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REVIEW ARTICLE

Tocilizumab in Patients with COVID-19 Pneumonia: A Systematic Review

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ABSTRACT

Background: The use of IL-6 blocking agents has been proposed as a therapeutic option for COVID-19 pneumonia in view of the involvement of this cytokine in inflammation. Tocilizumab is the most widely evaluated IL-6 blocker within this context. In this review we looked at the evidence for safety, efficacy and outcomes of tocilizumab treatment for COVID-19 pneumonia.

Methods: A systematic search in PubMed, covering 2020 and part of 2021, yielded a sample of 19 randomized clinical trials. The present review was conducted and reported following PRISMA-IPD guidelines.

Results: The selected trials were conducted in Europe (n=6; 31.5%), Asia (n=6; 31.5%), multiple continents (n=3; 15.7%), North America (n=2; 10.5%), South America (n=1; 5.2%), and Africa (n=1; 5.2%), evaluating 7,961 adult patients, of whom 4,061 received tocilizumab and 3,630 received standard care or placebo. Tocilizumab reduced mortality in most patients (n=2985; 87.9%). Benefits were also observed with regard to hospital discharge (2 trials; one of them had a cohort of 2022 tocilizumab users, of whom 56% were benefited; the other had a cohort of 350 tocilizumab users, whom were benefited in a hazards ratio of 1.44), clinical outcomes (2 trials, with a total of 392 patients, perceived tocilizumab in a positive manner [n=350/HR=1.44 and n=42/83,3%]; 4 trials saw no benefit [n=73/39% and n=294/OR=1.26]), and the composite outcome of mechanical ventilation and death (n=2003; 32%). Patients undergoing treatment with tocilizumab and controls did not differ significantly with regard to adverse events.

Conclusion: Tocilizumab reduced the need for mechanical ventilation in hospitalized patients and improved clinical parameters. The ability of tocilizumab to reduce mortality remains uncertain. The groups displayed similar levels of adverse effects.

Keywords: Tocilizumab, COVID-19, Pneumonia, Mechanical Ventilation, Clinical Parameters, Mortality, Outcomes.

1. Introduction

The growing global death toll of COVID-19 infection [1,2], along with the lack of targeted therapy and current reliance on mainly supportive measures, is a significant source of concern, exacerbating the burden on healthcare systems. The clinical spectrum of COVID-19 ranges widely from asymptomatic infection to severe pneumonia with respiratory failure that can lead to invasive mechanical ventilation and/or death. Initially, COVID-19 management primarily involved addressing specific symptoms, with supportive care in intensive care units (ICUs) reserved for critically ill patients, as targeted therapies were not yet available [2-4]. In this context, the severity of COVID-19 is largely attributed to a dysregulated immune response, in which the activation of the IL-6 amplifier would induce cytokine storm, a hallmark of dysregulated inflammation[3-5] and this exaggerated inflammatory response triggered by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes high morbidity and mortality[5]. So, to relieve this situation, some treatments have emerged as promising treatment options for critically ill patients, including IL-6 receptor blocking agents [3-5].

Severe COVID-19 cases, with manifestations like lung damage, septic shock and multiple organ failure, exhibit a cytokine storm-like pattern, and some believe COVID-19 infection to be associated with dysregulated immune response, hyperinflammation and exacerbated acute respiratory distress syndrome (ARDS). In fact, in early serology studies, the level of IL-6 (an inflammatory cytokine) was found to be higher in severe forms than in mild forms, making it reasonable to assume that, in general, elevated IL-6 levels are predictive of poor clinical outcomes. This observation has been pivotal in driving the exploration of anti-inflammatory therapies as a means to reduce morbidity and mortality in COVID-19 cases[5-6].

Tocilizumab (TCZ), an IL-6 receptor antagonist, is used routinely to treat diseases such as rheumatoid arthritis, temporal arteritis, and juvenile idiopathic arthritis. It appears to improve outcomes in patients with COVID-19 pneumonia and is the most commonly proposed IL-6 receptor antagonist in this condition[7-10]. However, randomized trials and cohort studies of TCZ in patients with varying degrees of COVID-19 disease severity have so far yielded inconsistent results. Previous systematic reviews and meta-analyses investigating TCZ were published, including observational studies[11-17]. Two studies evaluated 10 and 9 randomized controlled trials, respectively, and concluded that in COVID-19 patients with moderate to critical COVID-19, use of TCZ was associated with better survival, however, the results of some studies are conflicting regarding the efficacy of TCZ in patients with COVID-19 pneumonia[10,18-19]. Despite these conflicting findings, TCZ continues to be a focal point of investigation for its role in improving outcomes in patients with COVID-19, and the authors have included all randomized clinical trials published up to this point which investigate the impact of TCZ on mortality, safety and efficacy in COVID-19 patients.

Additionally, dexamethasone and baricitinib plus remdesivir are other immunomodulatory treatment for COVID-19 pneumonia which have been shown to reduce mortality and recovery time and accelerate improvement in clinical status among patients with COVID-19[20,21]. So, this review aims to evaluate the rationale for using TCZ in the treatment of COVID-19 pneumonia, summarizing key findings from clinical trials regarding the safety, efficacy, and impact on patient outcomes. By examining the available evidence, this review seeks to clarify the role of TCZ in the therapeutic landscape of COVID-19 and provide insights into its potential benefits and limitations.

2. Method

We systematically searched the PubMed database for English-language articles on TCZ use in hospitalized patients with COVID-19 pneumonia published in 2020-2021 (until 27 July 2021) in order to gather primary evidence regarding safety, efficacy and outcomes. Only randomized clinical trials (RCTs) were included in this review, since observational studies are prone to bias, such as confounding by indication, survivor bias and residual confounding. The review was conducted and reported following PRISMA-IPD guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data) (Figure 1) [22]. The key words used in the search were 'COVID-19', 'pneumonia' and 'tocilizumab'. Sixteen publications were identified, two of which were excluded (one was not in English, and one was not an RCT). The remaining RCTs were reviewed for demographic variables (sex, age), clinical variables (clinical presentation, onset of symptoms, progression), safety, treatment efficacy and outcome (overall mortality and mechanical ventilation requirement). Subsequently, an eligible RCT was excluded due to the absence of structured results corresponding to the adopted categories of variables. Another 6 RCTs were located via citation matching, making up a final sample of 19 publications. Initially, we considered including observational studies but abandoned the idea due to concerns over statistical power and bias. Interventions included tocilizumab vs. placebo or standard of care. The exclusion criteria adopted by the evaluated RCTs were similar: age <18 years, pregnancy, breastfeeding, hypersensitivity to TCZ, evidence of active TB, clear evidence of active bacterial, fungal or viral disease, elevated ALT or AST, low neutrophil or platelet counts, diagnosis of rheumatism and/or immune-related disease, imminent death, previous use of anti-rejection or immunomodulatory drugs, absence of requirement for supplemental oxygen, active diverticulitis or peptic ulcer, and high risk of GI perforation.

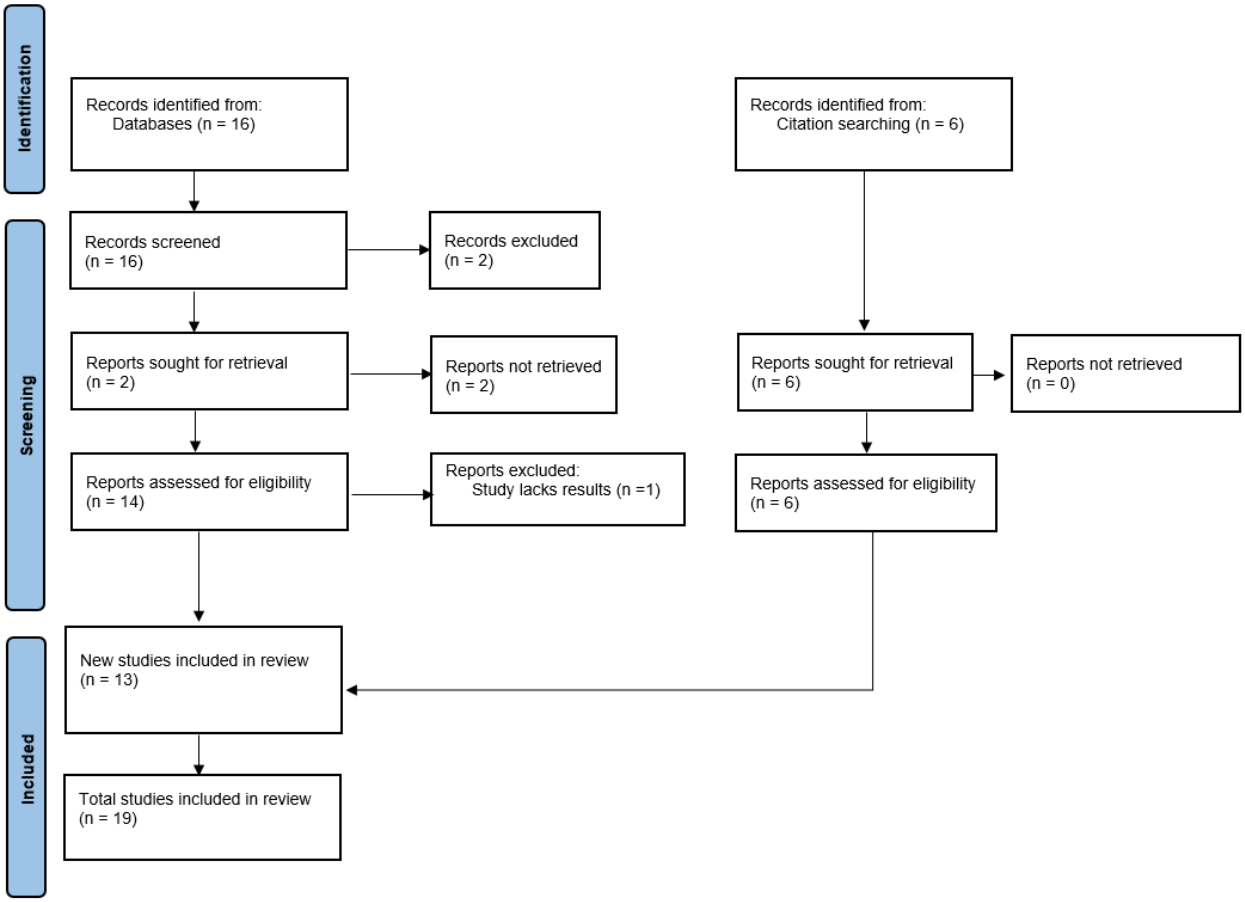

Figure 1: Flowchart of the selection process for identification of tocilizumab treatment in patients with COVID-19 pneumonia.

3. Results

A total of 19 publications were included (Figure 1, Table 1). The selected RCTs were conducted in Europe (n=6; 31.5%), Asia (n=6; 31.5%), multiple continents (n=3; 15.7%), North America (n=2; 10.5%), South America (n=1; 5.2%), and Africa (n=1; 5.2%).

Taken together, the 19 RCTs included 7,961 adult patients (TCZ n=4,061, controls n=3,630). In addition to TCZ, the treatment groups received glucocorticoids (n=2), sarilumab (n=1), a combination of antiviral agents and glucocorticoids, a combination of chloroquine and hydroxychloroquine, a combination of lopinavir and ritonavir and/or favipiravir and anticoagulants, or a combination of antiviral agents, hydroxychloroquine, subcutaneous IFN-β1a and antibiotics (n=1).

The RCTs evaluated the following outcome parameters: progression to mechanical ventilation or death (n=2), death from any cause without mechanical ventilation (n=1), ICU admission and rate of nonelective mechanical ventilation (n=1), progression to invasive mechanical ventilation (n=3), mortality (n=6), disease progression under invasive mechanical ventilation (n=1), clinical improvement (n=7), mortality without oxygen support (n=1), mortality with oxygen support (n=6), risk of NIV and mechanical ventilation (n=1), pulmonary inflammation (n=1), recovery from hypoxia (n=1), and probability of discharge (n=1). More specifically:

- TCZ use was found to reduce mortality in several of the evaluated RCTs, totaling 2,985 patients (87.9%) [23-29]. Overall improvement in clinical status was observed in n=350/HR=1.64 (95% CI, 1.25 to 2.14) and n=294/OR=1.26 (95% CI, 0.97 to 1.64) of the patients participating in 2 out of 6 RCTs[10, 24-26, 30, 31].
- All RCTs (2) adopting hospital discharge as outcome parameter identified TCZ use as a positive factor. More specifically, one (n=2022; 57%) identified a RR of 1.22 (1.12 to 1.33; p<0.0001) and other (n=350) identified a HR of 1.35 (95% CI, 1.02-1.79) [23, 24].
- All RCTs (2) evaluating the composite outcome of 'progression to mechanical ventilation or death' identified TCZ as a positive factor, more specifically, one (n=249) identified a cumulative percentage of 12% (95% CI, 8.5 to 16.9) and other (n=2022) identified a RR of 0.84 (95% CI, 0.77 to 0.92; p<0.0001)[23, 32].
- The outcome parameters 'requirement of invasive ventilation' (14%; n=6/42) and 'clinical improvement' (83.3%; n=35/42) yielded inconclusive findings (18). The same was true for the outcome parameters 'risk of progression to non-invasive ventilation', 'high flow oxygen', and 'mechanical ventilation or death in 14 days' (24%; n=15/64), which obtained 95% CI, 13% to 35%[31].

4. Discussion

4.1 MORTALITY

In this systematic review (19 RCTs) that included 7,961 adult patients (TCZ n=4,061, controls n=3,630), a significant survival benefit of tocilizumab versus usual care was shown in some studies. The mortality benefit was driven mainly by RECOVERY trial that included many patients both in ICU and non-ICU settings with progressive COVID-19[23], and the REMAP-CAP trial that included critically ill patients receiving organ support in intensive

care[24]. Reinforcing these findings, a study investigated prospectively patients with severe Covid-19-associated cytokine storm syndrome and concluded that strategy involving a course of high dose methylprednisolone, followed by TCZ if needed, may accelerate respiratory recovery (HR: 1.8; 95% 1.2 to 2.7) (7 days earlier), lower (65%) hospital mortality (HR: 0.35; 95% 0.19 to 0.65) and reduce (71%) the likelihood of invasive mechanical ventilation in Covid-19-associated (HR: 0.29; 95% 0.14 to 0.65) than supportive care only[29].

Our review exclusively included RCTs because observational studies or case series might hamper data interpretation with less statistical power. Notably, COVID-19 pneumonia has a high mortality rate, especially if treatment is delayed. Late onset of TCZ administration seems to be the primary cause of treatment failure, associated with comorbidities such as diabetes and hypertension and the severity of pulmonary involvement at the time of treatment with TCZ. However, the optimal timing for onset of anti-cytokine therapy in COVID-19 pneumonia patients has not been established. Hence, the need for adapting or developing measures to minimize negative outcomes and for identifying the ideal window of therapeutic opportunity.

In a study evaluating clinical and serological variables associated with favorable response to anti-cytokine therapies, IL-6 inhibition was found to improve long-term survival when initiated in the early stages of COVID-19 pneumonia, before the establishment of severe respiratory failure [33]. Some of the RCTs included in this review failed to confirm the ability of TCZ to reduce mortality, but no consensus on this point has been reached. In any case, the largest trial included in this review (2,022 patients, corresponding to 68.7% of the 2,945 TCZ patients for whom mortality was assessed) did in fact report a reduction in mortality[23], suggesting that the window of opportunity for treatment with TCZ (the use in the earliest stages of COVID-19 pneumonia) seems to be the main factor influencing the clinical outcome of patients. Despite randomization in many studies, imbalance in the percentage of older patients between the treatment groups was observed[30] and other confounding factor in the interpretation of the results.

Mortality in patients with severe or critical infection was higher for TCZ than for standard care (17% vs. 3%) [26], and TCZ did not always reduce mortality in moderate and/or advanced stages of the disease[26,30]. Other trials, however, found the use of IL-6 receptor antagonists to prevent disease progression and increase survival, especially when started early[24,33]. Interestingly, a meta-analyses that included 52 studies (nine randomized controlled trials (RTC) and 43 observational) with a total 27,004 patients, observed that the use of tocilizumab was associated with a reduction in mortality; 11% in RCTs (risk ratio [RR] 0.89, 95% CI 0.82 to 0.96) and 31% in observational studies (RR 0.69, 95% CI 0.58 to 0.83). This study demonstrated reduction in mortality and it was evident in observational studies regardless of the use of systemic corticosteroids, while that was not the case in the RCTs[12].

Of note, it should be taken into account that to some extent the efficacy of TCZ in the treatment of COVID-19 pneumonia depended on the patients' condition (age, comorbidities such as obesity, associated diseases), disease stage (mild, moderate, severe) and timing of therapy, and that the treatment administered to the control groups in the reviewed RCTs varied according to the clinical sitecenter where each trial was conducted, potentially interfering in the results.

4.2 CLINICAL IMPROVEMENT

The reviewed RCTs used several parameters to quantify clinical improvement, including clinical and laboratory variables, with mostly positive outcomes. For example, fever was significantly and non-dose-dependently reduced after a few hours of TCZ therapy. CRP, a critical inflammatory marker of acute disease, was significantly reduced by treatment with anti-IL-6 agents, and neutrophil and lymphocyte counts increased[26,27,31,34]. In addition, TCZ was associated with lower IL-6 levels, shorter hospital and ICU stay, and better lung status on CT or radiography[35]. This may be explained by the fact that COVID-19 infection can cause a cytokine storm after 7-8 days of symptoms, triggering an uncontrolled immune reaction with excessive production of pro-inflammatory cytokines, activating innate and adaptive immunity. This phenomenon increases the risk of sepsis and pulmonary complications, such as pneumonia and ARDS. The use of TCZ reduced the inflammatory response and improved prognosis by inhibiting IL-6 receptors[36-38]

Hospital discharge was more likely and earlier for TCZ patients than for controls, in hospitalized COVID-19 patients with hypoxia and systemic inflammation, TCZ improved survival and other clinical outcomes[23]. These benefits were seen regardless of the amount of respiratory support and were additional to the benefits of systemic corticosteroids. On the other hand, an American trial comparing TCZ to standard care in a sample of hospitalized patients with moderately advanced infection requiring supplemental oxygen found no significant difference with regard to supplemental oxygen discontinuation and intubation prevention. In fact, this subject has conflicting results and others concluded that TCZ prevents progression to moderate or severe disease[30,34,35]. Finally, response to treatment with TCZ was weaker in elderly patients with high IL-6 levels, possibly because IL-6 is a host response to the infection rather than a component of a self-amplifying inflammatory loop that would benefit from suppression[30].

4.3 PROGRESSION TO INVASIVE MECHANICAL VENTILATION

Some patients with COVID-19 pneumonia require supplemental oxygen, non-invasive or invasive airway support, or mechanical ventilation. Only a few of the reviewed RCTs specifically evaluated this parameter, but most reported positive outcomes. The benefits of TCZ were evaluated in hospitalized patients with mostly moderate to severe disease and requiring supplemental oxygen. In these cases, anti-IL-6 agents reduced the need for mechanical ventilation, especially after 14 days of illness[27,31], perhaps because the level of IL-6 (the main interleukin involved in hyperinflammatory reactions) increases in the acute phase COVID-19 infection[39,40]. When soluble IL-6R-IL-6 anchors to membrane gp130 (trans-signaling), monoclonal anti-human IgG1 antibodies

compete for binding with the IL-6 receptor, reducing pro-inflammatory activity and improving prognosis[41-43].

Moreover, patients who received TCZ associated with high doses of glucocorticoids displayed better and quicker respiratory recovery and needed mechanical ventilation less frequently. Even in patients with noncritical COVID-19 pneumonia, TCZ reduced oxygen requirements and the need for non-invasive ventilation[29,34]. Reinforcing these findings, a clinical trial randomizing 389 patients, concluded that in hospitalized patients with COVID-19 pneumonia who were not receiving mechanical ventilation, tocilizumab reduced the likelihood of progression to the compound outcome of mechanical ventilation or death (HR, 0.56 (95% CI, 0.33–0.97) P=0.04), however, there was no difference in the incidence of death from any cause[32].

4.4 ADVERSE EFFECTS AND INFECTIONS

TCZ can cause adverse effects ranging from mild to severe, but to our knowledge no study has consistently evaluated this end-point. The most common adverse effects of TCZ are hypersensitivity, abnormal liver function, stroke, hemorrhage, sepsis, myocardial infarction, lymphopenia, neutropenia, ARDS, and cardiac/respiratory arrest. However, in the reviewed RCTs the prevalence of these complications was lower in the TCZ group than in the control group (standard care or placebo)[25, 31]. In an RCT involving 180 patients, about 30% experienced adverse events, of which 37% were severe. Events were more frequent in the TCZ group than in the control group (standard care), though not significantly[44].

None of the other RCTs reported significant differences in the occurrence of severe events, but in some trials the frequency of new infections increased with TCZ[26,27,31]. One RCT found the frequency of serious adverse events to be lower in patients on TCZ (34.9%) than in patients receiving placebo (38.5%), suggesting an acceptable safety profile for TCZ in the treatment of COVID-19 pneumonia[25]. Notably, a systematic review and meta-analysis that evaluated the efficacy and secondary infection risk of TCZ in COVID-19 patients found that TCZ significantly decreased mortality in patients without any increased rik of secondary infection, however, they found that TCZ significantly increased the risk of fungal co-infections in COVID-19 patients[45].

Overall, immunosuppressants seem that significantly decreased mortality and had no effect on increased risk of secondary infections. Nonetheless, TCZ showed a significantly increased risk of fungal co-infections in these patients.

4.5 EFFICACY OF TOCILIZUMAB IN THE TREATMENT OF COVID-19 PNEUMONIA

The clinical trials selected for this review provide ample discussion of the efficacy of TCZ in the treatment of COVID-19 pneumonia, with some authors advocating its use and others abstaining from issuing an opinion.

Part of the debate revolves around the pathophysiology of SARS-CoV2, a pathogen believed to promote an event known as cytokine storm, suggesting the pivotal role of IL-6 in COVID-19 which leads to hyperinflammation and a prothrombotic state. Drugs capable of blocking cytokine storms are likely to alleviate symptoms, shorten hospital stay and reduce mortality from the disease[5-7]. Supporting this notion, a randomized, controlled, open-label multicenter trial concluded that TCZ can improve hypoxia without unacceptable side effect profile and for patients with bilateral pulmonary lesions and elevated IL-6 levels, TCZ could be recommended to improve outcome[46].

TCZ has been shown to reduce IL-6 production *in vitro*. This appears to be reflected in the slight comparative overlap of the number of patients who did not require ICU admission and/or mechanical ventilation[10,23-30,32-35,44,45-48]. Their findings revealed a correlation of early TCZ administration with lower mortality rates among critically ill COVID-19 patients with best clinical outcome[20]. Nevertheless, TCZ was not effective at reducing hospital stay, which was almost the same length in the treatment and control groups[10,23-30,32-35,44,46-49]. It would therefore seem that, currently and to a large extent, the risk/benefit ratio of TCZ use depends on clinical experience, dosing, disease severity, timing and routes of TCZ administration and the divergence in clinical outcome of some studies can be justified by bias in patient selection in relation to the severity of the patients and the time of drug use, since in patients in late stages of COVID-19 with multiple organ dysfunction, the mortality rate is high despite therapy.

Three limitations of this study may be pointed out: i) no meta-analysis was performed, ii) the reviewed trials adopted different criteria and methods, and iii) the analysis of the outcome parameters was not entirely consistent between the trials. On the other hand, limiting the sample to randomized clinical trials allowed us to make meaningful comparisons, since other systematic reviews included studies with lower statistical power.

5. Conclusion

Cumulative evidence shows that TCZ seems to reduce the risk of mechanical ventilation in hospitalized patients with COVID-19 pneumonia and improves several clinical parameters, although the claim that TCZ reduces mortality remains to be confirmed. TCZ did not significantly increase the likelihood of adverse events or infections. Current treatments for COVID-19 pneumonia are far from efficacious, and more blinded, placebo-controlled randomized clinical trials are needed to support the results of this systematic review.

Conflict of interest:

The authors report no conflicts of interest.

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Author contributions

AHCV, LCM and CBJ extracted and analyzed the data, wrote the manuscript, and prepared the figures and tables. CEMR and JFC instructed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Table 1: Characteristics of the published clinical trials

Author (year)	N	Study type and country	Cohort selection	Regimen of TCZ group	Previous Disease	Patients discharged after using TCZ	Analytical method	Limitations	Outcomes
Soin A et al. (2021)[33]	179 patients, 91 of whom received TCZ and standard care	Open-label, multicenter, randomised, controlled, phase 3 trial (India)	>18 years of age, with confirmed COVID infection by WHO criteria and with moderate to severe COVID cases	1st dose: IV 6 mg/kg 2nd dose (if no clinical improvement was noticed or if it worsened within 12 hours to 7 days of 1st dose): idem	DM2: 31 SAH: 36 COPD: 1 RTaMD: 4 RaUD: 4 CD: 15	78 patients	Modified intention to treat (ITT)	Unmasked study without placebo Most patients received corticosteroids during the trial; approximately 50% received remdesivir; small sample size	TCZ may reduce mortality if applied early in severe COVID patients. However, the study does not support the use of the drug for COVID-19.
RECOVERY Collaborative Group (2021)[13]	4116 patients, 2022 of whom received TCZ and standard care	Randomized, controlled, open-label (UK)	Hospitalized patients Clinically or laboratory-confirmed disease. Hypoxia ($SatO_2$ <92% on air or requiring oxygen therapy) and evidence of systemic inflammation (CRP ≥75 mg/L)	Dose was equivalent to body weight (800 mg if weight >90 kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg; and 8 mg/kg if weight ≤40 kg). In the absence of clinical improvement, the 2nd dose could be given within 12-24h.	DM: 569 CD: 435 COPD: 473 TB: 3 HIV: 7 RaUD: 132	1401 patients	ITT	16% of patients in the TCZ group reportedly did not receive this treatment and the reasons for this were not recorded. The size of the effects of TCZ reported underestimates the actual effects.	The use of TCZ reduces 28-day mortality and the length of patient hospitalization. In addition, a reduction in disease progression and intubation rate

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Author (year)	N	Study type and country	Cohort selection	Regimen of TCZ group	Previous Disease	Patients discharged after using TCZ	Analytical method	Limitations	Outcomes
Rashad A et al [34] (2021)	109 patients, 46 of whom received TCZ	Randomized controlled trial (Egypt)	Respiratory rate >30 cycles/minute. Bilateral chest CT infiltration >30%. PaO_2/FiO_2 <150 or $SatO_2$ <90% on >6L/min. Two positive tests of the following: CRP >10 g/L, lymphocytes <600mm^3, D-dimer >500 ng/mL, ferritin >500 mg/ml	TCZ 1st dose: IV 4 mg/kg over 1 hour 2nd dose: equal to 1st dose; repeated after 24 hours. Pulse dexamethasone Infusion: 4 mg/kg/day for 3 days Maintenance dose: 8 mg/day for 10 days	DM: 16 SAH: 26 Kidney diseases: 4	ND	Per protocol (PP)	All patients were given azithromycin	Dexamethasone showed better survival than TCZ
REMAP-CAP investigators (2021)[14]	865 patients, 353 of whom received TCZ	Platform trial (multiple countries)	Critically ill (ICU admission, receiving *respiratory or cardiovascular support) Patients >18 years of age Clinically suspected disease or microbiologically confirmed	TCZ 1st dose: 8 mg/kg (maximum 800 mg) IV over one hour. 2nd dose: repeated 12-24 hours later if insufficient clinical improvement Sarilumab: IV 400 mg once daily	ND	255 patients	PP	Open-label design Some data is missing (ongoing study; some patients remain in the hospital Unawareness of the Bayesian model to many clinicians Many interventions are ongoing — possible interactions are still to be reported	Improved 90-day survival when using IL 6 inhibitors (such as TCZ and Sarilumab)

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Author (year)	N	Study type and country	Cohort selection	Regimen of TCZ group	Previous Disease	Patients discharged after using TCZ	Analytical method	Limitations	Outcomes
Wang D et al. (2021)[35]	65 patients, 33 of whom received TCZ	Randomized, controlled, open-label, multicenter trial conducted (China)	18-85 years old. Elevated plasma IL-6 levels. Moderate (with bilateral pulmonary lesions) or severe disease. Moderate: fever or other respiratory symptoms, bilateral pulmonary lesions with chest imaging; Severe: respiratory rate ≥ 30 breaths per min or/and SpO2 ≤ 93% while breathing room air or/and PaO2/FiO2 ≤ 300 mmHg	1st. dose: IV 400 mg 2nd dose: administered if the patient remained febrile for 24h after the 1st dose	ND	31 patients	ITT	Open-label study Absence of placebo group Limited number of patients The time between the onset of disease and randomization was relatively long in some instances. Presence of adjunctive therapy (corticosteroids)	No statistically significant difference is presented between the two groups. However, treatment with TCZ showed an improvement in patients with hypoxia.

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Author (year)	N	Study type and country	Cohort selection	Regimen of TCZ group	Previous Disease	Patients discharged after using TCZ	Analytical method	Limitations	Outcomes
Rosas IO et al. (2021)[15]	438 patients, 294 of whom received TCZ	Randomized, controlled phase 3 trial (multicenter - 9 countries in Europe and North America)	Adults (≥18 years of age) Severe COVID-19 pneumonia (confirmed by positive PCR and bilateral chest infiltrates on chest radiography or CT) $SatO_2 \leq 93\%$ or less or a PaO_2/FiO_2 <300 mm Hg.	1st dose: IV 8 mg/kg maximum of 800 mg. 2nd dose (TCZ or placebo): equal to 1st dose, 8 to 24h after 1st dose	DM: 105 CD: 88 SAH: 178 Obesity: 63 Hepatic impairment: 88 COPD: 49	236 patients	Modified ITT	Differences in the local practice Insensitivity to events before the time point of assessment Lack of an established minimum clinically significant difference for therapeutic effect Lack of standardized treatment across trial sites Probable selection bias	No significant difference in clinical status between the TCZ group and the placebo group at day 28 was found

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Author (year)	N	Study type and country	Cohort selection	Regimen of TCZ group	Previous Disease	Patients discharged after using TCZ	Analytical method	Limitations	Outcomes
Veiga VC et al (2021)[16]	129 patients, 65 of whom received TCZ plus standard of care	Randomized controlled trial (Brazil)	Severe or critical COVID-19 with evidence of pulmonary infiltrates confirmed by chest radiography or CT. Supplementary oxygenation. Mechanic ventilation for <24 h. At least two of the following: d-dimer >2.74 nmol/L; CRP >50 mg/L; ferritin >300 µg/L, or LDH > upper limit of normal	Single IV dose (8 mg/kg) and standard care	DM: 22 SAH: 30 Obesity: 15 CD: 8 RaUD: 5 Asthma: 4 COPD: 2 Solid malignancy: 4 Hematological malignancy: 1	54 patients	ITT	Open label trial Relatively small sample size No records on the number of patients assessed for eligibility Post-randomization, information regarding treatment with other drug classes was gathered	TCZ + standard care was not superior to standard care alone regarding improvement of clinical status by 15 days TCZ might have increased mortality
Zhao H et al. (2021)[36]	26 patients, of whom 5 received TCZ, and 14 received TCZ plus favipiravir.	Multicenter trial (China)	Laboratory-confirmed cases (Chinese guidelines). >18 years of age. Increased serum IL-6	1st dose: IV 4-8 mg/kg (recommended 400 mg); infusion time should be > 1 hour 2nd dose: same as 1st dose; given to patients with fever, if this symptom were still present within 24 hours after 1st dose	DM: 1 CD: 3	5 patients	PP	Small sample use of favipiravir in some patients. Lack of comparison of different dose gradients	TCZ combined with or without favipiravir can effectively improve pulmonary inflammation (less clinical symptoms, faster blood routine exams returning to normal) and inhibit the deterioration of the disease

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Author (year)	N	Study type and country	Cohort selection	Regimen of TCZ group	Previous Disease	Patients discharged after using TCZ	Analytical method	Limitations	Outcomes
Hermine O et al (2021)[21]	64 TCZ vs. 67 usual care	Randomized clinical trial (France)	Confirmed COVID-19 infection (positive rRT-PCR and/or typical chest on CT scan) Moderate, severe, or critical pneumonia (O2 >3 L/min), WHO Clinical Progression Scale or higher but without non-invasive ventilation or mechanical ventilation	Day one: 8 mg/kg IV Day three: additional dose of 400 mg IV (if O_2 requirement was not decreased by > 50%)	Usual care		ITT	Unblinded trial No patronization on usual care group among different centers Small sample intervals Treatment effect may be overestimated Trial did not evaluate early usage of TCZ A narrow segment of COVID-19 patients targeted	TCZ may reduce the need for mechanical ventilation and non-invasive ventilation or death by day 14 No mortality reduction by day 28 was observed.

Table 1: Characteristics of the published clinical trials

Author (year)	N	Study type and country	Cohort selection	Regimen of TCZ group	Previous Disease	Patients discharged after using TCZ	Analytical method	Limitations	Outcomes
Hamed D et al. (2021)[37]	76 patients, 26 of whom received TCZ plus Methylprednisolone.	Randomized controlled trial (United Arab Emirates)	Hospitalized patients over 18 years of age Confirmed COVID-19: positive RT-PCR oropharyngeal swab Development of lung infiltrates involving >50% of lung fields.	IV methylprednisolone alone or with a single dose (IV 400 mg) of TCZ + usual care (chloroquine/hydroxychloroquine, lopinavir/ritonavir, and/or favipiravir and anticoagulants)	DM and/or SAH: 20	21 patients	PP	Small samples size Retrospective selection of control group Almost half of the patients in the control group had received MP Open-label design Encountered comorbidities were limited to DM and HTN	Severe COVID-19 patients who required oxygen support treated with MP had reduced mortality by 45 days MP treatment was also associated with lower rates of ICU admission and ventilation and a shorter length of ICU, say Adding TCZ to the MP regimen did not improve any of the studied outcomes

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Author (year)	N	Study type and country	Cohort selection	Regimen of TCZ group	Previous Disease	Patients discharged after using TCZ	Analytical method	Limitations	Outcomes
Della-Torre E et al. (2020)[22]	210 patients; 25 of whom received TCZ	Clinical trial (Italy)	Confirmed COVID-19 (RT-PCR on the nasopharyngeal swab and radiologically confirmed bilateral pneumonia PaO_2/FiO_2 ratio ≤ 300 mmHg on high flow supplemental O_2 + hyperinflammed phenotype (elevation of LDH, and at least one of the following:C-reactive protein (CRP) ≥ 100 mg/L; IL-6 ≥ 40 pg/ml; or ferritin ≥ 900 ng/ml)	A single infusion of IV 400 mg; to be repeated after 24 h if respiratory function worsened .	CD: 3 DM: 4 Cancer: 2 HPB: 12 COPD: 1	ND	PP.	Non-randomized retrospective observational design	IL-1 and IL-6 inhibition improved long-term survival when initiated in the early phases of COVID-19 pneumonia; before the start of severe ARDS

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Author (year)	N	Study type and country	Cohort selection	Regimen of TCZ group	Previous Disease	Patients discharged after using TCZ	Analytical method	Limitations	Outcomes
Strohbehn G et al. (2020)[23]	32 patients treated with TCZ	Phase II clinical trial (USA)	Hospitalized patients >18 years Positive PCR Chest radiography findings (e.g., radiologist evaluated bilateral ground-glass opacities or hazy bilateral infiltrates consistent with viral or atypical pneumonia) Documented fever (≥ 38.0°C) in the 24 hours prior to the time of TCZ administration CRP ≥ 40 mg/L	Group A 200 mg and, later (if no safety events), 120 mg Group B 80 mg and, later (if no safety events), 40 mg Pretreatment and post-treatment CRP (decline <25%), along with worsening of clinical condition, triggered administration of the 2nd dose	28 patients have comorbidities not specified in the study	27 patients	PP	Single-center study Absence of randomized control arm Use of CRP as a biochemical outcome; therapeutic guide	Low dose TCZ is associated with rapid improvement in clinical and laboratory measures of hyper inflammation in hospitalized patients

Table 1: Characteristics of the published clinical trials

Author (year)	N	Study type and country	Cohort selection	Regimen of TCZ group	Previous Disease	Patients discharged after using TCZ	Analytical method	Limitations	Outcomes
Malekzadeh R et al (2020)[17]	126 patients treated with TCZ	Prospective, open-label uncontrolled multicenter trial (Iran)	Adult patient Confirmed COVID-19 infection: positive PCR or chest CT Fever ≥ 37.8 (oral), cough, SOB, or respiratory rate > 30/minute that had a SpO_2, of ≤ 93% Serum IL-6 of 3x the upper limit of normal or higher All subjects enrolled met WHO-China Joint Mission on COVID-19 criteria for severe disease. In addition, patients with respiratory failure requiring transfer to ICU were considered critical.	Subcutaneous (injections of 162 mg) 324 mg of TCZ for patients weighing < 100 kg and 486 mg for patients weighing> 100 kg + standard of care (varied by study center): supportive care, antiviral agents, hydroxychloroquine, subcutaneous IFN- β1a, and antibiotic agents	ND	96 patients	PP	Uncontrolled design	Subcutaneous TCZ has proven positive in treating critically ill patients needing O2. Thus, this drug has been shown to cause a significant reduction in mortality.

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Author (year)	N	Study type and country	Cohort selection	Regimen of TCZ group	Previous Disease	Patients discharged after using TCZ	Analytical method	Limitations	Outcomes
Stone J et al (2020)[20]	242 patients; 161 of whom received TCZ	Randomized controlled trial (USA)	19 to 85 years old COVID-19 infection confirmed (nasopharyngeal swab PCR or serum IgM) At least two of the following: fever within 72h before enrollment, pulmonary infiltrates, or a need for supplementary O_2 At least one of following: CPR >50 mg/l, ferritin >500 ng/ml, d-dimer >1000 ng/ml, or LDH >250 U/L	Single-dose: 8 mg/kg IV (maximum of 800 mg)	DM: 45 SAH: 80 COPD: 15 Asthma: 15 History of Cancer: 22 RaUD: 29 CD: 32	152 patients	Modified ITT	The primary event rate was lower than anticipated. Imbalance in the % between older patients in the treatment groups	TCZ was not effective for intubation or death prevention in moderately ill hospitalized COVID-19 patients
Dastan F et al. (2020)[18]	42 patients treated with TCZ	Non-controlled prospective trial (Iran)	Age > 18 years Positive RT-PCR IL-6 : 10 pg/mL Severe COVID-19 infection Critical COVID-19 infection No improvement despite receiving 72 h of standard care	Single IV infusion of 400 mg over 2 h	DM: 9 SAH: 16 COPD: 2 Bronchiectasis: 1 MS: 3 RA: 1 Malignancy: 1	35 patients	PP	Small size Lack of randomized control group	TCZ resulted in lower mortality, mainly when initiated during the first (severe) stage

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Author (year)	N	Study type and country	Cohort selection	Regimen of TCZ group	Previous Disease	Patients discharged after using TCZ	Analytical method	Limitations	Outcomes
Perrone F et al. (2020)[24]	180 TCZ vs. 121 controls	Multicenter phase 2 clinical trial (Italy)	Patients hospitalized due to clinical signs of pneumonia with positive PCR test and $SatO_2$ at rest in ambient air ≤93% or required oxygen support or mechanical ventilation (either non-invasive or invasive)	1st dose: 8 mg/kg (maximum of 800mg) 2nd dose: equal to 1st dose, administered after 12h (to the discretion of the investigator, if the respiratory function failed to improve)	Not reported		ITT (for all patients enrolled) Modified ITT (patients who had received at least one dose of TCZ)	Single-arm study design The discrepancy between timing of drug availability and the high request at the time of the study Many missing data Indication bias and immortal time bias	Older age and lower PaO_2/FiO_2 ratio negatively affected survival. TCZ might be more effective in patients not requiring mechanical respiratory support at baseline
Salvarani C et al (2020)[10]	126 patients; 60 of whom received TCZ	Randomized clinical trial (Italy)	Positive RT-PCR for COVID-19 from a respiratory tract sample Acute respiratory failure (PaO_2/FiO_2 between 200-300 mmHg) Inflammatory phenotype (temperature > 38°C during last 2 days and/or CRP ≥ 10 mg/dL and/or CRP level increased to at least 2x the admission measurement	1st dose: administration within 8 h from randomization; IV 8 mg/kg (maximum of 800 mg) 2nd dose: 12h after 1st dose	DM: 10 SAH: 27 COPD: 2 Obesity: 16	57 patients	ITT	Open-label design	No benefit compared to standard care was observed compared to standard care.

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Author (year)	N	Study type and country	Cohort selection	Regimen of TCZ group	Previous Disease	Patients discharged after using TCZ	Analytical method	Limitations	Outcomes
Salama C et al. (2020)[38]	389 patients; 249 of whom received TCZ	Randomized controlled trial (International)	18 years of age or older Hospitalization with COVID-19 pneumonia Positive PCR test Positive radiographic image	(8 mg per kilogram of body weight intravenously or placebo)	ND	223 patients	Modified ITT	Not reported	No impact on survival TCZ reduced composite progression to death or mechanical ventilation
Ramiro S et al. (2020)[19]	86 controls vs. 86 patients treated with glucocorticoids, 37 of whom combined with TCZ	Randomized controlled trial (Netherlands)	COVID-19 diagnosis (presence of suggestive clinical signs and symptoms plus either a positive PCR test or a chest CT) + evidence of CSS: a $SatO_2$ ≤94% or RF >30/min and at least two out of the following: CRP >100mg/L), ferritin >900µg/L at one occasion, or a twofold increase of the level at admission within 48 hours) and D-dimer >1500µg/L)	1st day: IV 250mg of methylprednisolone Followed by IV-MP 80mg on days 2-5 and option for 2-day extension TCZ between days 2-5 , Single-dose IV TCZ 9mg/kg (maximum of 800mg)			PP	Prognostic similarity at baseline cannot be assumed Residual confounding by unmeasured variables is likely All control patients were admitted at least 3 weeks earlier than the patients in the treatment group	A course of high-dose MP, followed by TCZ may accelerate respiratory recovery, lower hospital mortality, and reduce the likelihood of invasive mechanical ventilation in COVID-19-associated CSS

ITT=intention to treat; PP=per-protocol; ND=not described; DM=diabetes mellitus; SAH=systemic arterial hypertension; COPD=chronic obstructive pulmonary disease; RTaMD=respiratory, thoracic and mediastinal disorders; RaUD=renal and urinary disorders; CD=cardiac disorders; TB=tuberculosis; MS=multiple sclerosis; RA=rheumatoid arthritis.