investigators (NS and TS) independently screened both titles and abstracts to exclude non-relevant trials. Discrepancies were resolved by a third author (NA). Relevant full-text articles were retrieved and analyzed for eligibility using the pre-defined inclusion criteria.

Data collection and analysis

Two investigators (NS and TS) independently extracted information from selected trials using a standardized data collection form. Data were collected on the following: country of trial, total number of participants, dosing of interleukin-6 receptor antagonist, age and number of patients receiving mechanical ventilation, noninvasive ventilation (NIV) or high-flow nasal oxygen (HFNO) at enrolment.

Primary and secondary outcomes

Primary outcome was 28-30day mortality. Secondary outcomes included markers of progression to severe disease which were defined as either requirement for mechanical ventilation, intensive care admission, or a composite of the above.

Subgroup analyses

Our predefined subgroup analysis included only patients admitted to ICU at enrollment. IL-6 inhibition may be expected to provide the greatest benefit in those at greatest risk of death. Therefore, we performed a meta regression to investigate the relationship between treatment effect and overall risk. Additionally, as tocilizumab is an IL-6 inhibitor, responsible for regulation of CRP we anticipated it would provide the greatest benefit in those with a higher baseline CRP. We thus performed a meta regression to evaluate the interaction between baseline CRP and treatment effect.

Risk of bias assessment

Methodological quality of the included randomized control trials was assessed using the Cochrane Collaboration's tool for assessing risk of bias (RoB2)[10] independently by two authors (NS and TS), with any discrepancies reconciled by a third (NA). The following domains were assessed: randomisation process, assignment to intervention, missing outcome data, measurement of outcome,

selection of the reported result, other bias, and overall bias. The risk of bias in each domain was judged as either low, high or some concerns.

Grading the quality of evidence

Two authors (NS and TS) assessed the quality of each outcome measure in accordance with the grading of recommendations assessment, development, and evaluation (GRADE) approach (GRADEpro Guideline Development Tool. McMaster University, 2015).[11] Quality was downgraded on the basis of the following certainty assessment; risk of bias, inconsistency, indirectness, imprecision, and other considerations. Discrepancies were resolved using a third author (NA). Publication bias was assessed using a funnel plot and Harbord's test.[12] The overall quality of evidence was subsequently rated as "high", "moderate", "low" or "very low".

Statistical analysis

We combined individual trial data for mortality with the reference group taken as the group not randomized to an IL-6 antagonist. The meta-analysis was performed using the review manager ('Revman') for Mac (version 5.1, Cochrane Collaboration, Oxford, UK). Statistical heterogeneity was assessed using the I^2 methodology. I^2 values >30%, >50% and >75% were considered to indicate moderate, substantial, and considerable heterogeneity among trials, respectively. A random-effects model was used to analyze data. All p-values were two-tailed and considered statistically significant if <0.05. Data on dichotomous outcomes are presented as odds ratio (OR), 95% confidence intervals, p-values; I^2 values. Meta-regression was performed to investigate the effect of overall risk using control group event rate, and average baseline CRP of the treatment group at enrollment, using a random effects model (Dersimonian-Laird) in Stata (version 16.1, StataCorp, College Station, TX, USA. 2019).

Because type 1 errors may result from meta-analyses with too small sample sizes, we performed Trial Sequential Analysis (TSA) using TSA program version 0·9·5·10 (www.ctu.dk/tsa). TSA tests the credibility of the ascertained results by combining both an estimation of information size (a cumulative

sample size of included trials) with an adjusted threshold of statistical significance for the cumulative meta-analysis. Meta-analysis monitoring boundaries (Trial Sequential Monitoring Boundaries) and the required information size (RIS) were quantified, alongside diversity adjusted information size (D^2) and adjusted 95% confidence intervals. Diversity adjustment was performed according to an overall type I error of 5% and power of 80%. Given the novelty of both COVID-19 and the use of IL-6 inhibitors in respiratory disease, RIS was calculated using the Relative Risk Reduction (RRR) obtained from our actual meta-analysis of 15·7%.

Protocol changes

The following changes were made to our PROSPERO published protocol. The definition of our control group was extended to include patients receiving standard care or placebo, and other potential COVID-19 treatments either in or out of a clinical trial given the number of platform trials identified. Only one trial reported outcomes for patients stratified by respiratory support thus we were unable to perform this subgroup analysis. We used the random effect models, rather than a fixed effects model due to the number of trials identified but have included the results using both a fixed effects model and risk ratios as a sensitivity analysis. We performed an additional sensitivity analysis on patients who received sarilumab to investigate a drug versus class treatment effect, and on the trials at low risk of bias.

Results

Search strategy

Our search strategy identified 2175 results. Following removal of duplicates, 1520 articles remained. Of these, 1504 were excluded on the basis of title/abstract. Of the remaining 16, five were excluded at full review as two were non-randomised,[13,14] two were review articles,[15,16] and one was performed on non-COVID patients.[17] Of the remaining 11 articles,[18-28] one trial used sarilumab[22] and one did not report mortality data;[18] the corresponding authors were contacted but did not reply. Thus, nine trials were used for the primary outcome analysis,[19-21,23-28] ten for sensitivity analysis, [19-28] and ten for secondary analyses.[18-21,23-28] (**Figure 1**). Mortality at day 28- 30 was not reported in one trial;[19] we contacted the corresponding author but the data were not available. In-hospital mortality was therefore used for this trial.

Trial characteristics

Only five trials enrolled patients requiring mechanical ventilation.[19,21,23,27,28] Seven trials enrolled patients receiving NIV,[18,19,21,23,24,27,28] while five enrolled patients receiving HFNO.[19,21,23,26,27] Two trials recruited patients on supplemental oxygen alone. [20,25] (**Table 1**) Nine trials used tocilizumab, [18,20,21,23-28] one trial used sarilumab,[22] and one trial used either tocilizumab or sarilumab.[19] Subsequent analyses were performed using data from patients receiving tocilizumab only, with sarilumab used for a sensitivity analysis.

Eight trials used an initial dose of 8 mg/kg, which could be repeated at treating physician discretion within 24 hours in seven trials,[18,19,23-27] or on day 3 in one trial.[20] One trial used a dose of 6 mg/kg, which could be repeated within seven days if clinical worsening or no improvement.[28] One trial used a weight-based dosing strategy which could be repeated with 24 hours at physician discretion. [21] Four trials used a placebo control,[22-25] whilst the control group was defined as standard care in the remaining trials. All trials allowed the use of additional COVID-19 treatments, in

particular glucocorticoids were used as a co-intervention in 72% of enrolled patients. (**Online Table 1**) Rates of reported adverse events were low, with no differences between the tocilizumab and control arms. (**Online Table 2**)

Primary Outcome

Mortality was defined at 28-30 days in eight trials,[20,21,23-27] and in-hospital mortality in one trial.[19] The total of 6493 patients with 3358 (51·7%) allocated to the tocilizumab arm and a mean weighted mortality of 26·6%. Tocilizumab treatment was not associated with an improvement in mortality compared to standard care (24·4% vs. 29·0%; OR 0·87 [0·74 - 1·01]; p = 0·07; I^2 = 10%; TSA adjusted CI 0·66 – 1·14). The cumulative Z-curve crossed neither the conventional nor the TSA boundary for benefit or harm, but did cross the boundary for futility having exceed the required information size (RIS). (**Table 2 and Figure 2a-b**) At time of reporting of mortality, 1086 (32·3%) patients in the tocilizumab group, and 1172 (37·4%) patients in the control group remained as inpatients.

Subgroup analyses

Three trials[19,21,23] reported mortality for critically ill patients (n=1482) requiring intensive care unit (ICU) admission at enrolment which did not demonstrate a statistically significant mortality benefit (34·7% vs. 39·6%; OR 0·84 [0·65 – 1·10]; p = 0·20; I^2 = 24%). (**Online Figure 1**)

Meta regression suggested a weak relationship between treatment effect and overall risk of mortality (**Figure 2c**). There was weak evidence of mortality benefit for higher levels of overall risk (logOR vs %risk beta = -0·018 [-0·037 – -0·002]; p = 0·07). However, there was no evidence of a relationship with baseline CRP (logOR vs. baseline CRP beta = 0.005 [-0.005 – 0.016]; p = 0.32).

Sensitivity Analysis

We performed an analysis on the two trials using sarilumab.[21,22] This included 858 patients with 377 (43·9%) allocated to the sarilumab group and a mean weighted mortality of 22·0%. Sarilumab was not associated with a mortality benefit (10·6% vs. 31·0%; OR 0·86 [0·35 – 1·51]; p = 0·39; I^2 = 42%)

An additional analysis was performed incorporating all IL-6 inhibitors. This included 6957 patients of which 3738 (53·7%) were allocated to the treatment arm with a weighted mean mortality of 25·5%. IL6-antagonism was not associated with a mortality benefit (23·0% vs. 28·5%; OR 0·86 [0·74 – 1·01]; p = 0·06; I^2 = 10%).

A sensitivity analysis of five trials with low risk of bias[20,23-26] was performed which included 1314 patients of which 827 (62.9%) were allocated to the treatment arm. Tocilizumab use was not associated with a mortality benefit (12·3% vs. 10·7%; OR 1·09 [0·75 – 1·57]; p = 0·65; I^2 = 0%).

An additional sensitivity analysis was performed assessing mortality benefit using a fixed effects model. Tocilizumab was associated with a mortality benefit on conventional analysis only (OR 0·85 [0·76 - 0·96]; p = 0·006; I^2 = 10%; TSA adjusted CI 0·70 – 1·04). However, analysis using relative risk (RR) with a random effects model showed a mortality benefit (RR 0·89 [0·82 - 0·96]; p = 0·005; I^2 = 10%; TSA adjusted CI 0·80 – 0·99), as did a fixed effects model (RR 0·89 [0·83 - 0·97]; p = 0·006; I^2 = 0%; TSA adjusted CI 0·81 – 0·99).

Secondary Outcomes

Seven trials including 3196 patients reported progression from a supplemental oxygen requirement to mechanical ventilation[20,21,23-26,28]. Of these, 1742 (54·5%) were allocated to the tocilizumab arm with a mean weighted incidence of 9·5%. Tocilizumab was associated with a reduction in requirement for mechanical ventilation compared to standard care on conventional analysis only (8·7% vs. 10·5%; OR 0·70 [0·54 – 0·89]; p = 0·004; I^2 = 0%; TSA adjusted CI 0·43 - 1·13). The cumulative Z-curve crossed the conventional boundary for benefit, but not the TSA boundary with 31·7% of RIS cases accrued. (**Figure 3**)

Progression to ICU admission was reported in four trials including 620 patients, with 338 (54·5%) allocated to the tocilizumab group and a weighted mean incidence of 37·9%.[20,23,26,28] Tocilizumab

was not associated with a reduced rate of ICU admission (34·9% vs. 41·5%; OR 0·73 [0·38 – 1·39]; p = 0·34; I^2 = 25%; TSA adjusted CI 0·05 – 10·14) with 12·9% of the RIS accrued. (**Online Figure 2**)

Trials reported progression to severe disease as either a composite of 'progression to intubation, ECMO, or death',[19] 'clinical failure (died, withdrew during hospitalization, transferred to ICU or required invasive ventilation)'[23] in one trial each, or 'mechanical ventilation and death'[18,20,21,24-27] in seven trials. This included 5346 patients, of which 2796 were allocated to the tocilizumab arm with a mean weighted incidence of 32·8%. Tocilizumab was associated with a reduced progression to severe disease (28·9% vs. 36·6%; OR 0·72 [0·59 – 0·89]; p = 0·002; I^2 = 26%; TSA adjusted CI 0·58 - 0·90). The cumulative Z-curve crossed both the conventional and TSA boundary for benefit with 85·1% of the RIS accrued. (**Online Figure 3**)

Risk of Bias and Grade Recommendation

The risk of bias was high due to the open label approach taken in six trials.[19-21,26-28] Ten trials included industry sponsorship.[19-27] Three trials released their results as pre-prints prior to peer review[19,21,22] (**Online Table 3**). Inconsistency amongst the trials was low due to low heterogeneity excluding 'ICU admission', and indirectness was adjudicated to be not serious due to the populations and outcomes measured in the trials. Imprecision was judged to be very serious for both 'need for mechanical ventilation' and 'need for ICU admission' due to TSA analysis showing low percentages of RIS cases accrued. Whilst the funnel plot for publication bias was asymmetrical, this was towards the negative trials. Harbord's test suggested a small trial effect (p = 0.11), which when adjusted for overall risk effect disappeared (p = 0.82). Overall, the quality of evidence by GRADE assessment was marked either 'moderate' or 'very low' (**Online Table 4 and Online Figure 4**).

Discussion

Among all hospitalized patients with COVID-19, there is some evidence that tocilizumab use may be associated with an overall mortality benefit although trial sequential analysis suggests futility in continuing trial recruitment. The well-established association between elevated CRP and illness severity in COVID-19 [6] raises the possibility of a mortality benefit in the sickest patients. This finding is supported by meta-regression which suggests a survival benefit for patients at higher mortality risk. This mortality benefit was seen only in the REMAP-CAP and RECOVERY trials where patients in the control arm had the highest mortality compared to other trials. ICU admission and advanced respiratory support were pre-requisites for trial enrolment into REMAP-CAP, in contrast to four of the other trials where these were exclusion criteria.

Among patients with less severe disease, tocilizumab may reduce progression to severe disease and reduce the need for mechanical ventilation. However, TSA suggests that further data are required before firm conclusions can be drawn. Caution is required in interpreting the findings given not all patients who receive tocilizumab will be considered appropriate for mechanical ventilation. For example, in the RECOVERY trial, which provides the bulk of the data, almost two thirds of the patients not mechanically ventilated at enrollment who subsequently died, did not receive ventilation. With many ongoing RCTs, the potential benefits of tocilizumab in milder cases of COVID-19 may become clearer.

Following early reports of a cytokine storm associated with severe COVID-19 disease, several immunomodulatory drugs were repurposed with the hope of discovering effective therapeutic strategies.[5] A search of clinicaltrials.gov on 3rd July 2020 identified 1366 registered trials for COVID-19 disease, of which 279 were RCTs assessing immunomodulatory therapies. These include targets against 39 different immune pathways using 90 different drugs or therapies; 47 registered RCTs were evaluating inhibition of IL-6.[5]

While IL-6 values in COVID patients are significantly lower than seen in other inflammatory conditions including non-COVID ARDS, sepsis, and cytokine release syndrome,[8] it does discriminate between patients with mild and severe COVID-19 disease.[7] Early observational studies describing the reduction in systemic inflammation biomarkers (CRP, fever) in response to tocilizumab supports the biological plausibility of its use in COVID-19 disease, despite the lack of clinical data supporting its use in non-COVID-19 ARDS.[29] The timing of administration of tocilizumab early in the disease remains consistent across trials, although the broad enrollment criteria used may have diluted the effect, as may have the high level of corticosteroid co-prescribing which may explain the lack of correlation seen between treatment effect and baseline CRP value. Early administration of interleukin-6 receptor blockade may interrupt the inflammatory cascade preventing deterioration from mild respiratory failure to into ARDS, multi-organ failure and eventually death.

There are several limitations to this analysis. It is not possible to evaluate the effect of different dosing strategies on outcome. Seven trials permitted a second dose of tocilizumab, but only one reported outcomes in relation to dose administered.[19] The number of co-interventions (including steroids and anti-viral medication) varied between trials, which we were unable to adjust for. The concurrent use of systemic corticosteroids is of particular relevance given the outcome benefit reported in patients receiving oxygen or advanced respiratory support at randomization.[4] Both the RECOVERY and REMAP-CAP trials demonstrate that estimates of the treatment effect for patients treated either with tocilizumab (or sarilumab) and corticosteroids in combination were greater than with an IL-6 antagonist alone. In both these trials, which account for 75% of the total population, and 88% of the deaths, co-administration of corticosteroids was high. There was no associated mortality benefit seen with tocilizumab in the subset of patients not administered corticosteroids in the RECOVERY trial, suggesting either some interaction between corticosteroids and tocilizumab, or that there is no additional benefit of tocilizumab. Additionally, this data may provide some reassurance surrounding

excessive immunosuppression and risk of increased mortality with co-administration of steroids and tocilizumab.

The reported incidence of infectious and other complications varied significantly between trials. This may relate to differences in definitions, screening, and reporting of complications, and variations in patient follow-up. Whilst there is no evidence of increased rates of adverse events with tocilizumab, this finding should be interpreted with caution given the number of reported events is lower than might be expected.

Crucially, the data in this meta-analysis are heavily weighted by two trials[19,21] with the highest overall risk of mortality. These trials, were prone to high risk of bias, having an open label trial design and patients being allocated to treatments based on drug availability at participating sites which may explain why sensitivity analysis of low risk of bias trials failed to show a mortality benefit. Whilst the TSA analysis suggest futility in ongoing recruitment, this should be interpreted in this context and that a smaller, but still significant clinical effect may still exist which would alter the futility boundaries.

It remains difficult to reconcile directly conflicting trial data, where two trials reported a significant improvement in mortality with tocilizumab [19,21] while another was terminated early due to an excess mortality risk.[27] Further high-quality trial data are required before firm conclusions can be made to guide clinical practice. This includes longer term outcomes as a third of patients remained as inpatients at the data censure cut-point, raising the possibility that tocilizumab may just prolong time to death.

In summary, there is some evidence that tocilizumab use may be associated with a short-term mortality benefit in patients with COVID-19, but further high-quality data is required. Among patients not requiring advanced respiratory support, tocilizumab may also prevent progression to mechanical ventilation.

Declarations

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Author data access: All authors had access to data

Author contributions: Study conception: NA; Literature search: NS, TS and NA; Data extraction: NS and TS; Assessment of bias: TS and NS; Statistics: TS, GA and NA; Drafting manuscript: TS and NA; Critical review: EN and MS; Finalizing manuscript: All authors

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Figure Legends

Figure 1: PRISMA flow chart

Flow chart of included and excluded trials.

Figure 2: Effect of Tocilizumab on mortality in included trials

a. Forest plot of mortality in RCTs listed in descending order of control group mortality. Size of squares for odds ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals.

b. Trial sequential analysis of mortality in RCTs. Uppermost and lowermost curves represent trial sequential monitoring boundary lines for benefit and harm respectively. Horizontal lines represent the traditional boundaries for statistical significance. Triangular lines represent the futility boundary. The cumulative Z-curve represents the trial data. A diversity-adjusted required information size (RIS) of 5622 was calculated using α=0·05 (two sided), β=0·20 (power 80%). Relative risk of mortality reduction was 15·7%. The cumulative Z-curve crosses neither the conventional nor the TSA boundary for benefit or harm, but did cross the boundary for futility having exceed the required information size (RIS)

c. Meta regression of log odds ratio for mortality vs. risk (%).

Figure 3: Effect of Tocilizumab on risk of need for mechanical ventilation

a. Forest plot of risk of progression to mechanical ventilation. Size of squares for odds ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals.

b. Trial sequential analysis of risk of progression to mechanical ventilation. Uppermost and lowermost curves represent trial sequential monitoring boundary lines for benefit and harm respectively. Horizontal lines represent the traditional boundaries for statistical significance. Triangular lines represent the futility boundary.

Table 1: Baseline characteristics for included trials

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Author/ Group / NCT registration	Country	Recruitment dates	Recruitment window	Tocilizumab dosing	Control group (n)	Treatment group (n)	Control group (age)	Treatment group (age)	Control group (numbers ventilated)	Treatment group (numbers ventilated)	Control group (numbers on NIV)	Treatment group (numbers on NIV)	Control group (numbers on HFNO)	Treatment group (numbers on HFNO)
Gordon (REMAP-CAP) NCT02735707	Multi-national	April 19, 2020 – November 19, 2020	Within 24hrs of ICU admission	8 mg/kg (maximum 800 mg) repeated at 12-24hrs if needed	402	353	61 ± 13	62 ± 13	121/402 (30·1)	104/353 (29·5)	169/402 (42·0)	147/353 (41·6)	110/402 (27·4)	101/353 (28·6)
Horby (RECOVERY) NCT04381936	United Kingdom	April 14, 2020 - Jan 24, 2021	Within 21 days of primary randomization	800 mg if weight >90kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg; and 8mg/kg if weight ≤40 kg repeated 12 – 24hrs later if needed	2094	2022	64 ± 14	63 ± 14	294/2094 (14.0)	268/2022 (13.3)	867/2094 (41.4)	819/2022 (40.5)	(included with NIV)	(included with NIV)
Hermine (CORIMUNO) NCT04331808	France	March 31,2020 - April 18,2020	Within 72hrs of SAR-CoV-2 diagnosis	8 mg/kg on day 1 (and 3 if needed)	67	63	64 ± 4	65 ± 5	0	0	0	0	0	0

Rosas (COVACTA) NCT04320615	Multi-national	NS	NS	8 mg/kg (maximum 800 mg) repeated at 8-24hrs if needed	144	294	67 ± 14	61 ± 15	54/144 (37·5)	111/294 (37·8)	40/144 (27·8)	68/294 (23·1)	(included with NIV)	(included with NIV)
Salama (EMPACTA) NCT04372186	Multi-national	NS	Within 48 hours of hospital admission	8 mg/kg (maximum 800 mg) repeated at 8-24hrs if needed	128	249	56 ± 15	56 ± 14	0	0	0	0	0	0
Salvarani (RCT-TCZ-COVID-19) NCT04346355	Italy	March 31, 2020 - June 11, 2020.	NS	8 mg/kg (maximum 800 mg) repeated at 12hrs	63	60	61 ± 4	62 ± 6	0	0	0	0	NS	NS
Soin (COVINTOC) CTRI/2020/05/025369).	India	May 30, 2020 - Aug 21, 2020	NS	6 mg/kg (maximum 480 mg) repeated up to 7 days later if needed	88	91	54 ± 6	56 ± 5	4/88 (5%)	5/91 (5%)	20/88 (23%)	28/91 (31%)	NS	NS
Stone (BACC) NCT04356937	United States	April 20, 2020 - June 15,2020	Upon hospital admission	8 mg/kg, (maximum 800mg)	81	161	56 ± 6	60 ± 7	0	0	5	5	0	0

Veiga (TOCIBRAS) NCT04403685	Brazil	May 8, 2020 – July 17, 2020	NS	8 mg/kg, (maximum 800mg)	64	65	57 ± 14	57 ± 16	10	11	26	15	(included with NIV)	(included with NIV)
Zhao NCT04310228	China	February 2, 2020 – March 15, 2020	NS	4-8 mg/kg repeated at 24hrs	7	19	69 ± 13	66 ± 14	0	0	1	0	0	0

NIV: Non-invasive ventilation; HFNO: High flow nasal oxygen; NS: Not stated

Table 2: Primary, sub-group, secondary, and sensitivity outcome data for included trials

Table 2: Primary, sub-group, secondary, and sensitivity outcome data for included trials						
Outcome	**References**	**Intervention group**	**Control group**	**Conventional effect estimate (95% CI)**	**Overall effect**	**I^2 (%)**
Overall mortality	[19-21,23-28]	821/3358 (24·4%)	909/3135 (29·0%)	0·87 (0·74 – 1·01)	Z = 1·82 p = 0·07	10
ICU Patient Mortality	[19,21,23]	254/732 (34·7%)	297/750 (39·6%)	0·84 (0·65 – 1·10)	Z = 1·27 P = 0·20	24
Disease Progression						
Mechanical ventilation	[20,21,23-26,28]	152/1742 (8·7%)	152/1454 (10·5%)	0·79 (0·54 – 0·89)	Z = 2·86 P = 0·0042	0
ICU admission	[20,23,26,28]	118/338 (34·9%)	117/282 (41·2%)	0·73 (0·38 – 1·39)	Z = 0·96 P = 0·34	60
Composite outcome	[18-21,23-27]	808/2796 (28·9%)	943/2577 (36·6%)	0·75 (0·67 – 0·84)	Z = 3·14 P = 0·002	26
Sensitivity analysis						
Combined IL-6 antagonists mortality	[19-28]	861/3738 (23·0%)	916/3219 (28·5%)	0·86 (0·74 – 1·01)	Z = 1·85 P = 0·06	10
Sarilumab mortality	[19,23]	40/377 (10·6%)	149/481 (30·9%)	0·72 (0·35 – 1·51)	Z = 0·86 P = 0·39	42

ICU: Intensive Care Unit

Figure 1: PRISMA Flow Chart

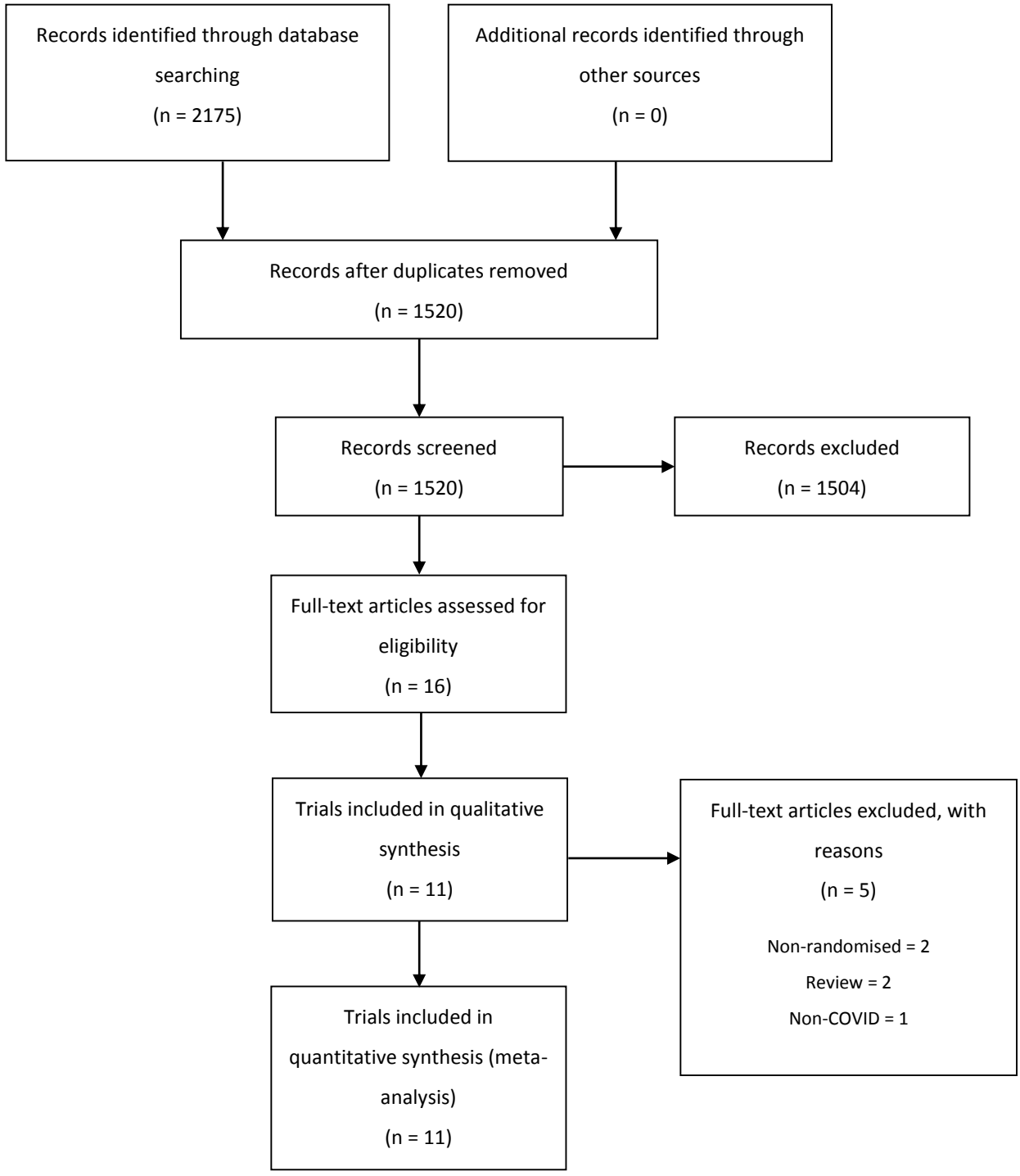

Figure 2

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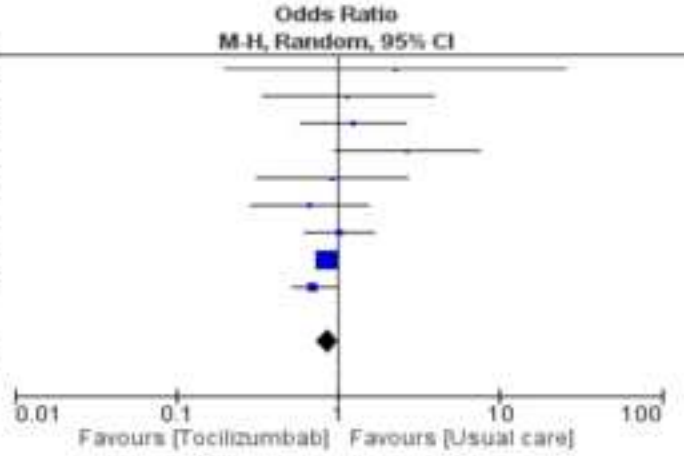
a.

Study or Subgroup	[Tocilizumbab] Events	Total	[Usual care] Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Salvarani (RCT-TCZ-COVID-19)	2	60	1	66	0.4%	2.24 [0.20, 25.37]
Stone (BACC)	9	161	4	82	1.6%	1.15 [0.34, 3.87]
Salama (EMPACTA)	26	249	11	128	4.3%	1.24 [0.59, 2.60]
Veiga (TOCIBRAS)	14	65	6	64	2.3%	2.65 [0.95, 7.42]
Hermine (CORIMUNO)	7	63	8	67	2.1%	0.92 [0.31, 2.71]
Soin (COVINTOC)	11	91	15	88	3.3%	0.67 [0.29, 1.55]
Rosas (COVACTA)	58	294	28	144	8.8%	1.02 [0.62, 1.68]
Horby (RECOVERY)	596	2022	694	2094	57.2%	0.84 [0.74, 0.96]
Gordon (REMAP-CAP)	98	353	142	402	20.1%	0.70 [0.52, 0.96]
Total (95% CI)		**3358**		**3135**	**100.0%**	**0.87 [0.74, 1.01]**
Total events	821		909			

Heterogeneity: Tau² = 0.01; Chi² = 8.85, df = 8 (P = 0.36); I² = 10%

Test for overall effect: Z = 1.82 (P = 0.07)



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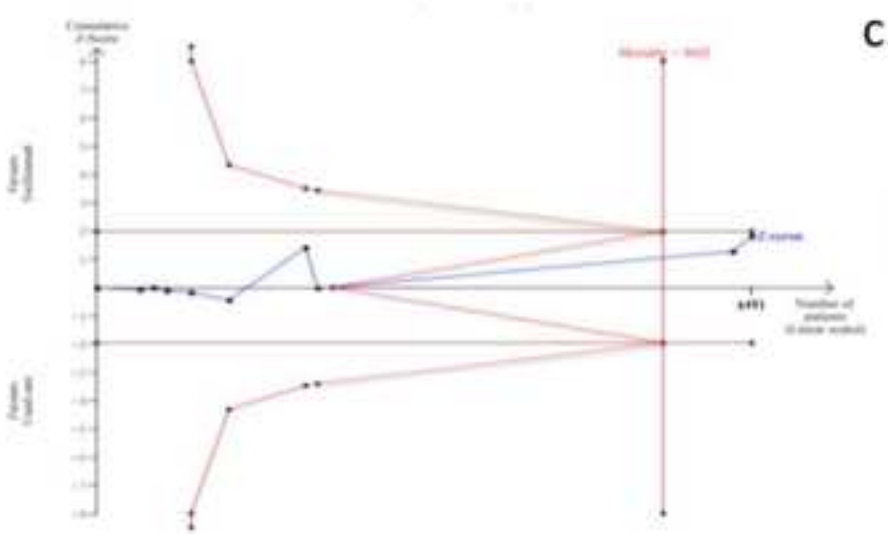

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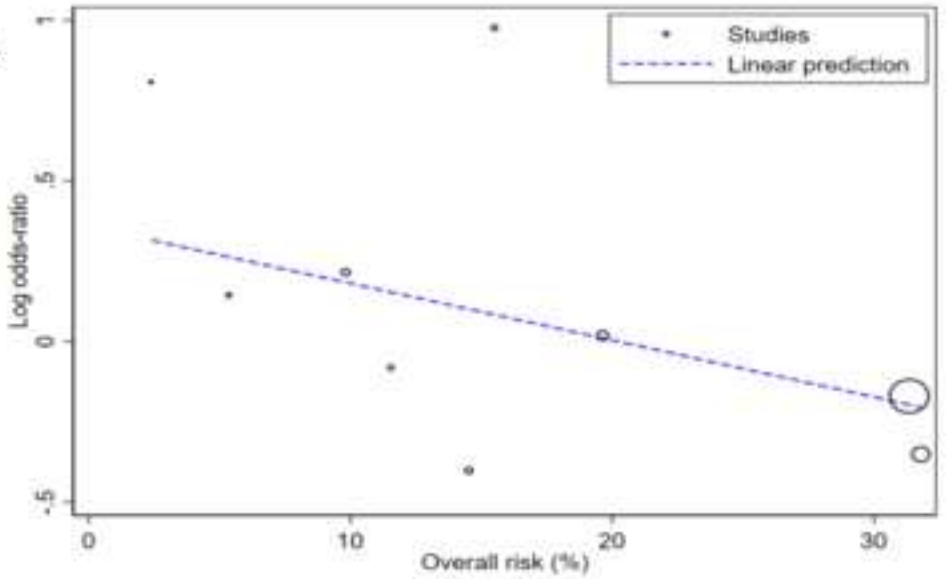

Figure 3

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a.

Study or Subgroup	[Tocilizumbab] Events	Total	[Usual care] Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Hermine (CORIMUNO)	5	63	14	67	5.3%	0.33 [0.11, 0.97]
Horby (RECOVERY)	45	935	63	933	40.1%	0.70 [0.47, 1.04]
Rosas (COVACTA)	51	183	33	90	21.6%	0.67 [0.39, 1.14]
Salama (EMPACTA)	20	249	16	128	12.9%	0.61 [0.31, 1.23]
Salvarani (RCT-TCZ-COVID-19)	6	60	5	66	4.0%	1.36 [0.39, 4.69]
Soin (COVINTOC)	14	91	13	89	9.3%	1.05 [0.46, 2.36]
Stone (BACC)	11	161	8	82	6.9%	0.69 [0.26, 1.76]
Total (95% CI)		**1742**		**1454**	**100.0%**	**0.70 [0.54, 0.89]**
Total events	152		152			

Heterogeneity: Tau² = 0.00; Chi² = 4.10, df = 6 (P = 0.66); I² = 0%

Test for overall effect: Z = 2.86 (P = 0.004)