



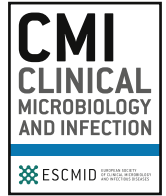
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## Systematic review

# Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis, first update

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## ABSTRACT

**Objectives:** Cytokine release syndrome with elevated interleukin-6 (IL-6) levels is associated with multi-organ damage and death in severe coronavirus disease 2019 (COVID-19). Our objective was to update the data in a living systematic review of the literature concerning the efficacy and toxicity of the IL-6 receptor antagonist tocilizumab in COVID-19 patients.

**Methods:** Data sources were Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Web of Science, Scopus up, preprint servers and Google from 8th October 2020 till 24th February 2021. Eligible studies were randomized controlled trials (RCTs) and observational studies at low or moderate risk of bias. The participants were hospitalized COVID-19 patients, and intervention was tocilizumab versus placebo or standard of care. We pooled crude risk ratios (RRs) of RCTs with a random effects model and evaluated inconsistency between studies with  $I^2$ . We assessed the certainty of evidence using the GRADE approach.

**Results:** Of 1600 citations, eight RCTs and 28 cohorts were eligible. The eight RCTs had low risk of bias, and with 6311 patients they examined the effect of tocilizumab on short-term mortality; pooled RR was 0.91 (95%CI 0.78–1.07,  $I^2$  25%). Only the REMAP-CAP and RECOVERY trials, with the majority of their patients on concomitant corticosteroids, showed lower 30-day mortality with tocilizumab use: RR 0.74 (95%CI 0.59–0.93) and 0.89 (95%CI 0.81–0.97), respectively. Seven RCTs, with 5391 patients, examined the effect of tocilizumab on risk of mechanical ventilation; pooled RR was 0.84 (95%CI 0.76–0.93),  $I^2$  0%, with a corresponding number needed to treat of 20 (95%CI 14.3–33.3). Eight RCTs, with 5340 patients, examined the effect of tocilizumab on a composite of poor outcome; pooled RR was 0.82 (95%CI 0.76–0.90,  $I^2$  3%). Data from the RCTs showed a lower risk of infections and no higher risk of serious adverse events with tocilizumab: pooled RR 0.67 (95%CI 0.45–0.99, eight RCTs) and 0.85 (95%CI 0.63–1.16, seven RCTs), respectively. Among 28 cohorts with 15 484 patients, the pooled adjusted RR for mortality was 0.53 (95%CI 0.43–0.67,  $I^2$  76%).

**Conclusions:** Cumulative high-certainty evidence shows that tocilizumab reduces the risk of mechanical ventilation in hospitalized patients with severe COVID-19. Moderate-certainty evidence shows that tocilizumab reduces the risk of poor outcome and the risk of secondary infections in hospitalized COVID-

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## Introduction

Cytokine release syndrome with elevated levels of interleukin-6 (IL-6) is associated with multiorgan damage and death in severe coronavirus disease 2019 (COVID-19). As of October 2020, cumulative moderate-certainty evidence from randomized controlled trials (RCTs) showed that the IL-6 receptor antagonist tocilizumab reduces the risk of mechanical ventilation in hospitalized COVID-19 patients, without affecting short-term mortality [1]. This report is the first update of our living systematic review assessing the efficacy and safety of tocilizumab in COVID-19 patients [1].

## Methods

Using the same methodology and search databases detailed in our previous review [1], we searched for new studies published through 24th February 2021 and updated our analysis using the same quality assessment tools and analytical methods. As several RCTs have been published since our initial review, and as per peer reviewers' and editor's recommendations, this update includes observational studies up to January 2021, and future updates will include only data from RCTs. We also contacted all first authors of eligible RCTs for additional data for subgroup analyses.

## Results

We evaluated an additional 1600 abstracts from peer-reviewed publications. We also searched for unpublished manuscripts using the medRxiv services and [Researchsquare.com](https://www.researchsquare.com), Google, and the references of eligible studies and review articles. Only one author responded to our queries for additional data for subgroup analyses.

We identified eight multicentre RCTs [2–9], of which one was stopped early for possible futility (RCT-TCZ-COVID-19) [9], one for possible benefit (REMAP-CAP) [8], and one for possible harm (TOCIBRAS) [7]. As of this update the results of the RECOVERY trial [6] have been published as a preprint only. [Table 1](#) summarizes the characteristics of eligible RCTs and includes the design, setting, inclusion criteria, disease severity and definition of endpoints. Three RCTs [2,7,8] included a proportion of patients with critical COVID-19, while the others enrolled patients with moderate to severe COVID-19. Three trials (RECOVERY, RCT-TCZ-COVID-19 and TOCIBRAS) [6,7,9] required the presence of high inflammatory markers (such as C-reactive protein) for enrolment, although all trials reported a high range of inflammatory markers in their patient populations. All RCTs used the tocilizumab dose of 8 mg/kg, and six RCTs allowed a second dose if needed. The median time between the onset COVID-19 symptoms and the first dose of tocilizumab ranged from 7 to 11 days. The proportion of patients who received concomitant corticosteroid treatment was small (8–36%) in the RCT-TCZ-COVID-19 [9], CORIMUNO-TOCI [5], BACC Bay Tocilizumab [4] and COVACTA [2] trials. Most patients (>69%) in the RECOVERY [6], EMPACTA [3], REMAP-CAP [8] and TOCIBRAS [7] trials received concomitant corticosteroids therapy.

We identified ten additional cohort studies published since our first review [10–19]. A total of 28 cohort studies, at moderate risk of

bias, reported on adjusted effect estimates of mortality. [Supplementary Material Table S1](#) illustrates the general characteristics of the included cohort studies. All studies reported on patients hospitalized with COVID-19 with varying degrees of disease severity.

## Updated data synthesis

In total, 36 studies were eligible (eight RCTs and 28 cohorts). Eight RCTs were deemed at low risk of bias ([Supplementary Material Figs S1 and S2](#)). Although five RCTs were open-label studies [5–9], there was no evidence of performance bias or outcome assessment bias ([Supplementary Material Figs S1 and S2](#)). Only the REMAP-CAP [8] and RECOVERY [6] trials, with the majority of their patients on concomitant corticosteroids (>80%), showed lower 30-day mortality with tocilizumab use, RR 0.74 (95%CI 0.59–0.93) and 0.89 (95%CI 0.81–0.97), respectively. Eight RCTs [2–9], with 6311 patients, examined the effect of tocilizumab on short-term mortality ([Fig. 1A](#)); pooled RR was 0.91 (95%CI 0.72–1.07,  $I^2$  25%). Seven RCTs ([Fig. 1B](#)) [2–7,9], with 1274 patients, examined the effect of tocilizumab on risk of mechanical ventilation; pooled RR was 0.84 (95%CI 0.76–0.93),  $I^2$  0%, with a corresponding number needed to treat of 20 (95%CI 14.3–33.3).

Eight RCTs, with 5340 patients, examined the effect of tocilizumab on a composite of poor outcome; pooled RR was 0.82 (95%CI 0.76–0.90,  $I^2$  3%) ([Fig. 1C](#)). The definition of this composite outcome in each trial is summarized in [Table 1](#).

Using available data from five studies [2,3,5–7], we assessed the effect of steroids on the composite of mortality or mechanical ventilation in patients taking tocilizumab versus controls. The risk ratios for patients receiving steroids and those not receiving steroids were 0.87 (95%CI 0.68–1.12) and 0.99 (95%CI 0.85–1.16) respectively. Additionally, there was no interaction between the use of mechanical ventilation and the effect of tocilizumab on mortality based on data from three studies [2,6,7]. The risk ratios for patients receiving and those not receiving mechanical ventilation are 1.02 (95%CI 0.79–1.31) and 0.98 (95%CI 0.89–1.07), respectively.

Data from the RCTs showed a lower risk of infections ([Fig. 2A](#)) and no difference in the risk of developing serious adverse events ([Fig. 2B](#)) with tocilizumab: pooled RR 0.67 (95%CI 0.45–0.99, eight RCTs) and 0.85 (95%CI 0.63–1.16, seven RCTs), respectively. The follow-up period for infections was 28 days in all studies except for the EMAPCTA and REMAP-CAP trials. There were no significant differences in the infection rates that may be attributed to longer follow-up duration.

Among 28 cohorts at moderate risk of bias ([Supplementary Material Fig. S3](#)), with 15 484 patients, the pooled adjusted RR for mortality was 0.53 (95%CI 0.43–0.67,  $I^2$  76%). This association was observed over all degrees of COVID-19 severity ([Supplementary Material Fig. S4](#)). Contour-enhanced funnel plot and Egger's test for small-study effects ( $p$  0.27) did not show evidence of publication bias ([Supplementary Material Fig. S5](#)).

Survivor bias was addressed in the analysis in 11 out of 28 studies only. The pooled RR of the 11 studies that adjusted for survivor bias was 0.48 (95%CI 0.35–0.67). To study the potential effect of survivor bias on the observed results, we multiplied the RR

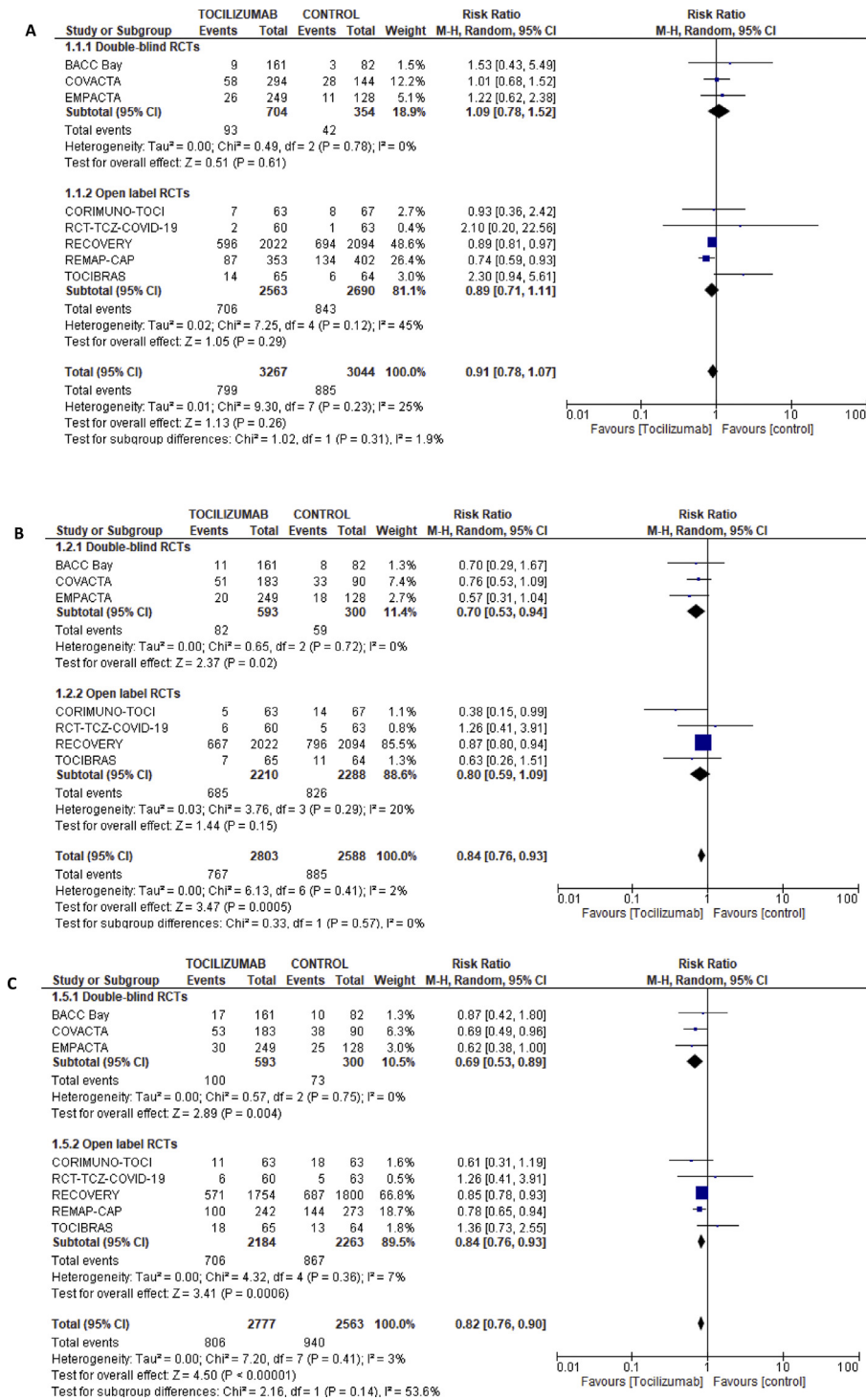
**Table 1**  
Characteristics of completed randomized controlled trials of tocilizumab for coronavirus disease 2019 (COVID-19) patients

RCT	Design and setting	Enrolment dates	Inclusion criteria <sup>a</sup>	MV (%)	Steroids (%) (TCZ)	Steroids (%) (Control)	Days to TCZ (TCZ) <sup>b</sup> Median (IQR) or mean (SD)	Days to TCZ (control) Median (IQR) or mean (SD)	Mortality	Composite of poor outcome	Follow-up duration for secondary infections
RCT-TCZ-COVID-19 NCT04346355	Open label: 60 TCZ versus 66 controls Italy, 24 centres	31st March 2020 till 11th June 2020	Severity of illness: severe High inflammatory marker: yes Progressive disease: no	0%	8%	4.5%	7 (4–11)	8 (6–11)	30 days	Death or continuous need for hospitalization at day 30	Cutoff date was June 24, 2020
CORIMUNO-TOCI NCT04331808	Open label: 64 TCZ versus 67 controls France, 9 centres	31st March 2020 till 18th April 2020	Severity of illness: moderate to severe High inflammatory marker: no Progressive disease: no	0%	33%	61%	10 (7–13)	10 (8–13)	28 days	Death or continuous need for hospitalization at day 28	28 days
BACC Bay Tocilizumab Trial NCT04356937	Double-blind, placebo-controlled: 161 TCZ versus 81 controls USA, 7 centres	20th April 2020 till 15th June 2020	Severity of illness: severe High inflammatory marker: yes Progressive disease: no	0%	11%	6%	9.0 (6.0–13.0)	10.0 (7.0–13.0)	28 days	Death or MV at day 28	28 days
COVACTA NCT04320615	Double-blind, placebo-controlled: 294 TCZ versus 144 controls 9 countries, 67 centres	3rd April 2020 till 28th May 2020	Severity of illness: severe to critical High inflammatory marker: no Progressive disease: no	37.5%	36.1%	54.9%	11.0 (1.0–49.0)	10.0 (2.0–50.0)	28 days	Death, withdrawal during hospitalization, transfer to ICU, or requirement for invasive MV within 28 days of baseline	28 days
EMPACTA NCT04372186	Double-blind, placebo-controlled: 249 TCZ versus 128 controls 6 countries, 69 centres	14th May 2020 till 18th August 2020	Severity of illness: severe High inflammatory marker: no Progressive disease: no	0%	80.3%	87.5%	8.0 (0.0–31.0)	8.0 (0.0–36.0)	28 days	Death or MV by day 28	60 days
REMAP-CAP NCT02735707	Open label: 366 TCZ versus 412 controls 6 countries, 113 sites	19th April 2020 till 19th November 2020	Severity of illness: critical High inflammatory marker: no Progressive disease: no	29.4%	>80%	>80%	From hospital admission: 1.2 (0.8–2.8)	From hospital admission: 1.2 (0.8–2.8)	30 days	Death or MV or ECMO for non-intubated patients	90 days
TOCIBRAS NCT04403685	Open label: 65 TCZ versus 64 controls Nine hospitals in Brazil	8th May 2020 till 17th July 2020	Severity of illness: severe to critical High inflammatory marker: yes Progressive disease: no	16%	69%	73%	10.0 (3.1)	9.5 (3.0)	29 days	Composite of death or MV at day 15	29 days
RECOVERY NCT04381936	Open label: 2022 TCZ versus 2094 controls 1 country, 177 sites	23rd April 2020 till 24th January 2021	Severity of illness: severe and critical High inflammatory marker: yes Progressive disease: yes	14%	82%	82%	9 (7–13)	10 (7–14)	28 days	Death or MV by day 28	28 days

MV, mechanical ventilation; ICU, intensive care unit; TCZ, tocilizumab; ECMO, extracorporeal membrane oxygenation.

<sup>a</sup> Severity of illness based on NIH classification for the majority of patients.

<sup>b</sup> From symptom onset.

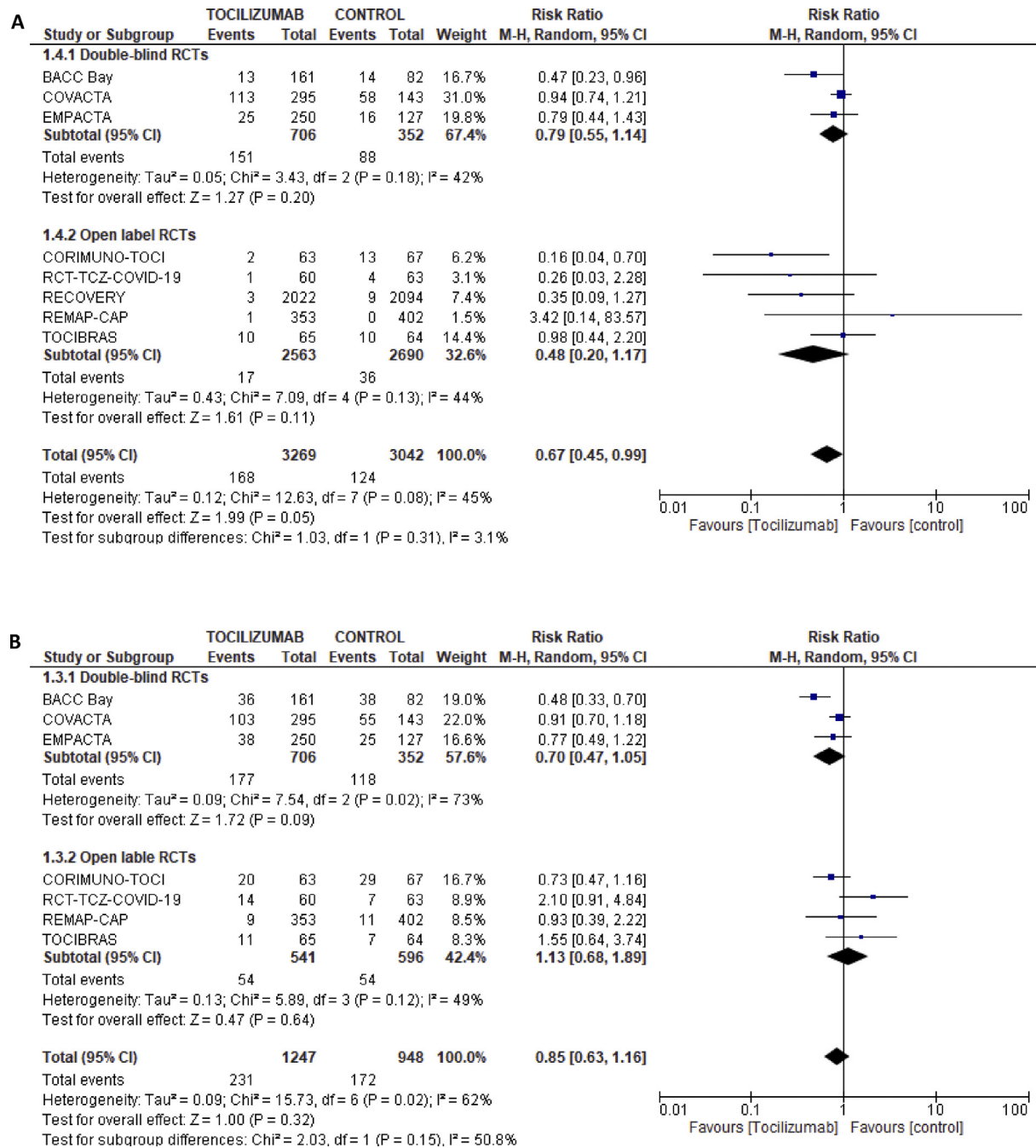


**Fig. 1.** (A) Forest plot for the effect of tocilizumab on 28–30 days mortality in randomized controlled trials. (B) Forest plot for the effect of tocilizumab on risk for mechanical ventilation in randomized controlled trials. (C) Forest plot for the effect of tocilizumab on 28–30 days composite of poor outcome in randomized controlled trials. Definitions of composite outcomes for each trial are listed in Table 1.

or HR of studies that did not adjust for survivor bias and their corresponding 95% CIs by 1.6 and pooled the new adjusted effect estimates. The corrected pooled adjusted RR for mortality from the 28 cohorts was 0.69 (95% CI 0.53–0.89, I<sup>2</sup> 83%) (Supplementary Material Fig. S6).

*GRADE of evidence*

Data from RCTs, at low risk of bias, showed with high certainty that in hospitalized COVID-19 patients tocilizumab reduces the risk of mechanical ventilation with a corresponding number needed to



**Fig. 2.** (A) Forest plot for relative risk of infections with tocilizumab versus control in randomized controlled trials. (B) Forest plot for relative risk of serious adverse events with tocilizumab versus control in randomized controlled trials.

treat of 20 (95%CI 14.3–33.3). Additionally, moderate-certainty evidence also suggests that tocilizumab is associated with a reduced risk of secondary infections, and a composite of poor outcome. Certainty of evidence was downgraded due to a wide confidence interval in the RR of infection, and due to possible performance bias for outcomes such as ICU admission in the composite outcome. We observed with moderate certainty that tocilizumab has no significant effect on mortality. The pooled RR of 0.91 (95%CI 0.72–1.07) was imprecise, with a wide 95%CI, suggesting that more studies may be needed for a definitive answer.

For the cohort studies, the overall quality of evidence (classified as low in observational studies) remained low given the moderate

risk of study bias, low risk of publication bias, direct evidence, low inconsistency, and precise estimate. Although  $I^2$  was high for the pooled mortality risk estimate, it was driven by the magnitude of the association rather than its direction.

## Discussion

In this updated systematic review and meta-analysis of eight RCTs, as of February 2021, we observed with high certainty that tocilizumab reduces the risk of mechanical ventilation in hospitalized COVID-19 patients. We also observed, with moderate certainty, that tocilizumab reduces the risk of poor outcome and the

risk of secondary infections in hospitalized COVID-19 patients. We discuss in our prior review [1] the possible molecular mechanisms for this observed effect.

We did not observe a significant effect of tocilizumab on the risk of mortality or adverse events. Only the two largest RCTs—the RECOVERY [6] and REMAP-CAP [8], in which >80% of the patients were treated concomitantly with corticosteroids—showed an improved survival in patients receiving tocilizumab. We could not examine the interaction between corticosteroid use, mechanical ventilation, timing of tocilizumab, inflammatory markers, and the effect of tocilizumab on different outcomes. We contacted all authors of the eight RCTs asking them for data for different subgroups; only one author provided us with the needed data.

Despite the eight published trials in the past year, it is still difficult to specify which population will benefit from tocilizumab in COVID-19. Ambiguity is compounded when taking into consideration the differences in trial designs, such as inclusion criteria of patients with different disease severity, and the temporal trends in standard of care (such as the use of steroids) (Table 1). There are many variables that may dictate who will benefit from tocilizumab treatment, such as patient characteristics, disease severity, timing of treatment, and duration of illness (Table 1). Data from the RECOVERY trial showed that the survival benefit was restricted to patients who received concomitant steroids rather than patients who did not: RR 0.80 (0.70–0.90) versus 1.16 (0.91–1.48) respectively. We concur with the recommendations by the expert panels of the Infectious Disease Society of America [20] and National Institute of Health COVID-19 Treatment Guidelines [21] that tocilizumab should be used in combination with dexamethasone in hospitalized adults with COVID-19 who: (a) within the prior 24–48 hours have required high-flow supplemental oxygen, non-invasive or mechanical ventilation, and (b) are receiving low-flow oxygen and have increasing oxygen requirements and elevated inflammatory markers despite dexamethasone.

Interestingly, we found a significantly lower risk of secondary infections in the tocilizumab group as compared to the treatment group. This finding goes against the notion that immunomodulators are generally associated with higher infection rates. A possible explanation for our finding is that tocilizumab may play a role in curbing immune exhaustion associated with sepsis in general and COVID-19 in particular. In one study of 499 COVID-19 patients [22], the numbers of total T cells, CD4<sup>+</sup> and CD8<sup>+</sup> T cells were significantly reduced, especially in patients requiring ICU care. In comparison to healthy controls, COVID-19 patients showed markedly higher percentages of PD-1/CD8<sup>+</sup> and CD4<sup>+</sup> T cells, a sign of T-cell exhaustion in COVID-19 patients. These findings were more pronounced in those requiring ICU care and suggest that the decrease in T cells seen in COVID-19 patients may be the result of high serum concentration of tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ), IL-6, and IL-10 which negatively regulate T-cell survival or proliferation. On the other hand, patients with sepsis in general experience a high rate of secondary infections due to impairments in the adaptive immune response and immune exhaustion (reviewed by Brady et al.) [23]. Another possible explanation for the lower infection rate in the tocilizumab group is the lower risk of clinical deterioration and need for mechanical ventilation with tocilizumab use. ICU stay and mechanical ventilation are associated with high risk of nosocomial infections.

## Conclusion

Cumulative high-certainty evidence shows that tocilizumab reduces the risk of mechanical ventilation in hospitalized patients,

while moderate-certainty evidence shows that tocilizumab reduces the risk of poor outcome and the risk of secondary infections. This review will continuously evaluate the role of tocilizumab in COVID-19 treatment. It is crucial that all RCT teams urgently contribute their trials data for a meta-analysis that incorporates subgroup analyses, and that they explore any heterogeneous treatment effects of tocilizumab.

## Author contributions

IT and ZK contributed equally to this work. IT: conception and design of the study. IT, ZK, LH, VV and TK: acquisition of the data. IT, ZK and MR: analysis of the data. IT, ZK, LH, VV, MR and TK: interpretation of data. IT and ZK: drafting of the article. All authors: critical revision of the article for important intellectual content and final approval of the version to be submitted.

## Transparency declaration

The authors declare no conflicts of interest. No funding was received for this work.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2021.04.019>.

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