Tocilizumab in the treatment of COVID-19 - a meta-analysis

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Abstract

Objective: To evaluate whether IL-6 inhibitor tocilizumab (TCZ) reduces mortality among hospitalized COVID-19 patients.

Methods: Systematic review and meta-analysis of randomized controlled trials (RCTs) comparing TCZ versus placebo/control, for treatment of adults with COVID-19. Primary outcome was 28-30 days all-cause mortality. Search was conducted up to April 1st 2021. Two independent reviewers screened citations, extracted data, and assessed risk of bias. Relative risk (RR) with 95% confidence intervals (CI) were pooled. We performed subgroup analysis for patients with critical illness and sensitivity analyses.

Results: Eight RCTs were included, assessing 6,481 patients with mostly severe non-critical COVID-19 infection. TCZ was associated with a reduction in all-cause 28–30-day mortality compared to placebo/control (RR=0.89, 95%CI 0.82-0.96). Among the subgroup of critically ill patients no reduced mortality was demonstrated (RR=0.94, 95%CI 0.74-1.19). No mortality benefit with TCZ was demonstrated in trials that used steroids for >80% of patients. TCZ was associated with significantly reduced risk for mechanical ventilation (MV); for combined endpoint of death or MV; and for intensive care unit (ICU) admission. No significant difference in adverse events was demonstrated. Risk of serious superinfection was significantly lower with TCZ (RR=0.57, 95%CI 0.35-0.93).

Conclusion: The treatment with TCZ reduces 28-30 days all-cause mortality, ICU admission, superinfections, MV and the combined endpoint of death or MV. Among critically ill patients, and when steroids were used for most patients, no mortality benefit was demonstrated. Additional research should further define sub-groups that would benefit most and preferred timing of administration of TCZ in severe COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) is an emerging respiratory disease caused by the novel corona virus and causes severe mortality and morbidity world-wide (1,2). Patients suffering from severe COVID-19 infection, tend to present with an exaggerated inflammatory response consisting of proinflammatory cytokines and chemokines, predominantly interleukin-6 (IL-6) (3–5). The IL-6 receptor monoclonal antibody, Tocilizumab (TCZ), inhibits IL-6 signaling pathway and is currently under use for inflammatory disorders as rheumatoid arthritis and giant cell arteritis. (6) Several observational studies have examined the role of IL-6 blockade with TCZ in patients with moderate and severe COVID-19 infection (7,8). A systematic review of observational studies has shown reduced mortality with TCZ by a risk ratio (RR) of 0.27, 95% confidence interval (CI) 0.12 - 0.59 (9), and another review showed both reduced mortality and reduced need for mechanical ventilation with TCZ (10). Since these results are based on observational data alone, higher levels of evidence by examining results from RCTs is necessary. In this systematic review and meta-analysis, we aimed to examine the current evidence from RCTs on the efficacy and safety of TCZ in the treatment of COVID-19 infection. We aimed to define sub-groups who would benefit most from this therapy. Considering the priority of the results for decision-making, and taking into account expected new evidence from several similar ongoing trials, we planned to conduct this review as a living systematic review. (11)

Methods

This review was conducted and reported in accordance with PRISMA guidelines. (12)

Inclusion criteria

Randomized controlled trials (RCTs), regardless of publication status, were included. We included trials assessing hospitalized adult patients with COVID-19 infection, diagnosed as defined in individual trials. The intervention assessed was any TCZ versus usual care with or without placebo. We excluded studies that directly compared IL-6 inhibitors with other drugs for COVID-19 infection (corticosteroids, immunomodulators, antivirals). We excluded studies that did not report on mortality. In studies that included more one intervention, we extracted results only for the TCZ and control arms.

Outcomes assessed

The primary outcome was all-cause 28- or 30-days mortality, or when lacking these data, all-cause mortality as reported by authors at the closest time point. Secondary outcomes included long-term survival, need for MV, combined endpoint of death or MV, intensive care unit (ICU) admission, length of hospital / ICU stay, need for oxygen / oxygen free days, number discharged alive, and adverse events (AEs), including any AEs, serious AEs (SAEs) and superinfections. Outcome measures were collected on an intention-to-treat (ITT) basis. In cases in which such data were not presented, modified ITT (mITT) or per-protocol results were used. For the outcome of MV, if this was not reported separately, we deduced the result from the combined endpoint of death or MV.

Search methods

We searched PubMed, medRxiv.org, LILACS, Cochrane library, clinicaltrials.gov and ECCVID 2020 conference proceedings (ESCMID conference on corona virus disease), up to April 1st 2021. We also hand-searched all references of included trials, websites of the drugs manufacturers, and previous meta-analyses for additional trials. For the PubMed search the

term "IL-6 inhibitors" and specific inhibitors / antibodies names and their MESH terms were crossed with the terms "COVID-19", "corona virus disease 2019", "SARS COV 2" and with the Cochrane highly sensitive filter for RCTs (13). For other data sources, we used the search string "tocilizumab" and "COVID-19". No language restrictions were used. All authors were contacted to complement data by e-mail.

Data collection

Two reviewers independently inspected each reference identified by the search, scanned full-texts of relevant studies, applied inclusion criteria and extracted the data. Disagreements in data extraction were resolved by discussion with a third reviewer. Risk of bias was assessed in duplicate using domain-based evaluation, classifying studies primarily according to the risk of non-random allocation, i.e. allocation concealment and sequence generation. These were graded as low, unclear and high risk for bias, as recommended in The Cochrane Handbook (13). Additional domains assessed included blinding, incomplete outcome data and selective outcome reporting. We graded the strength of the evidence and built a summary of evidence (SOF) table using the GRADEpro tool (14). We also inspected adherence to WHO classification of COVID-19 infection severity (15) and reporting of AEs (16).

Data analysis

For dichotomous data, individual study results are expressed as RR with 95% confidence intervals (CI). RRs and mean differences were pooled using a fixed effect model (Mantel-Haenszel method) (17). Heterogeneity was defined by a chi-square test of heterogeneity <0.1 or an I^2 measure of inconsistency >40%. If significant heterogeneity was identified, we used random effect model. We performed sensitivity analyses by the adequacy of allocation concealment and generation, blinding, publication status, and concomitant steroid use. Predefined subgroup analyses included COVID-19 infection severity, baseline laboratory

values and age. Due to the small number of included trials, we did not use a funnel plot to assess small-studies effects.

As a living systematic review, we plan to repeat the search monthly and update the meta-analysis with each new trial. The updates will discontinue when authors of this review will decide that a reasonable level of certainty has been reached for the study's question. (11)

Results

The search yielded 747 results of which 36 were potentially relevant. Twenty-eight records were excluded, thus, eight trials (seven published (18–24), one pre-print (25) were included in the meta-analysis (Supplemental Figure 1, PRISMA flow chart). Details regarding the characteristics of trials are presented in Table 1. The trials were conducted between March 2020 and January 2021 and recruited 6,481 patients, among them, 63.5% were recruited in the RECOVERY trial (25).

The criteria of COVID-19 severity for inclusion in the original trials was: moderate to severe pneumonia in six trials; severe to critical patients in one (22) and critically ill patients (receiving cardiorespiratory support) in one trial (24). Of the seven trials including moderate-severe and severe to critical patients , three trial included patients under MV at randomization as follows: 14% (25), 16.2% (22) and 37% (23) ; two other included 15% (19), and 4% (21) patients hospitalized in ICU at randomization. (For severity definitions in individual trials see Table 1 and Supplemental Table 1). Microbiological confirmation of COVID-19 infection was required for inclusion in included trials (by molecular methods in five trials or by IgM antibodies in one trial (21)). However in three trials, 6% (25), 10% (18) and 15.4% (24) of the patients, had no microbiological confirmation. The intervention assessed was one dose of intravenous TCZ 8 mg/kg, reported to be administered within less than 24 hours from randomization (or within 24 hours after the first randomization for the RECVOERY trial (25)) or need for respiratory support in six trials (See Table 1). A second dose was allowed after 8-24 hours in six trials, based on clinical decision, and was mandatory in one trial (20). Placebo was used in 3/8 trials (19,21,23). Usual care included antivirals, steroid s, anticoagulants, and others (See Supplemental Table 3 for detailed concomitant treatments). The median time from symptoms onset to randomization was reported in all but one trial (24), which reported time from hospital admission, and was between 8 to 10 days. The

primary outcome of the trials consisted of death at day 28 (25); death or need for MV at day 14 (18,20,22), day 28 (19,21,23) and in-hospital mortality (24); and / or clinical improvement as defined by authors, consisting of improvement on oxygenation, freedom of respiratory support, ICU and hospital discharge (or readiness to discharge), days-free organ support and / or improvement on COVID-19 severity scale. The follow up duration was 28-30 days post-randomization. Hermine et al. (18) and the REMAP-CAP (24) continued follow-up to 90 days and Rosas et al. (23) for 60 days.

The median age of included patients was ~60 years, most were men (58-70%), and had various comorbidities, detailed in Supplemental Table 2. All studies excluded immunocompromised patients, except the trial by Veiga et al., in which less than 8% of patients received immunosuppressive drugs (22) and the RECOVERY trial (25) that included HIV patients (<1% of patients).

Risk of bias assessment

Risk of bias assessment is detailed in Table 2. Low risk sequence generation and allocation concealment were reported in all trials. Three of the eight trials were double blinded (19,21,23) while the other were unblinded. Results were analyzed by intention-to-treat when available, or for the largest population available otherwise. In one trial (18), concerns were raised regarding selective outcome reporting, as the primary outcome was changed during the recruitment. Informed consent and ethical committee approval were described in all trials. All trials received industrial sponsorship. Two trials were terminated early due to futility / safety ((20,22). GRADEpro tool for examining the SOF is detailed in supplemental tables. AEs were reported in concert with the common terminology criteria for reporting of adverse events (CTCTE) or MedDRA hierarchy guidelines in six trials, and a central safety

committee (24,25). Definitions for severe AEs were not stated / graded in four trials (18,20,24,25). (See Table 2)

Primary outcome – all-cause mortality at 28 days

Mortality at 28-30 days was reported by seven trials, and in-hospital mortality was reported in one (24) and varied significantly from 2% to 32.1%. On meta-analysis, all-cause mortality at 28 days, was significantly reduced by TCZ compared to usual care, RR 0.89, 95% CI 0.82-0.96, I^2=4%, 8 trials (Figure 1a). After exclusion of the RECOVERY trial (25) which consisted 77% of the total weight, from the analysis, the effect estimate remained similar but without statistical significance, RR 0.89, 95% CI 0.75-1.06. Sensitivity analysis restricted to trials that used steroids in over than 80% of patients in both arms (19,22,24,25) showed no mortality benefit with TCZ RR 0.92, 95% CI 0.74-1.14, with substantial heterogeneity (Supplemental Figure 2). Sensitivity analysis by blinding showed no difference in mortality compiling data from three double blinded trials (RR 0.97, 95% CI 0.69-1.37, I^2=0%), as opposed to reduced mortality in open-label trials (RR 0.88, 95% CI 0.81-0.96, I^2=35%) (Supplemental Figure 3).

Mortality at 28 days / in-hospital for the subgroup of critically ill patients was reported in three trials (23–25) and was similar between TCZ and usual care, RR 0.94, 95% CI 0.74-1.19, with significant heterogeneity (I^2=60%) (Figure 1b). Subgroup analysis of the mortality outcome was reported only in the RECOVERY trial (25) based on age groups, sex, ethnicity, time from symptoms onset (over / under 7 days), type of respiratory support and use of corticosteroids. Other trials reported subgroup analysis for the outcome of death or MV and not for mortality alone.

Mortality at 14-15 days was reported in three trials (18,20,22), and was significantly increased with TCZ, RR 2.18, 95% CI 1.01-4.69, I^2=31%). Salama et al. (19) reported

mortality at 60 days which was similar between TCZ and placebo (29/250, 11.6% vs.5/127, 11.8%). The REMA-CAP trail (24) reported 90-day survival as a time to event variable, with an adjusted hazard ratio of 1.60, SD 0.21 of TCZ compared to control.

Secondary outcomes

Need for MV was reported at 14 days (18) and at 28 days (21,23,25) or both (22). TCZ was associated with a significantly reduced risk for MV, RR 0.79, 95% CI 0.68-0.91, I^2=0% (Figure 2a). The combined endpoint of death or MV at 14 / 28 days was reduced with TCZ, RR 0.83, 95% CI 0.74-0.90, I^2=0%. (Figure 2b). Need for ICU admission was reported in four trials, with significantly reduced rates in the TCZ arm (RR 0.68, 95% CI 0.50-0.92, I^2=6%). Ventilator free days at 28 days were reported in two trials (22,23) without significant difference between TCZ (median 22, 95% CI 18.0 to 28.0) vs placebo (median 16.5, 95% CI 11.0 to 26.0), p=0.32 and RR 1.36 95% CI 0.733-2.55, respectively. The REMAP-CAP trial (24) reported, among critically ill patients, a significant reduction in median organ support-free days until day 21 with TCZ vs control (median 10, IQR -1, 16 vs 0, IQR -1, 15); significant both for respiratory support-free days (adjusted OR 1.74, SD 0.25), and cardiovascular support-free days (adjusted OR 1.70, SD 0.26). The RECOVERY trial (25) reported new onset of non-invasive and invasive ventilation, and cessation of MV, which were not statistically significant reduced with TCZ. Other efficacy outcomes were without significant difference and are summarized in Table 3. These included need for oxygen supply measures, change in severity scale, discharge rates and duration of stay. No results on AEs were reported for the REMAP-CAP (24) and the RECOVERY trials (25). There was no significant difference in AEs and SAEs between the arms (RR 0.97, 95% CI 0.88-1.07, I^2=28%, and RR 0.87, 95% CI 0.72-1.06, I^2=0%, respectively). Superinfections were reported in 6 trials, only Hermine et al. (18) reported separately bacterial, fungal and viral infections.

Overall rates of superinfections and severe superinfections were higher with placebo / usual care, RR 0.64, 95% CI 0.64-0.97, I^2=44%, and RR 0.57, 95% CI 0.35-0.93, I^2=42%, respectively (Supplemental Figure 4). Neutropenia, reported in four trials, was significantly increased in the TCZ arm (RR 8.70, 95% CI 2.34-32.39).

Subgroup analyses

We could not perform most of the pre-planned subgroup analyses due to significant variation of the outcomes reported and lack of published data. Stone et al. (21) and Veiga et al. (22) reported no significant difference between TCZ and placebo for the outcome of MV or death among elderly patients (age>=65 and >=60 years, respectively). Rosas et al. (23) reported no difference between arms among patients with critical COVID-19 (under MV at randomization) for the outcome of difference in clinical status on the 7-point ordinal scale at day 28. Two trials reported no difference between arms among patients with higher IL-6 levels for the outcome of MV or death. Stone et al. (21) used an IL-6 cut-off level of either >24.4 or >40 pg/ml and Salvarini et al. (20) ≥30 and ≥80 pg/ml. The REMAP-CAP trial (24) reported the most significant benefit for the intervention among patients in the CRP highest tercile (for hospital survival - adjusted OR - mean (SD) 1.62 (0.61)). Veiga et al., (22) in contrast, reported no significant difference in 28-day mortality or MV among patients with CRP>5 mg/dL (OR 1.40, 95%, CI 0.59-3.33). All the patients in the RECOVERY trial had increased CRP at baseline. In the subgroup of patients who were under MV at enrollment to the RECVERY trial, no mortality benefit was demonstrated, RR 0.94 (0.73-1.19).

Discussion

We performed a systematic review and meta-analysis of all RCTs comparing TCZ with placebo/control for the treatment of hospitalized patients with COVID-19. Compiling data from eight trials, including 6,481 patients with a disease of moderate severity at least, we demonstrated that TCZ was associated with a significantly reduced 28-day all-cause mortality (RR 0.89, 95% CI 0.82-0.96). This result was derived mainly from the RECOVERY trial (25), which consisted of 63% of all the included patients. Excluding this trial, the point estimate remained in favor of TCZ, although without statistical significance (RR 0.89, 95% CI 0.75-1.06). Sensitivity analysis by blinding showed significant difference in mortality only in open-label trials. However, among critically ill patients from three trials, no significant mortality was demonstrated (RR 0.94, 95% CI 0.74-1.19). Moreover, in trials that used corticosteroids for >80% of patients, no mortality benefit was demonstrated, RR 0.92, 95% CI 0.74-1.14, with substantial heterogeneity (derived by the trial of Veiga et al. (22)) Need for MV was significantly reduced by TCZ, as well as a composite endpoint of death or MV, and ICU admission rates. Overall AEs and SAEs did not differ between groups, although any and serious infections (were significantly less common in the TCZ arm. This was regardless of higher neutropenia rates in the TCZ arm, ranging between 2.9 to 14%. The reduced mortality signal was mainly driven by the RECOVERY trial. The limitations of this trial include its being published only as a preprint at this time, open-label design, use of a second randomization which may be prone to treatment response bias, and use of the drug in specific sites according to site drug availability (25). Among critically ill patients, no difference in mortality was demonstrated in our meta-analysis. The REMAP-CAP trial which included critically ill patients, reported reduced mortality with TCZ (24). Combining this trial with two other trials reporting mortality for a sub-group of similar patients (23,25) demonstrated no difference in mortality. This outcome is limited by the difference in timeframe for assessing

mortality (REMAP-CAP et al. - in-hospital mortality, Rosas et al. and the RECOVERY trial – 28 days mortality); and by differences in severity definitions. (See Supplemental Table 1) (25).

Several large observational studies, including hospitalized patients with COVID-19 of variable severity, have demonstrated significantly lower mortality, need for MV and/or ICU admission rates with TCZ vs control patients. (7,8,26,27) Thirty-day mortality rates in these observational studies mostly exceeded 20%, as opposed to most included RCTs in this meta-analysis, demonstrating mortality rates ranging between 1.5 and 15%, besides Rosas et al., that reported mortality rates of ~20%, The REMAP-CAP trial. that reported ~36% mortality in the control arm, and the RECVOERY trial that reported overall mortality of 31.3% (23–25). This probably reflects inclusion of non-critical patients in most of the RCTs, as well as limited external validity of these studies, excluding immunocompromised patients, a group known to suffer from higher mortality due to COVID-19. (28) Two of the observational studies reported higher rates of superinfections with TCZ vs control, (8,27) however a third study showed no difference. (7)

We demonstrated reduced MV and ICU admission in our meta-analysis. It should be considered that these outcomes are not "hard" outcomes as all-cause mortality, and might be influenced by local practices. Wide variability has been described in rates of MV across different countries, ranging from ~2 to 33% of hospitalized COVID-19 patients in general, and ~30 to 90% of those admitted to ICU. Similarly, substantial differences in reasons for admission and severity grade are described between ICUs across the globe. (29) The association between need for MV and death is also variably reported and is probably limited

by short follow up periods, though rates of death are consistently high among ventilated patients, suggesting the importance of this outcome despite its limitations. (30)

Various groups have tried to set core outcomes for COVID-19 treatment trials. All included respiratory status as an outcome. Definitions and timeframes vary, including proportion without respiratory failure at ≥ 28 days, (31) ventilator free days, (32) time to first receiving ventilation during hospital stay, (33) and need for MV within 28 days and up to 6 months. (34) The COVID-19-Core Outcomes Set (COS) Workshop Investigators recently summarized current recommendations for core outcomes and called for further work to identify valid core outcomes. (35) For future trials, we believe it is important to clarify the "respiratory outcomes" requested, including their timeframes.

Infections are a well-known complication of tocilizumab. In rheumatoid arthritis patients, serious infections with tocilizumab were reported to occur at a rate of 4.7 per 100 patient-years, with a rate of 0.23/100 patient-years for opportunistic infections. (36) Nevertheless, lower rates of serious infections were documented in the TCZ arm in our meta-analysis. This could be related to lower rates of mechanical ventilation, possibly reducing the risk for ventilator associated pneumonia and other ICU nosocomial infections. It should be noted however that only two trials provided definition of "serious infections" and differentiated bacterial and fungal infections. (18,20) Fungal infections specifically were described in one trial, reporting two cases in the control arm. (18) Coronavirus associated pulmonary aspergillosis (CAPA) has been demonstrated to be common among COVID-19 intubated patients, reaching 28% in an Italian series, in which most patients received steroids and TCZ. (37) Further data are needed in order to determine the risk of CAPA in COVID-19 patients treated with TCZ. Infectious complications in future TCZ trials should be reported in a structured way, detailing source of infection and causative pathogens. (38)

Both IDSA and CDC COVID-19 treatment guidelines (39,40) recommend routine use of TCZ for COVID-19 patients, though definition of patients differ. IDSA guidelines recommend TCZ for patients requiring supplemental oxygen (or higher degree of ventilatory support) who have elevated inflammatory markers; CDC guidelines recommend TCZ for patients admitted to ICU with any respiratory support beyond supplemental oxygen. For non-ICU patients with similar respiratory support, TCZ is recommended only for patients with elevated inflammatory markers. These heterogeneous guidelines and the results of our meta-analysis emphasize the need for both additional RCTs (in accordance with current guidelines for treatment with steroids) and an individual participant data meta-analysis, evaluating the efficacy of TCZ in specific subgroups of severity.

This meta-analysis is limited by the small number of included RCTs and relatively small number of included patients in some of the trials; the inclusion of a major pre-print article; mostly open-label trials; and the variability of concomitant anti-COVID-19 treatments in included trials. Mortality difference was driven mainly from one trial, and was not significant analyzing separately double-blind trials and critically ill patients. Considering the natural course of COVID-19, 14-28 day timeframe may be argued as too early for mortality reporting, as well as for superinfections. The exclusion of immunocompromised patients and, in most trials, the exclusion of critical COVID-19 patients, limits the external validity of the results. Accurate reporting of outcomes in each of these subgroups, perhaps possible to obtain using individual patient data meta-analysis design, could guide clinicians to the optimal timepoint for TCZ administration. Strengths of this meta-analysis include the high-quality grading of included trials in terms of allocation concealment and generation; and the low heterogeneity between trials for most outcomes.

In summary, compiling data from eight RCTs, we found a significant benefit in 28-day all-cause mortality in patients with moderate to severe COVID-19 receiving TCZ versus placebo/control. Need for MV, ICU admission and the outcome of death or MV also significantly favored TCZ. However, for critically ill patients, and in trials using steroids for most patients, no significant difference in mortality was demonstrated. Additional trials should further delineate which patients are most likely to benefit from TCZ based on their severity scale, respiratory support, receipt of other therapy and time form symptoms onset.

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Table 1: Characteristics of included trials

Trial ID	**Country**	**No randomized**	**Confirmation of COVID-19**	**COVID-19 severity publication [1]**	**COVID-19 severity accepted definition [2] and scales**	**TCZ administration**	**Exclusion of immunocompromised patients**
Hermine Oct 2020 JAMA (18)	France	131	Positive PCR and/or typical CT scan PCR confirmed infection documented in 90%	"Moderate or Severe Pneumonia" – non-ventilated, non-ICU patients	Moderate to Severe / WHO-10-point Clinical Progression Scale score (0-10) = 5	IV 8mg/kg D1, 2nd dose D3 400mg if no response	Neutropenia (ANC < 1000/ml)
Salvarani Oct 2020 JAMA (20)	Italy	126	Positive PCR	Non-ICU patients with no invasive or noninvasive mechanical ventilation	Severe / scale not provided	IV 8mg/kg within 8 hours from randomization, 2nd dose after 12h	Neutropenia (ANC < 500/ml); treated with immuno-depressors or anti-rejection drugs
Stone Oct 2020 NEJM 2:1 (21)	USA	243	Positive PCR or serum IgM antibody assay	Moderate pneumonia – 80% non-ICU patients, none ventilated at baseline	Moderate to Severe / n (%) of patients with 7-ordinal scale ≥ 3: 205/243 (84%)	Single IV dose 8mg/kg within 3h from informed consent	Neutropenia (ANC < 500/ml); receiving immunosuppressive therapy believed to placed them at risk for an infection; other biologic or small-molecule immunosuppressive; Oral or IV

							corticosteroid for non-COVID19 indication within the last 7 days at a dose of ≥ 10 mg prednisone or equivalent per day
Rosas 2021 NEJM 2:1 (23)	US, Canada and Europe	452	Positive PCR and evidenced by chest X-ray or CT scan	"Severe pneumonia" ~37% ventilated at randomization	Severe to critical / n (%) of patients with 7-ordinal scale ≥ 3: 423/438 (97%)	IV 8mg/kg, 2nd dose after 8-24h if no response	Neutropenia (ANC < 500/ml); oral anti-rejection or immunomodulatory drugs with the past 3 months
Salama Dec 2020 NEJM (19)	Brazil, Kenya, Mexico, Peru, South Africa, US	389	Positive PCR and evidenced by chest X-ray or CT scan	Patients who did not require noninvasive or invasive mechanical ventilation; ~15% hospitalized in ICU at baseline	Severe / n (%) of patients with 7-ordinal scale ≥ 3: 342/ 377 (91%)	IV 8mg/kg, 2nd dose after 8-24h if no response	Neutropenia (ANC < 500/ml); oral anti-rejection or immunomodulatory drugs with the past 3 months
REMAP-CAP 2021 NEJM(24)	Europe, Saudi Arabia, Australia, New Zealand	895	Suspected or proven COVID-19	Patients receiving respirator or cardiovascular support[3]	Critical	IV 8mg/kg within 24h of organ support, 2nd dose allowed after 12-24h	"Known condition or treatment resulting in ongoing immune suppression including neutropenia prior to this hospitalization"
Veiga 2021 BMJ (22)	Brazil	129	Positive PCR and evidenced by chest X-ray or CT scan	Patients receiving supplemental oxygen or mechanical ventilation and	Severe to critical / n (%) of patients with 7-ordinal scale ≥ 3:	Single IV dose 8mg/kg within 24 hours of ventilation	Neutropenia (ANC < 500/ml);" Other clinical conditions that contraindicate

				had abnormal levels of at least two serum biomarkers (C reactive protein, D dimer, LDH, or ferritin).	108/129 (83.8%) severe, 21/129 (16.2%) critical		tocilizumab, according to the attending physician"
Horby 2021 MedRxiv (25)	United Kingdom	4116	Suspected or proven COVID-19	oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L	Moderate to critical no support 1868/4116 (45.3%) Noninvasive 1686/4116 (40.9%) MV 562/4116 (13.6%)	Weight adjusted IV dose 8/mg/kg. 2nd dose allowed after 12-24h	None

ICU – intensive care unit; ANC – absolute neutrophil count; TCZ – tocilizumab; LDH - lactate dehydrogenase; MV – mechanical ventilation

[1] As reported in the publication. For detailed definitions see supplemental table 1
[2] According to FDA definition (30)
[3] Including: invasive or non-invasive mechanical ventilation (including via high flow nasal cannula if flow rate >30 L/min and FIO2 >0.4); and/or intravenous infusion of any vasopressor or inotrope.

Table 2: Risk of bias for included trials

Trial ID	Allocation generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other bias	Adequacy of serious AEs (SAEs) reporting [1]
Hermine Oct 2020 JAMA (18)	A	A	Open	A	C	Change of primary outcome during trial	Graded according to CTCAE, no definition of severe
Salvarani Oct 2020 JAMA (20)	A	A	Open	A	A	Early termination due to futility	Graded according to CTCAE, no definition of severe
Stone Oct 2020 NEJM 2:1 (21)	A	A	DB	A	A	No	Graded according to CTCAE, SAE defined as ≥ 3
Rosas 2021 NEJM 2:1 (23)	A	A	DB	A	A	No	Graded according to MedDRA Hierarchy
Salama Dec 2020 NEJM (19)	A	A	DB	A	A	No	Graded according to CTCAE, SAE defined as ≥ 3
REMAP-CAP 2021 NEJM (24)	A	A	Open	A	A	No	No definition provided
Veiga 2021 BMJ	A	A	Open	A	A	Early termination due to	Graded according to

(22)						safety	MedDRA Hierarchy
Horby 2021 MedRxiv (25)	A	A	Open	A	A	No	Not stated

AEs – adverse events; SAEs – serious adverse events

[1] Adequate reporting of serious adverse event was defined if definition was according to The Common Terminology Criteria for Adverse Events (CTCAE) (at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) or Medical Dictionary for Regulatory Activities system organ class and preferred term (MedDRA Hierarchy, at https://www.meddra.org/how-to-use/basics/hierarchy). SAEs were defined as grade ≥ 3.

Table 3 – Additional outcomes

Outcome	**No. of trials reporting outcome**	**Effect measure compiled/reported**
Median duration of receipt of supplemental oxygen until day 28 (days)	2 (21,22)	No significant difference (TCZ - median 5.0, IQR 3.8–7.6 days, placebo - median 3.9, IQR 1.1–9.2 days) (20), 6 (5-12) vs 10 (8-14) (22)
Number of patients independent of oxygen supply at 28 days	2 (18,21)	RR 1.08, 95% CI 0.95-1.23
Number of patients with deterioration in severity scale (4-28d)	2 (18,21)	RR 0.89, 95% CI 0.59-1.3
Number of patients discharged 28 days	3 (18,20,25)	RR 1.08, 95% CI 0.96-1.22
Duration of hospital stay until day 28	4 (19–21,24,25)	Two reported no significant difference (18,23) Four reported significantly shorter duration with TCZ (HR 1.35, 95% CI) 1.02 to 1.79) (23), Adjusted HR 1.42 mean SD 0.13 (24), risk ratio 0.70 (0.55 to 0.87) (22), 20 vs. >28 (25)
Duration of ICU stay until 28 days	1 (23) 1 (24)	Difference –5.8, 95% CI –15.0 to 2.9 Adjusted HR - mean (SD) 1.43 (0.13)
Mortality at day 14-15	3 (18,20,22)	RR 2.18, 95% CI 1.01-4.69
Long term survival 90 days	1 (24)	Adjusted HR - mean (SD) 1.60 (0.21)

TCZ – tocilizumab; IQR – interquartile range; RR – relative risk; CI – confidence interval; HR – hazard ratio; SD – standard deviation