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International Journal of Antimicrobial Agents 56 (2020) 106103

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Tocilizumab for severe COVID-19: a systematic review and meta-analysis

Shao-Huan Lan[a,1], Chih-Cheng Lai[b,1], Hui-Ting Huang[c], Shen-Peng Chang[d], Li-Chin Lu[e], Po-Ren Hsueh[f,g,*]

[a] School of Pharmaceutical Sciences and Medical Technology, Putian University, Putian 351100, China
[b] Department of Internal Medicine, Kaohsiung Veterans General Hospital, Tainan Branch, Tainan, Taiwan
[c] Department of Pharmacy, Chi Mei Medical Center, Liouying, Taiwan
[d] Yijia Pharmacy, Tainan 70846, Taiwan
[e] School of Management, Putian University, Putian 351100, China
[f] Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[g] Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 4 June 2020
Accepted 19 July 2020

Keywords:
Tocilizumab
SARS-CoV-2
COVID-19
Mortality
Intensive care unit
Mechanical ventilation

ABSTRACT

This systemic review and meta-analysis aimed to assess the efficacy of tocilizumab for the treatment of severe coronavirus disease 2019 (COVID-19). Candidate studies up to 24 May 2020 were identified from PubMed, Cochrane Library, Embase, medRxiv and bioRxiv. Treatment outcomes included mortality, risk of intensive care unit (ICU) admission and the requirement for mechanical ventilation (MV). Seven retrospective studies involving 592 adult patients with severe COVID-19, including 240 in the tocilizumab group and 352 in the control group, were enrolled. All-cause mortality of severe COVID-19 patients among the tocilizumab group was 16.3% (39/240), which was lower than that in the control group (24.1%; 85/352). However, the difference did not reach statistical significance [risk ratio (RR) = 0.62, 95% confidence interval (CI) 0.31–1.22; I^2 = 68%]. Additionally, risk of ICU admission was similar between the tocilizumab and control groups (35.1% vs. 15.8%; RR = 1.51, 95% CI 0.33–6.78; I^2 = 86%). The requirement for MV was similar between the tocilizumab and control groups (32.4% vs. 28.6%; RR = 0.82, 95% CI 0.14–4.94; I^2 = 91%). However, these non-significant differences between the tocilizumab and control groups may have been the result of baseline characteristics of the tocilizumab group, which were more severe than those of the control group. Based on low-quality evidence, there is no conclusive evidence that tocilizumab would provide any additional benefit to patients with severe COVID-19. Therefore, further recommendation of tocilizumab for COVID-19 cases should be halted until high-quality evidence from randomised controlled trials is available.

1. Introduction

Since the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was identified at the end of 2019, coronavirus disease 2019 (COVID-19) has become a huge threat to global health [1,2]. As of 26 May 2020, COVID-19 had been confirmed in 5 404 512 patients and had resulted in 343 514 deaths [3]. The full spectrum of clinical manifestations of COVID-19 ranges from asymptomatic carriage and mild acute respiratory disease, to severe pneumonia and even acute respiratory distress disease (ARDS) [4]. Although the overall fatality rate was reported as 6.36% [3], most of the deaths were attributed to severe COVID-19 cases [5].

COVID-19 is a novel emerging infectious disease associated with a complicated pathogenesis; however, laboratory evidence of severe SARS-CoV-2 infections suggests that cytokine release syndrome (CRS) plays a crucial pathogenic role [6–8]. Although many proinflammatory cytokines are involved in CRS, interleukin-6 (IL-6) is the most important, although it was also found to be a poor prognostic factor [9,10]. Anti-IL-6 agents have been proposed as a promising treatment regimen for COVID-19 [11–13]. Tocilizumab is a humanised monoclonal antibody that can target both membrane-bound and soluble forms of the IL-6 receptor, and several studies have evaluated its efficacy in the treatment of severe COVID-19

* Corresponding author. Present address: Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, Number 7, Chung-Shan South Road, Taipei 100, Taiwan.
E-mail address: hsporen@ntu.edu.tw (P.-R. Hsueh).
[1] These two authors contributed equally to this work.

https://doi.org/10.1016/j.ijantimicag.2020.106103
0924-8579/

[14–24]. In one series of 100 patients with severe COVID-19 pneumonia complicated by ARDS and hyperinflammatory syndrome [22], tocilizumab use showed a rapid and sustained response and was also associated with significant clinical improvement. In another study by Ramaswamy et al., although tocilizumab-treated patients displayed higher levels of biomarkers [C-reactive protein (CRP) and IL-6] indicative of cytokine storm at initial presentation, tocilizumab still provided a short-term survival benefit [18]. However, no consistent results were reported among these studies comparing tocilizumab and other treatment regimens for COVID-19. Therefore, this meta-analysis was conducted to investigate the impact of tocilizumab on the mortality of patients with COVID-19.

2. Materials and methods

2.1. Search strategy

All candidate studies were initially identified by conducting a systematic review of online databases, namely PubMed, Cochrane Library, Embase, medRxiv and bioRxiv until 24 May 2020 using the following search terms: 'tocilizumab', 'atlizumab', 'actemra', 'roactemra', 'sarilumab', 'kevzara', 'siltuximab', 'sylvant', 'CNTO-328', 'SARS-CoV-2', 'coronavirus', 'nCoV', 'pneumonia', 'coronavirus', '2019 nCoV' and 'COVID-19'. Further details regarding the search strategy are given in the Supplementary data.

2.2. Inclusion and exclusion criteria

Only studies comparing the clinical efficacy of the anti-IL-6 receptor antibody tocilizumab and its comparators for the treatment of COVID-19 and explicitly reporting at least one of the outcomes of interest, namely all-cause mortality, intensive care unit (ICU) admission and requirement for mechanical ventilation (MV), were included. Exclusion criteria were as follows: (i) case reports; (ii) single-arm studies; (iii) studies that did not report outcomes for tocilizumab in COVID-19; (iv) studies that did not compare outcomes for tocilizumab compared with placebo or control; (v) pharmacokinetic studies; and (vi) in vitro studies. To avoid bias, two authors (S-PC and S-HL) were responsible for searching and examining the articles independently. In the event of disagreement between the two authors, another author (C-CL) would help to resolve the issue and make a final decision. Data collected included author(s), year of publication, study design and country, patients' demographic characteristics, the regimen of tocilizumab and comparative agents, and the risk of adverse events. The primary outcome was all-cause mortality. Secondary outcomes included ICU admission and the requirement for IMV. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [25].

2.3. Statistical analysis

Statistical analysis was conducted using the software Review Manager v.5.3 (Cochrane Collaboration). The degree of heterogeneity was evaluated with the Q statistic generated from the χ^2 test. The proportion of statistical heterogeneity was assessed using the I^2 measure. Heterogeneity was defined as significant when the P-value was <0.1 or the $I^2 > 50\%$. A fixed-effects model and a random-effects model were applied when data were considered as homogenous or heterogeneous, respectively. The pooled risk ratio (RR) and 95% confidence interval (CI) were calculated, and a P-value of <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the studies

The search strategy initially yielded 358 references; after excluding 87 duplicate articles, 271 articles were subsequently screened. Finally, 15 articles were identified for full-text review for eligibility after excluding the remaining 256 articles by title and abstract. Eight articles were excluded after full-text review according to the exclusion criteria. Finally, only seven retrospective studies [14–20] were designed to compare the clinical efficacy of tocilizumab and its comparators in the treatment of patients with SARS-CoV-2 infection and were thus included in this meta-analysis (Fig. 1; Supplementary data). Overall, this meta-analysis involved a total of 592 patients, including 240 in the tocilizumab group and 352 in the control group. The characteristics of included studies and patients are shown in Tables 1 and 2, respectively. Except for one multicentre study [18], the remaining six were single-centre studies [14–17,19,20]. Three studies were conducted in Italy [14,15,17] and two each in France [16,19] and the USA [18,20]. Only two studies [19,20] had matched study and control group in terms of age, sex and disease severity. Except for one study [20] that did not report the frequency of administering tocilizumab, three studies [14,17,19] used tocilizumab once, one study [15] used tocilizumab twice and the remaining two studies [16,18] used tocilizumab both once and twice. A fixed dose of 400 mg or 8 mg/kg was the most commonly reported regimen of tocilizumab. In one study, Capra et al. [14] also used subcutaneous injection of tocilizumab of 324 mg for 27 patients. Because all included studies were retrospective observational trials, the risk of bias was assessed using the Newcastle–Ottawa scale [26]. The quality assessment score of each study was 6, indicating a high risk of bias for all seven studies.

3.2. Clinical outcome

Pooled analysis of the seven included studies [14–20] revealed that the all-cause mortality rate of patients with COVID-19 in the tocilizumab group was 16.3% (39/240), which was lower compared with the control group (24.1%; 85/352). However, the difference did not reach statistical significance (RR = 0.62, 95% CI 0.31–1.22; I^2 = 68%) (Fig. 2). Sensitivity analysis after deleting an individual study successively revealed the same findings. Similar findings were observed in the study conducted in Italy (RR = 0.81, 95% CI 0.07–9.72; I^2 = 87%) and the USA (RR = 0.78, 95% CI 0.51–1.20; I^2 = 0%). However, both studies in France showed that the tocilizumab group was associated with a lower mortality rate compared with the control group (RR = 0.44, 95% CI 0.22–0.89; I^2 = 0%).

Five studies [15–19] reported the rate of ICU admission and the pooled analysis showed a similar risk of ICU admission between the tocilizumab and control groups (35.1% vs. 15.8%; RR = 1.51, 95% CI 0.33–6.78; I^2 = 86%) (Fig. 3). Three studies [16,18,19] reported the requirement for MV and the pooled analysis revealed a similar risk between the tocilizumab and control groups (32.4% vs. 28.6%; RR = 0.82, 95% CI 0.14–4.94; I^2 = 91%) (Fig. 4).

4. Discussion

To the best of our knowledge, this is the first meta-analysis investigating the effect of tocilizumab on clinical outcomes of patients with severe COVID-19. Based on analysis of seven retrospective studies [14–20], it was found that tocilizumab could not provide any additional benefit for the clinical outcomes of severe COVID-19. Although the mortality rate of patients treated with

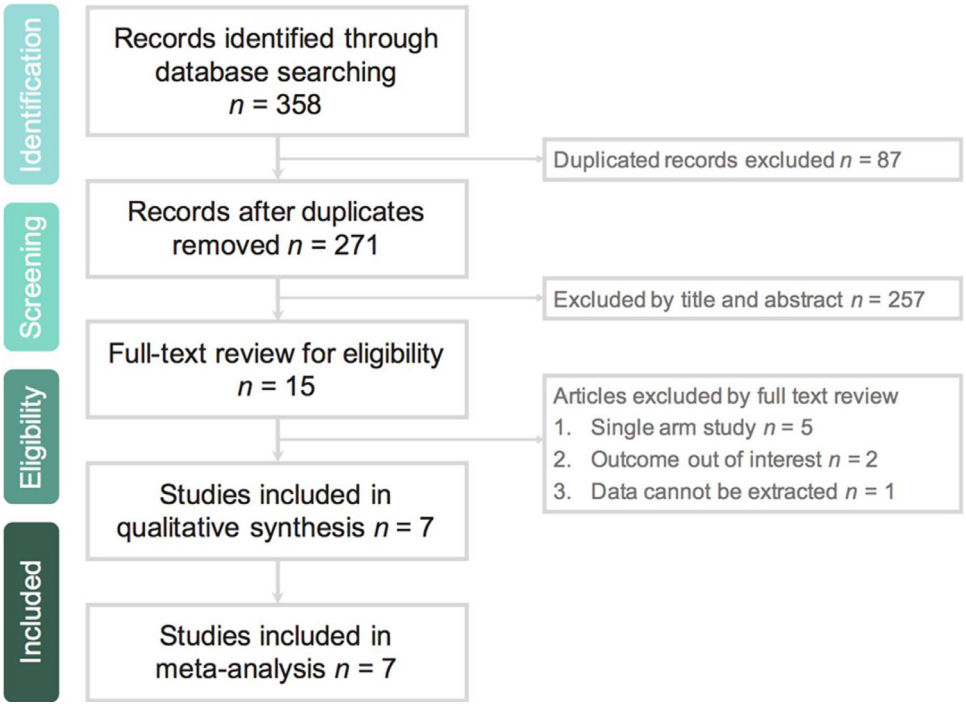

Fig. 1. Flow diagram of study selection.

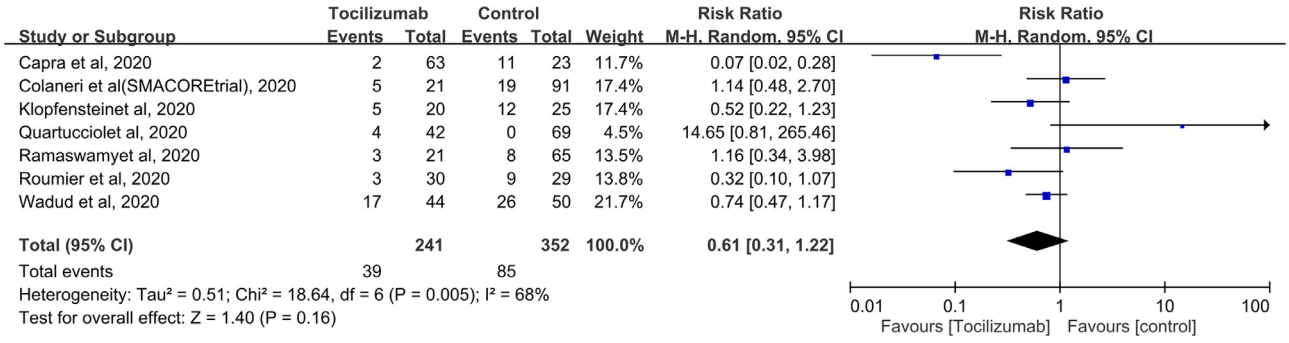

Fig. 2. Risk of mortality between tocilizumab and comparator groups.

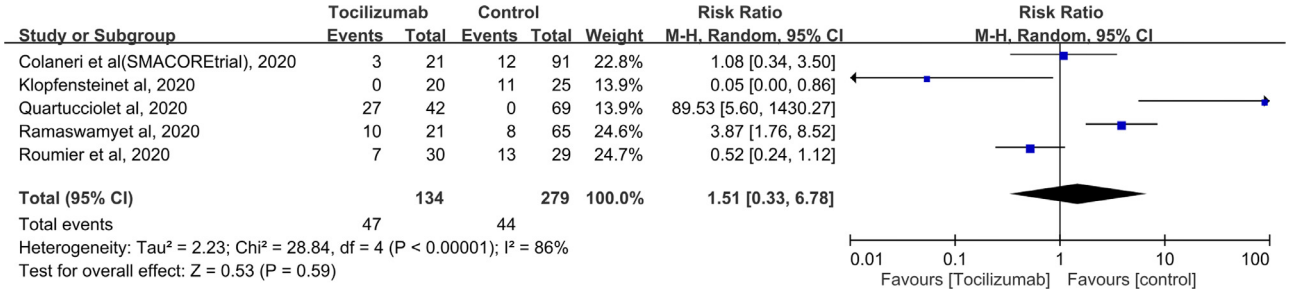

Fig. 3. Risk of intensive care unit (ICU) admission between tocilizumab and comparator groups.

tocilizumab was lower than that of the control group, the difference did not reach statistical significance. Only the subgroup analysis of two studies [16,19] conducted in France showed a significant difference in the mortality rates between the tocilizumab and control groups. Overall, the mortality rate for tocilizumab-treated patients with COVID-19 of the seven included studies [14–20] ranged from 3.2% to 38.6%, most probably reflecting the 'quality of care' as a whole, including surge capacity of the ICU as it parallels the number of available beds for the ICU despite the fact that dosage and population characteristics might play a role. This finding was consistent with several single-arm studies [21–24]. In an open-label prospective study involving 51 patients with severe COVID-19 pneumonia who received tocilizumab in Milan (Italy), 14 patients (27%) died, with a higher mortality rate among mechanically ventilated patients at baseline [21]. Another prospective study involving 100 patients with COVID-19 and ARDS requiring ventilatory support in Brescia (Italy), in which tocilizumab was administered at a dosage of 8 mg/kg using two consecutive intravenous infusions 12 h apart, and an optional third infusion based on clinical response, showed that the mortality was 20% ($n = 20$) [22]. Another

Table 1
Characteristics of included studies

Reference	Type of study	Study site	Regimen of tocilizumab (no. of patients)	Regimen of control group (no. of patients)	Primary outcome
Capra et al. [14]	Retrospective observational study	Single centre in Italy	400 mg i.v. once (n = 33), 324 mg s.c. once (n = 27), 800 mg i.v. (n = 2)	Hydroxychloroquine 400 mg daily and lopinavir 800 mg daily + ritonavir 200 mg daily (n = 23)	Survival rate
Colaneri et al. [15]	Retrospective observational study	Single centre in Italy	8 mg/kg i.v. and repeated after 12 h (n = 21)	Hydroxychloroquine 200 mg twice daily, azithromycin 500 mg daily and methylprednisolone (n = 91)	ICU admission and mortality
Klopfenstein et al. [16]	Retrospective case–control study	Single centre in France	1 or 2 doses (n = 20)	Hydroxychloroquine or lopinavir/ritonavir (n = 25)	Death, ICU admission
Quartuccio et al. [17]	Retrospective observational study	Single centre in Italy	8 mg/kg i.v. once (n = 42)	Standard of care (n = 69)	Fatality rate, levels of inflammatory markers
Ramaswamy et al. [18]	Retrospective case–control study	Multicentre involving three hospitals in the USA	400 mg fixed dose or 8 mg/kg (n = 21) once or twice	Standard of care (n = 65)	Death
Roumier et al. [19]	Retrospective case–control study [a]	Single centre in France	8 mg/kg at discretion of the treating physicians, renewable once in case of insufficient response to therapy (n = 30)	N/A (n = 29)	Death, invasive ventilation
Wadud et al. [20]	Retrospective case–control study [b]	Single centre in the USA	N/A (n = 44)	N/A (n = 50)	Duration of MV, mortality, and length of hospital and ICU stay

ICU, intensive care unit; i.v., intravenous; MV, mechanical ventilation; N/A, not available; s.c., subcutaneous.
[a] Matched study and control groups for age, sex and disease severity using the inverse probability of treatment weighted methodology.
[b] Matched study and control groups as close as possible for age, sex, body mass index (BMI) and HScore (calculated using inflammatory markers, e.g. ferritin, triglycerides, aspartate aminotransferase and fibrinogen).

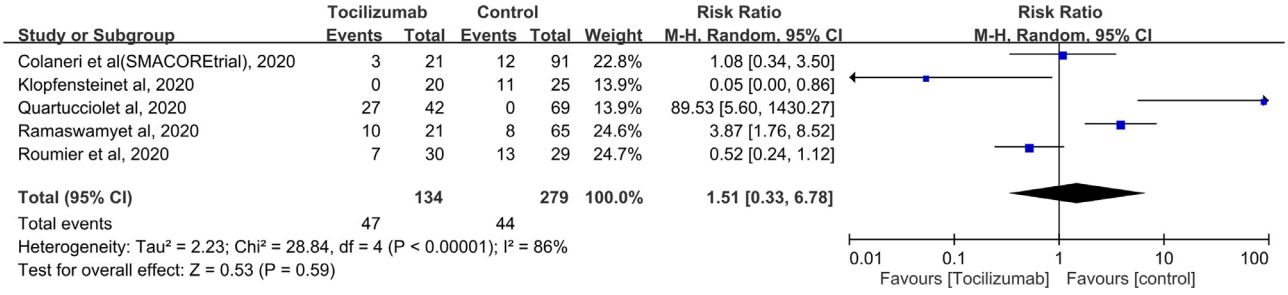

Fig. 4. Risk of requirement for mechanical ventilation between tocilizumab and comparator groups.

pilot prospective open, single-arm multicentre study of 63 patients with severe COVID-19 demonstrated that the overall mortality was 11% and that tocilizumab administration within 6 days from admission was associated with an increased likelihood of survival [hazard ratio (HR) = 2.2, 95% CI 1.3–6.7; P <0.05] [24]. One small study involving 25 patients showed that the mortality rate was only 12% (n = 3) [23]. In addition to all-cause mortality, the risk of ICU admission and the need for MV were similar between the tocilizumab and control groups. In summary, tocilizumab add-on for patients with severe COVID-19 was not associated with a better treatment outcome compared with those without tocilizumab treatment.

However, these findings should be interpreted cautiously. The baseline characteristics and disease severity of the study and control groups were not matched in several included studies (Table 2). In the study by Klopfenstein et al. [16], the tocilizumab group had a higher Charlson comorbidity index, indicating higher severity and worse survival compared with the control group (all P < 0.05). In the study by Quartuccio et al. [17], the tocilizumab group was relatively older and had higher levels of CRP and IL-6 compared with the control group. In the study by Ramaswamy et al. [18], the tocilizumab-treated group had higher levels of biomarkers, higher early warning scores at initial symptom manifestation and greater physiological instability during hospital stay compared with the control group. In that study, although the initial univariate comparison showed a similar risk of death between study and control groups (14.3% vs. 12.3%; P = 0.81), further multivariate analysis found that tocilizumab was associated with a 75% reduction in the risk of in-hospital death compared with the control group (HR = 0.25, 95% CI 0.07–0.90) [18]. In the study by Roumier et al. [19] that matched the tocilizumab and control groups for age, sex and disease severity using the inverse probability of treatment weighted methodology, tocilizumab significantly reduced the requirement for subsequent MV [weighted odds ratio (OR) = 0.42, 95% CI 0.20–0.89]. Although the study by Wadud et al. [20] tried to match the two groups in terms of age, sex, body mass index (BMI) and a score for the diagnosis of reactive haemophagocytic syndrome (HScore) calculated using inflammatory markers [ferritin, triglycerides, aspartate aminotransferase (AST) and fibrinogen] as closely as possible, however

Table 2
Demographic characteristics of patients in the included studies[a]

Reference	Inclusion criteria	Age (years)		No. (%) of males		CRP (mg/dL)		IL-6 (pg/mL)		Co-morbidity or severity	
		TCZ	Control	TCZ	Control	TCZ	Control	TCZ	Control	TCZ	Control
Capra et al. [14]	RR ≥ 30/min, SpO_2 ≤ 93% on room air or PaO_2/FiO_2 ≤ 300 mmHg	63.5 [54.5–73]	70 [55–80]	45 (73%)	19 (83%)	N/A	N/A	N/A	N/A	N/A	N/A
Colaneri et al. [15]	PaO_2/FiO_2 < 300 mmHg	62.3 ± 18.7	63.7 ± 16.3	19 (90.5%)	63 (69.2%)	21.38 ± 13.4	14.88 ± 14.4	N/A	N/A	N/A	N/A
Klopfenstein et al. [16]	Failure of standard treatment, oxygen therapy ≥5 L/min, >25% of lung damage on CT and ≥2 parameters of inflammation or biological markers of mortality	76.8 ± 11	70.7 ± 15	N/A	N/A	158 ± 70	105 ± 66	N/A	N/A	CCI: 5.3 ± 2.4	CCI: 3.4 ± 2.6
Quartuccio et al. [17]	Severe cases with raised CRP and IL-6 level	62.4 ± 11.8	56.2 ± 14.2	33 (78.6%)	44 (63.8%)	79.05 [44.77–186.22]	24.1 [7.35–72.6]	63.5 [37.2–135.5]	18.5 [10.25–33]	CCI ≥2: 5 ± 11.9	CCI ≥2: 12 ± 17.4
Ramaswamy et al. [18]	Oxygen saturation ≤88% concomitant with evidence of cytokine storm (CRP ≥ 7 mg/dL)	63.2 ± 15.6	63.8 ± 15.9	13 (61.9%)	36 (55.4%)	15.9 ± 6.9	11.2 ± 8.5	371.9 ± 443.0	64.4 ± 45.9	SOFA: 4.0 ± 4.9	SOFA: 2.1 ± 3.6
Roumier et al. [19]	Age <80 years, severe (i.e. requiring 6 L/min of oxygen therapy rapidly deteriorating, i.e. increase by ≥3 L/min of oxygen flow within previous 12 h), high CRP level	58.8 ± 12.4	71.2 ± 15.4	24 (80.0%)	23 (79.3%)	189.0 ± 104.4	167.4 ± 106.8	N/A	N/A	NEWS2 score ≥7: 24 (80.0%)	NEWS2 score ≥7: 24 (82.8%)
Wadud et al. [20]	ARDS requiring mechanical ventilation	55.5	66	37 (84.1%)	35 (70.0%)	N/A	N/A	N/A	N/A	HScore: 114	HScore: 92

ARDS, acute respiratory distress syndrome; CCI, Charlson comorbidity index; CRP, C-reactive protein; CT, computed tomography; IL-6, interleukin-6; N/A, not applicable; NEWS2, National Early Warning Score 2; RR, respiratory rate; SOFA, Sequential Organ Failure Assessment; TCZ, tocilizumab.

[a] Data presented as the mean ± standard deviation, median [interquartile range] or number (%).

the tocilizumab group still had higher average HScore as well as higher levels of IL-6, triglycerides, AST and ferritin compared with the control group (all $P < 0.0001$). Even under this condition, mortality rate remained lower in the tocilizumab group compared with the control group (38.6% vs. 52.0%, $P < 0.00001$). All of the above findings highlight that the tocilizumab group had more severe clinical outcomes compared with the control group and may explain why no additional benefit of tocilizumab was found in this meta-analysis.

Safety issues should be another concern when tocilizumab is used for patients with severe COVID-19. Only one study in this meta-analysis reported the adverse events in patients administered tocilizumab. In the study by Quartuccio et al. [17], 42.9% (18/42) in the tocilizumab group experienced bacterial superinfection, but none in the control group. This was consistent with a study by Kimming et al. [27] in which tocilizumab administration was independently associated with the presence of secondary bacterial infections (OR = 3.960, 95% CI 1.351–11.607; P =0.033). In addition, in the study by Morena et al. [21], the most common adverse event included increase of hepatic enzymes (29%), thrombocytopenia (14%), and serious bacterial and fungal infections (27%). In the report by Toniati et al. involving 100 patients [22], 2 patients developed septic shock and died and 1 patient had gastrointestinal perforation requiring urgent surgery. However, Alattar et al. [23] reported that the majority (92%) of patients experienced at least one adverse event in a small study involving 25 patients and the most prevalent adverse events were anaemia (16/25; 64%), alanine aminotransferase increase (11/25; 44%) and QT interval prolongation (5/25; 20%). Nevertheless, there is no conclusive evidence explaining which of these adverse effects were directly related to tocilizumab therapy. Overall, no conclusion can be derived from these findings and more studies are required to assess the tolerability of tocilizumab in patients with COVID-19.

In addition, this meta-analysis has several limitations that should be addressed. First, none of the included studies were randomised controlled trials and the reported clinical characteristics of the patients were not homogeneous. In addition to two studies that tried to match the study and control group in terms of disease severity, the tocilizumab group consistently had more severe symptoms compared with the control group in most of the studies in this meta-analysis. Second, various treatment regimens, including the dosage and frequency of tocilizumab in the study and the antiviral regimen groups, were applied in the studies. In addition, although the delay between onset of disease and treatment appears to be a very important variable, it was not reported in all of the selected studies. However, the timing of tocilizumab administration could affect the outcome of patients with severe COVID-19. Third, the number of studies and patients was small, which may result in type II statistical error. Thus, a further large-scale randomised controlled study is required to clarify the findings.

In conclusion, based on low-quality evidence, there is no suggestion that tocilizumab would provide any additional benefit for patients with severe COVID-19. Many issues, such as which population can benefit from tocilizumab, the appropriate timing, dosage and regimen of tocilizumab, and the risk of adverse effects remain unclear. Further recommendation of tocilizumab should therefore be halted until high-quality evidence from ongoing randomised trials for tocilizumab (ChiCTR2000029765; NCT04320615) and other anti-IL-6 agents [e.g. sarilumab (NCT04315298; NCT04324073) and siltuximab (NCT04329650)] is available.

Funding: None.

Competing interests: None declared.

Ethical approval: Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2020.106103.

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