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

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ABSTRACT

Background and Objective. COVID-19 contributes significantly to global morbidity and mortality. Age-related comorbidities elevate the risk of severe cases. Studies have recently demonstrated that widely available medications, including tocilizumab (TCZ), can manage severe symptoms. However, its effectiveness is unclear, particularly among the older population. Therefore, this review aimed to evaluate TCZ's efficacy in managing severe pneumonia in individuals aged 50 and older.

Methods. We systematically search several databases and gray literature including Web of Science, CINAHL, Academic Search Complete, PsycINFO, PsycArticles, SocINDEX, CENTRAL/Cochrane Library, PubMed/MEDLINE for original research articles in English across several study designs published in the year 2020-2022. A narrative synthesis was conducted to summarize the evidence. We employed the NIH quality assessment tool for observational cohort studies to evaluate risk of bias. Additionally, we utilized GRADE to appraise the certainty of evidence.

Results. Among 539 screened articles, only five studies met the selection criteria. Tocilizumab's impact on severe COVID-19 pneumonia revealed a diverse effect on mortality rate, with 29% in the TCZ group, and 40% in the controls died within 30 days of intubation (OR 0.61; 95% CI, 0.27-1.36). It is also reported that TCZ was not associated with mortality, despite faster decline in pulmonary function and prolonged fever. Hospital mortality in the TCZ group was significantly lower than in the controls, and age over 60 was the only significant risk factor. Moreover, administering TCZ reduced mechanical ventilation needs, with 82% extubated compared to 53% in controls. However, 45% in TCZ group was associated with a higher ventilator-associated pneumonia rate than in the untreated group which was 20% (P < 0.001). Despite this, TCZ-treated patients had shorter hospital stays.

Conclusions. The effects of tocilizumab on reducing mortality risk and improving the survival rate of COVID-19 patients with pneumonia remained inconclusive. Yet, the majority of results suggested that giving tocilizumab leads to shorter hospital stays, lowers the requirement for mechanical ventilation, and decreases the likelihood of ICU transfer. Tocilizumab is linked to the incidence of secondary infections; hence, this medication should be closely monitored for side effects.

Keywords: tocilizumab, COVID-19, repurposed drug, cytokine syndrome, pneumonia, standard care

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a new respiratory disease caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that has caused significant mortality and morbidity worldwide. Patients with severe SARS-CoV-2 infection have an increased inflammatory response consisting of proinflammatory cytokines and chemokines, most notably interleukin-6 (IL-6) which causes "cytokine storm syndrome."[1-3] Studies have recently demonstrated widely available medication

that can manage severe symptoms, one of which is the drug Tocilizumab.

Tocilizumab (TCZ), has been used as a treatment for rheumatologic disorders and T cell-induced cytokine release syndrome. TCZ is a humanized recombinant anti-IL-6 receptor monoclonal antibody that works by reducing inflammation by blocking the IL-6 receptor. Due to this, TCZ has been proposed as a potential treatment of COVID-19. Recent clinical trials in China suggest the effectiveness of TCZ in COVID-19 patients with cytokine storms.[4] Moreover, patients with significant bilateral lung opacity and high IL-6 levels can receive TCZ treatment. TCZ therapy significantly reduces the demand for mechanical or noninvasive ventilation or mortality. In recent research, the clinical efficacy of TCZ therapy have been observed, particularly in terms of mortality rates, hospitalization duration, and the need for mechanical ventilation in COVID-19 patients.[5-11]

The initial dosage is 4–8 mg/kg (the recommended dose is 400 mg) diluted to 100 ml with 0.9% normal saline, and the infusion time is more than 1 hour.[12] Numerous factors are associated with higher virus susceptibility and burden in patients infected with SARS-CoV-2.[13] Since comorbidities frequently grow with age, the older population may encounter a more severe COVID-19.[13] Therefore, this study aimed to determine if the administration of TCZ can improve survival and clinical outcomes of patients and focused on people 50 years old and above as they are the ones who are vulnerable to having COVID-19 with pneumonia.

METHODS

Review Protocol

We registered the protocol in PROSPERO (registration number: CRD42022329018) and conducted in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) reporting guidelines and synthesis without meta-analysis (SWiM).[14,15]

Inclusion Criteria

Participants

We reviewed studies that included patients with severe COVID-19 pneumonia. Fifty years old and above patients were included in the study.

Intervention

The intervention of interest was the utilization of TCZ and Standard care in elderly patients with COVID-19 Pneumonia.

Comparator

The comparator is the standard treatment given to elderly patients with COVID-19 Pneumonia.

Intervention

We incorporated outcomes assessing the efficacy of TCZ in elderly patients with COVID-19 pneumonia and their response to the treatment. Furthermore, we evaluated TCZ against standard COVID-19 treatment, focusing on reducing hospitalization duration, improving survival rates, and improving clinical outcomes among COVID-19 pneumonia patients aged 50 years and older.

Literature Search

The following electronic databases were used: Web of Science, CINAHL, Academic Search Complete, PsychINFO, PsycArticles, SocINDEX, CENTRAL/Cochrane Library, and PubMed/MEDLINE for articles published between January 1, 2020 - March 31, 2022. Moreover, the search for gray literature was conducted utilizing resources from the World Health Organization (WHO) and the Chinese Centers for Disease Control and Prevention (CDC). We conducted a hand search of the reference lists of full-text articles for additional studies to be screened and assessed their eligibility. The search selection process was exported in Endnote for screening the eligible articles.

Selection Criteria

Several study designs such as cross-sectional, cohort, and randomized controlled trials that are written in English were included. We formulated the search strategy which included search terms pertaining to elderly patients, severe COVID-19 with pneumonia, tocilizumab, and comparison with standard treatment, emphasizing reduced hospitaliza-tion. Excluded in this review are case reports, studies that are not published in the year 2020 to 2022, and studies on the usage of TCZ as a treatment for COVID-19 patients without pneumonia. Two researchers assessed the eligible articles to know if it met the inclusion criteria. In case the two researchers disagreed, another researcher helped to resolve the issue and made a final decision. A PRISMA 2020 flow diagram was used to show the screening (Figure 1).

Data Extraction

Two researchers examined the quality of the studies based on the author, the publication year, study designs, characteristics, clinical outcomes of the treatment of TCZ and the comparator, sample size, patients, age, and hospital admissions. In case the two researchers disagreed, another researcher helped to resolve the issue and made a final decision.

Risk of Bias and Quality of Evidence

The authors used the National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies to assess the risk of bias. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to assess the certainty of the evidence.[16,17]

Data Analysis

We used a narrative synthesis to evaluate and summarize the findings of this review. We were guided by the four major steps in reviews of effectiveness questions[18]: (1) Establishing a hypothesis regarding the way the intervention works, why it works, and for whom it works, (2) Developing a preliminary summary of the findings of the research included, (3) Evaluating data relationships throughout and between studies, (4) Identifying the robustness of the synthesis.

We employed narrative synthesis in summarizing and interpreting the data. Then the outcomes were reported on whether the findings had positive, negative, or mixed effects. Outcomes with 'positive effects' were considered if the findings suggested a significant effect in improving mortality, survival, shorter length of stay in both hospital and intensive care unit (ICU), and shorter mechanical ventilation (MV) duration and requirement. An outcome is considered to have a 'negative effect' if the findings showed no association and no significant effect. Moreover, the outcome was considered a mixed effect if the findings reported both positive and negative effects.

RESULTS

Screening Process

We gathered 392 articles from all databases, 143 articles using hand search and four using citation searching, with a total of 539 articles obtained. Upon initial screening, we excluded 356 articles, thus only 177 articles proceeded to full-text screening (Figure 1). There are 172 articles removed for the following reasons: different participants (n = 30), wrong intervention (n = 89), and not related to the study (n = 53). Overall, only 5 articles are included.

Characteristics of Studies

Table 1 summarizes the characteristics of the included observational studies.

Risk of Bias of Included Studies

The assessment for the risk of bias is presented in Table 2. Two authors independently assessed the risk of bias of the included studies using the NIH quality assessment tool, which includes relevant questions for evaluating bias. After addressing these questions, the studies were judged and scored as good, fair, or poor. Among the five included studies, quality assessment scores were 8 or higher which were rated as fair to good. Most of the studies clearly stated their objective,
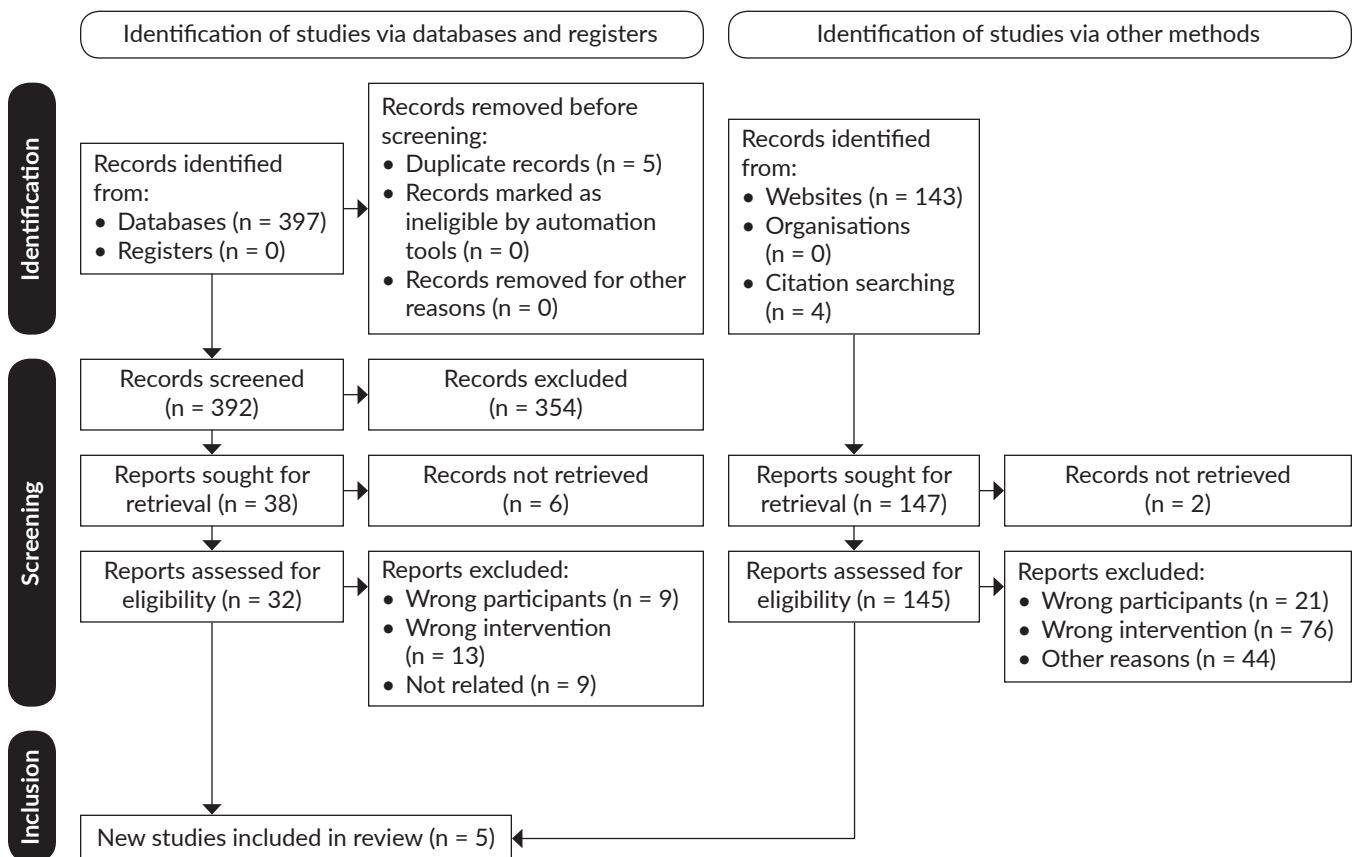

Figure 1. PRISMA 2020 Flow Diagram.

Table 1. Characteristics of Included Studies

Study and year	Country	Study design	Study population	Sample size	Mean age	Male (%)	Female (%)	Intervention	Comparator	Primary outcome
Somers et al., 2021	United States	Retrospective, single-center cohort observational study	Adult patients with severe COVID-19 pneumonia and required invasive mechanical ventilation	484	55 ± 14.9	Not reported	25	Intravenous tocilizumab (8 mg/kg)	Standard treatment	Survival probability after intubation
Pascual et al., 2021	Spain	Retrospective, cohort observational analysis	Adult patients with severe pneumonia caused by COVID-19	1480	61.0 ± 13.5	132 (67.0)	Not reported	600 mg (400 mg for weight <75 kg) followed by a second dose of 400 mg 12 h apart, or a unique dose of 600 mg (400 mg for weight <75 kg).	Standard treatment	Mortality and death
Fisher et al., 2021	United States	Retrospective, single-center cohort observational study	Adult patients with severe COVID-19 pneumonia and required invasive mechanical ventilation	115	56.2 (14.7)	29 (64.4)	Not reported	A mean dose of 4.8 mg/kg tocilizumab was administered. Three patients were given a second dose.	Standard treatment	Mortality
AlQahtani et al., 2022	Saudi Arabia	Retrospective, cohort observational study	Patients with severe to critical COVID-19 pneumonia and aged 60 years and above	135	60 (13.59)	87 (87)	Not reported	Tocilizumab dose ranges between 4–8 mg/kg and a maximum dose of 800 mg. Only 13% were administered with a second dose.	Dexamethasone	Hospital mortality
Gokhale et al., 2021	India	Retrospective, cohort observational study	Adult patients with severe COVID-19 pneumonia with persistent hypoxia	269	53 (44–60)	107 (70.9)	Not reported	Single intravenous dose of 400 mg tocilizumab.	Standard treatment	Death, mechanical ventilation, and $PaO_2:FiO_2$ <150

Table 2. Risk of Bias Summary of Included Observational Studies

Author, Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Overall rating
Somers, 2021	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	CD	Yes	CD	No	Yes	Fair
Pascual, 2022	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes	NR	NR	Yes	Fair
Fisher, 2021	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Fair
AlQahtani, 2022	Yes	Yes	Yes	Yes	No	Yes	Yes	CD	CD	No	Yes	No	CD	Yes	Fair
Gokhale, 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	CD	Yes	Good

Indicates whether yes, no, CD [cannot determine], NR [not reported]

1: Was the research question or objective in this paper clearly stated?
2: Was the study population clearly specified and defined?
3: Was the participation rate of eligible persons at least 50%?
4: Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5: Was a sample size justification, power description, or variance and effect estimates provided?
6: For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7: Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9: Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10: Was the exposure(s) assessed more than once over time?
11: Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12: Were the outcome assessors blinded to the exposure status of participants?
13: Was the loss to follow-up after baseline 20% or less?
14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

specified their study population, and recruited participants according to their inclusion and exclusion criteria. However, most of the included studies (80%) did not justify their sample size selection and did not assess the exposure more than once. Moreover, there is no clear information on the assessment of the repeated exposure, blinding of outcome assessors, and follow-up rate.[16]

Quality of the Evidence

Table 3 illustrates the quality of the evidence of the included studies and patients. Moderate certainty is present in the mortality rate and improved survival. Two studies exhibited association between TCZ and reduced mortality rate and improved survival whereas one study showed that the only predictor for reduced mortality rate was age. Furthermore, two studies have found no association. Moderate certainty was exhibited in length of stay (LOS) and discharge in hospital. Three studies found that there is a decrease in hospital stay for patients treated with TCZ and two studies found no significant difference of LOS between TCZ-treated patients and standard care-treated patients. Moreover, moderate certainty is also shown in requirement and duration of mechanical ventilation and extubation, and oxygen measurement in the TCZ group. Two studies showed decreased duration of MV utilization for TCZ-treated patients than in the control group while two studies showed no significant effect of TCZ in lowering the requirement of MV and having lower oxygen measurement. Low certainty

of the evidence is present for LOS and transfer in ICU and adverse effect. Two studies have shown association of TCZ in lowering the LOS in the ICU.

Study Findings

Five themes emerged from the narrative synthesis. These themes were used to report the outcome of interest of this study.

TCZ reduced mortality and improved survival in patients

Five studies assessed mortality and improved patient's survival with severe COVID-19 pneumonia.[19-23] Two studies reported reduction in mortality and improvement in survival of TCZ patients compared to standard treatment, and three studies found there was no association (GRADE certainty of evidence: Moderate). TCZ-treated patients showed better laboratory values after administration where patients had lower D-dimer (Mean = 2.4 vs 6.5 mg/dL; P = 0.005) and higher serum albumin (M = 155 vs 198; P = 0.001).[19] Similarly, the median survival in TCZ was prolonged than in the control, indicating a significantly lower risk of mortality in patients with severe COVID-19 pneumonia with persistent hypoxia than those treated with only the standard care (M = 18 vs. 9; P = 0.007).[23]

A retrospective cohort study in Spain showed that TCZ patients had greater in-hospital and overall mortality. In this study, 13 of 45 patients (29%) were administered TCZ and 28

Table 3. Quality of the Evidence

Outcome	Impact	Quantity	Certainty
Mortality rate and improved survival in patients	Two studies concluded that tocilizumab reduces the overall mortality rate compared to standard treatment; One study found that the only significant predictor was age between the tocilizumab group and control group; Two studies have reported that tocilizumab was not associated with lowering the mortality rate in patients with COVID-19 pneumonia. Moreover, two studies have also shown longer and improved survival in tocilizumab-treated patients than in control groups.	319 (5 observational studies)	Moderate
Length of hospital stay and discharge	Three studies found that there was a decrease in hospitalization days and more COVID-19 patients were discharged when administered with tocilizumab compared to standard treatment; One study found that there was no significant difference between tocilizumab and hospital discharge; One study found that hospitalization days were longer in tocilizumab-treated patients compared to control group. Moreover, the study also found that early tocilizumab administration was not associated with the length of hospital stay.	704 (5 observational studies)	Moderate
Length of stay and transfer in ICU	Two studies found that the length of stay in ICU is shorter in patients administered with tocilizumab compared to patients administered with standard treatment.	548 (2 observational studies)	Low
Requirement and duration of mechanical ventilation and extubation in TCZ group	Two studies found that there is a decreased number of patients requiring mechanical ventilation and a shorter median time of extubation in the tocilizumab-treated group compared to the control group; One study found that patients treated with TCZ required mechanical ventilation more than the control group; One study also found that there is no difference between the duration of mechanical ventilation in both TCZ and control.	269 (4 observational studies)	Moderate
TCZ and oxygen measurement	Two studies found that there are lower oxygen measurements such as partial pressure of oxygen (PaO_2), the fraction of inspired oxygen (FiO_2), and oxygen saturation (SaO_2) in patients treated with tocilizumab compared to standard treatment.	423 (2 observational studies)	Moderate
TCZ and adverse effects	Two studies found that tocilizumab was associated with an increased risk of secondary infection due to immunosuppressants, however, no other adverse reactions were noted and tocilizumab was well tolerated; One study found that there was no increased risk of secondary infection within 14 days of tocilizumab treatment.	362 (3 observational studies)	Low

of 70 controls (40%) died within 30 days of intubation [OR (Odds Ratio) 0.61; 95% CI (Confidence Interval), 0.27–1.36]. The mortality rate in the TCZ group was statistically lower, yet, this was not significantly associated with the baseline differences in the cohort study; thus, treatment with TCZ was not associated with lower mortality.[21] Moreover, a retrospective cohort study in Saudi Arabia reported that the majority were immunocompromised (44%) and obese (45%). In the control group, the majority of them had comorbidities such as hypertension, diabetes, heart disease, and obesity (43%). Most TCZ patients exhibited rapid decline in pulmonary function and prolonged fever than the control group (95% vs. 74% and 68% vs. 20%, respectively). However, the hospital mortality rate in the TCZ group was significantly lesser than the control groups indicating that age was the only significant risk factor for mortality where age 60 years and above exhibited higher mortality rate (OR = 1.030 and 95% CI = 1.004, 1.057).[22] These show that patients treated with TCZ have a higher chance of survival and reduced mortality rate compared to patients treated with standard treatment.

Requirement and duration of mechanical ventilation and extubation in TCZ group

The necessity and duration of mechanical ventilation and extubation have been demonstrated in four studies (GRADE certainty of evidence: Moderate).[19,21-23] Two groups were compared, patients receiving TCZ (78) and those not receiving TCZ (76), with a follow-up time of 47 days ranging 28-67 days. TCZ was commonly administered within 24 hours of intubation and a 26% minority of use for 48 hours after intubation. Throughout the study period, 56% of patients administered with tocilizumab were discharged alive, whereas only 40% of untreated patients achieved the same outcome (P = 0.04). Among the 17 patients remaining hospitalized in each group at the end of follow-up, the majority had been removed from mechanical ventilation: 82% of those treated with tocilizumab and 53% of the untreated group.[19] On the other hand, it was reported that there was no notable distinction in the percentage of patients extubated after fourteen days (44.4% compared to 34.2%), and the median time to extubation was 10 days for tocilizumab and 10.5 days for controls (P = 0.86).[21] Another study also found that following immunomodulator therapy, 38% of patients in the TCZ group (24 out of 63) and 34% in the DEX group (12 out of 35) required mechanical ventilation. In the TCZ group, 28 patients were successfully extubated with an average duration of mechanical ventilation lasting 12.8 days, while in the DEX group, five patients were extubated with a mean duration of 6.4 days.[22] Furthermore, it was reported that, in the tocilizumab group, 56 out of 151 patients initially utilized non-invasive ventilation, and 15 of them later required invasive ventilation. Conversely, the control group refrained from non-invasive ventilation initially due to concerns about aerosolization. Overall, 30 patients needed invasive ventilation, with 22 from the tocilizumab group and 8 from the control group.[23]

Association of TCZ and adverse effects

Three studies were identified to have an association between TCZ and adverse effects (GRADE certainty of evidence: Low).[19,21,23] Secondary infection possibly occurred due to immunosuppressants, but it was well tolerated and did not show any adverse reaction.[23] Due to IL-6 inhibition, there is a high risk of superinfection. Although the study mentioned that superinfection is vague to mechanically ventilated patients with severe COVID-19, the association of a single dose of TCZ with the risk is not well described. However, TCZ is associated with a higher occurrence of infection due to ventilator-associated pneumonia than untreated controls (54% vs 26%; P < 0.001), driven primarily by a large increase in ventilator-associated pneumonia (45% vs 20%; P < 0.001).[19] Furthermore, there is an association of bacteria such as staphylococcal pneumonia to severe COVID-19 infection, and half of the cases of both the TCZ and control group were due to *Staphylococcus aureus*. In contrast, within 14 days of treatment of TCZ, there was no increased risk of secondary infection.[21]

TCZ medication and LOS and discharge

To evaluate the relationship between TCZ and the length of stay (LOS) and hospital discharge of patients with COVID-19, five studies were examined.[19-23] Three studies showed that individuals receiving TCZ treatment experienced reduced hospitalization durations and had a higher probability of being discharged alive compared to those in the TCZ-treated group. Meanwhile, two studies found no significant association, and one of those studies reported that COVID-19 patients experienced longer hospital stays. These findings suggest that the LOS tends to be shorter among TCZ-treated patients compared to those receiving standard treatment (GRADE certainty of evidence: Moderate). Moreover, 56% of TCZ-treated patients were discharged alive, which is higher than the 40% discharge rate for those who did not receive TCZ (P = 0.04).[19] Similarly, 72 out of 151 patients (47.7%) treated with TCZ were discharged alive compared in the control group where 44 out of 118 (37.3%) have been discharged alive.[23] However, regardless of the time of administration, patients who received TCZ spent more time in the hospital than those who received standard treatment (13.2 vs. 10.0 days, P < 0.01; and 14.7 vs. 11.1 days).[20] Furthermore, in terms of hospital discharge within 30 days, there were no notable distinctions between the TCZ-treated group and the control group and the comparison group (44.4 vs 35.7; OR 1.44; 95% CI, 0.67 – 3.09).[21]

TCZ and length of stay and transfer in ICU

Two studies were reported to have an association with TCZ and length of stay and transfer in ICU (GRADE certainty of evidence: Low).[20,22] After receiving DEX, more patients in the DEX group 17/35, (48.6%) than the TCZ and corticosteroid group 20/100 (20%) needed to be transferred to the ICU. Additionally, After the immunomodulator was

given, the TCZ group had a lower percentage of transfer to the ICU than the DEX group (M = 20 vs 48.6%; p = 0.0011).[22] The ICU-LOS in the TCZ group was shown to be shorter than in the control group (M = 5.8 ± 4.3 vs 11.8 ± 7.0; p <0.001).[20] These findings suggest that TCZ group has shorter LOS and lower rate of ICU transfer compared to DEX group.

TCZ and oxygen measurement

Two studies assessed oxygen measurement [Arterial oxygen pressure (PaO$_2$), Fraction of inspired oxygen (FiO$_2$)] of patients administered with TCZ (GRADE certainty of evidence: Moderate)[19,23] All the included studies reported negative effects. Patients in TCZ group have lower median PaO$_2$ to FiO$_2$ (median, 155 vs 198; P = 0.001) which may also increase the risk of mortality due to poor oxygenation.[19] Similarly, TCZ use and higher oxygen saturation on multivariate Cox regression analysis was an independent predictor of survival with patients experiencing persistent hypoxia (oxygen saturation is 94% or PaO$_2$/FiO$_2$ ratio of less than 200), have found that those who 'survived' had higher oxygen saturation than 'non-survived group' (M = 88% with a range of 85–93% v/s M = 85% and range of 79–90%- p = 0.014) and were less tachypneic than 'non-survived group' (respiratory rate 30 v/s 36 breaths per min, p = 0.002), at the time of enrolment for TCZ.[23] These studies showed that TCZ-treated patients have decreased oxygen measurements compared to non-TCZ treated patients.

DISCUSSION

Tocilizumab (TCZ) had a varying effect in reducing risk of mortality and improving survival rate. Some studies have shown no significant association in reducing mortality risk due to age and pre-existing conditions between TCZ and the control group. However, there are findings indicating that TCZ has a positive effect on reducing mortality risk and improving survival rate. Majority of the included studies showed that TCZ positively affected patients' length of stay in hospital and ICU. Moreover, TCZ had variable effects on the requirement and duration of mechanical ventilation and secondary infection due to immunosuppressive effects with severe COVID-19 pneumonia in the hospital.

Tocilizumab was found to shorten the LOS in hospitalization and ICU stay, and also reduce the need for mechanical ventilation. However, there is no clear evidence that it can reduce mortality or improve survival. To explain, the risk for clinical deterioration was not reduced in comparison to standard treatment since there were no discernable differences between the number of ICU-admitted patients based on their LOS or overall mortality identified with TCZ and the control group.[24] It was evident that these findings were consistent with several studies. Likewise, the COVACTA trial reported that TCZ does not have a significant difference in improved survival or reduced the risk of mortality.[25]

However, TCZ decreases the duration and need for MV and length of hospital and ICU stay compared to standard treatment with control. Standard treatment patients required mechanical ventilation more frequently than patients in the TCZ group. The mortality and the need for MV were significantly lower in TCZ-treated patients than in the control group.[26] Patients on invasive ventilation were reduced after 14 days of treatment with TCZ.[27]

Administration of TCZ can improve patient survival and lessen the intubation days. Parallel to a one study in Qatar where the administration of TCZ at 24-72 hours shows a rapid improvement of the respiratory condition of the patients.[28] However, some studies show that the administration of TCZ requires mechanical ventilation more than the control group. A study in Italy provided the first hour of the administration of TCZ to severe and critical patients.[28] Clinicians suggest being aware as soon as TCZ is administered as respiratory failure can lead to a critical state.

Patients with severe COVID-19 showed improvements and shorter hospital stays after receiving TCZ treatment, similar to the findings of the RECOVERY Trial. This treatment lowered mortality, increased the chances of patients leaving the hospital successfully, and reduced the need for invasive MV, which aligns with other studies. The use of TCZ reduced the need for MV and resulted in shorter hospital stays for COVID-19 patients. Improved laboratory results while using TCZ also led to reduced hospitalization and ICU stays.[29] Nonetheless, there is no difference in hospital discharges between COVID-19 patients who received TCZ and standard care.[30] These findings could vary depending on the illness's severity, the dosage of treatment, or any additional conditions the patient may have.

Furthermore, TCZ was linked to an increased risk of secondary bacterial pneumonia. However, there was no noticeable variation in the results of treatment between patients who received TCZ and those who did not.[19] A study provided in Greece differed since patients in the untreated group had a higher percentage of developed secondary pneumonia than patients treated with TCZ.[31] In addition, a high risk of superinfection is common in mechanically ventilated patients driven by ventilator-associated pneumonia due to *Staphylococcus aureus* bacteria[22], similar to an observational study in Italy.[32] Moreover, one study reported that four patients developed a secondary bacterial infection: one *Pseudomonas aeruginosa* and *Staphylococcus aureus*, and two *Klebsiella pneumoniae* species.[27] Further observation is needed to determine the effectiveness and safety of TCZ for COVID-19 because secondary infection has been recorded.

CONCLUSION

The efficacy of TCZ in patients with severe COVID-19 aged 50 years and above showed mixed results in reducing mortality risk; however, it shortens hospital stay and may

improve survival rate as it decreases the need for mechanical ventilation and ICU transfer. Moreover, secondary infections may occur, and proper side effect monitoring is needed.

Recommendation

The utilization of sufficient numbers of randomized controlled trials and the conduct of meta-analysis will create a more substantial certainty of evidence for this research. More research is needed about the adverse effects of TCZ on older patients and the length of stay and transfer in ICU as the evidence is scarce.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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REFERENCES

1. Avni T, Leibovici L, Cohen I, Atamna A, Guz D, Paul M, et al. Tocilizumab in the treatment of COVID-19-a meta-analysis. QJM. 2021 Nov 5;114(8):577-86. doi: 10.1093/qjmed/hcab142. PMID: 34010403; PMCID: PMC8243364.
2. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020 Mar 19;91(1):157-60. doi: 10.23750/abm.v91i1.9397. PMID: 32191675; PMCID: PMC7569573.
3. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. 2020 [cited 2021 Nov]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
4. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. J Med Virol. 2020 Jul;92(7):814-8. doi: 10.1002/jmv.25801. PMID: 32253759; PMCID: PMC7262125.
5. Wei Q, Lin H, Wei RG, Chen N, He F, Zou DH, et al. Tocilizumab treatment for COVID-19 patients: a systematic review and meta-analysis. Infect Dis Poverty. 2021 May 18;10(1):71. doi: 10.1186/s40249-021-00857-w. PMID: 34001244; PMCID: PMC8128625.
6. Huang E, Jordan SC. Tocilizumab for COVID-19 - The ongoing search for effective therapies. N Engl J Med. 2020 Dec 10;383(24):2387-8. doi: 10.1056/NEJMe2032071. PMID: 33296566; PMCID: PMC7745168.
7. Singh TU, Parida S, Lingaraju MC, Kesavan M, Kumar D, Singh RK. Drug repurposing approach to fight COVID-19. Pharmacol Rep. 2020 Dec;72(6):1479-1508. doi: 10.1007/s43440-020-00155-6. PMID: 32889701; PMCID: PMC7474498.
8. Capra R, De Rossi N, Mattioli F, Romanelli G, Scarpazza C, Sormani MP, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med. 2020 Jun;76:31-5. doi: 10.1016/j.ejim.2020.05.009. PMID: 32405160; PMCID: PMC7219361.
9. Salvati L, Occhipinti M, Gori L, Ciani L, Mazzoni A, Maggi L, et al. Pulmonary vascular improvement in severe COVID-19 patients treated with tocilizumab. Immunol Lett. 2020 Dec;228:122-8. doi: 10.1016/j.imlet.2020.10.009. PMID: 33161002; PMCID: PMC7644186.
10. Campochiaro C, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. Eur J Intern Med. 2020 Jun;76:43-9. doi: 10.1016/j.ejim.2020.05.021. PMID: 32482597; PMCID: PMC7242960.
11. Patel A, Shah K, Dharsandiya M, Patel K, Patel T, Patel M, et al. Safety and efficacy of tocilizumab in the treatment of Severe Acute Respiratory Syndrome Coronavirus-2 pneumonia: a retrospective cohort study. Indian J Med Microbiol. 2020 Jan-Mar;38(1):117-23. doi: 10.4103/ijmm.IJMM_20_298. PMID: 32719218; PMCID: PMC7706820.
12. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? J Transl Med. 2020 Apr 14;18(1):164. doi: 10.1186/s12967-020-02339-3. PMID: 32290839; PMCID: PMC7154566.
13. Perrotta F, Corbi G, Mazzeo G, Boccia M, Aronne L, D'Agnano V, et al. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. Aging Clin Exp Res. 2020 Aug;32(8):1599-1608. doi: 10.1007/s40520-020-01631-y. PMID: 32557332; PMCID: PMC7298699.
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29:372:n71. doi: 10.1136/bmj.n71. doi:10.1136/bmj.n71. PMID: 33782057; PMCID: PMC8005924.
15. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without Meta-Analysis (SWiM) in systematic reviews: reporting guideline. BMJ. 2020 Jan 16:368:l6890. doi: 10.1136/bmj.l6890. PMID: 31948937; PMCID: PMC7190266.
16. National Heart, Lung, and Blood Institute. Study Quality Assessment Tools [Internet]. 2021 [cited 2022 May]. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools?fbclid=IwAR05gwO2skAXY-VJ-kHun0vY-Kf7jtm5HCGyfVO0gi19T2v8F3x-8wazhsM
17. The GRADE Working Group. What is GRADE [Internet]. 2022 [cited 2021 Nov]. Available from: https://www.gradeworkinggroup.org/
18. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance in the Conduct of Narrative Synthesis in Systematic Review [Internet]. 2006 April [cited 2021 Nov]. Available from: https://www.lancaster.ac.uk/media/lancaster-university/content-assets/documents/fhm/dhr/chir/NSsynthesisguidanceVersion1-April2006.pdf
19. Somers EC, Eschenauer GA, Troost JP, Golob JL, Gandhi TN, Wang L, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Clin Infect Dis. 2021 Jul 15;73(2):e445-e454. doi: 10.1093/cid/ciaa954. PMID: 32651997; PMCID: PMC7454462.
20. Cardona-Pascual I, Berlana D, Martinez-Valle F, Campany-Herrero D, Montoro-Ronsano JB. Effect of tocilizumab versus standard of care in adults hospitalized with moderate-severe COVID-19 pneumonia. Med Clin (Barc). 2022 Apr 8;158(7):301-7. doi: 10.1016/j.medcli.2021.03.005. PMID: 34147248; PMCID: PMC8101781.
21. Fisher MJ, Marcos Raymundo LA, Monteforte M, Taub EM, Go R. Tocilizumab in the treatment of critical COVID-19 pneumonia: a retrospective cohort study of mechanically ventilated patients. Int J Infect Dis. 2021 Feb;103:536-9. doi: 10.1016/j.ijid.2020.12.021. PMID: 33333252; PMCID: PMC7836535.
22. AlQahtani H, AlBilal S, Mahmoud E, Aldibasi O, Alharbi A, Shamas N, et al. Outcomes associated with tocilizumab with or without corticosteroid versus dexamethasone for treatment of patients with severe to critical COVID-19 pneumonia. J Infect Public Health. 2022 Jan;15(1):36-41. doi: 10.1016/j.jiph.2021.11.017. PMID: 34883296; PMCID: PMC8611824.
23. Gokhale Y, Mehta R, Kulkarni U, Karnik N, Gokhale S, Sundar U, et al. Tocilizumab improves survival in severe COVID-19 pneumonia with persistent hypoxia: a retrospective cohort study with follow-up from Mumbai, India. BMC Infect Dis. 2021 Mar 5;21(1):241. doi: 10.1186/s12879-021-05912-3. PMID: 33673818; PMCID: PMC7934984.
24. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized

clinical trial. JAMA Intern Med. 2021 Jan 1;181(1):24-31. doi:10.1001/jamainternmed.2020.6615. PMID: 33080005; PMCID: PMC7577199.

25. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. N Engl J Med. 2021 Apr 22;384(16):1503-16. doi:10.1056/NEJMoa2028700. PMID: 33631066; PMCID: PMC7953459.

26. Klopfenstein T, Zayet S, Lohse A, Balblanc JC, Badie J, Royer PY, et al. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. Med Mal Infect. 2020 Aug;50(5):397-400. doi: 10.1016/j.medmal.2020.05.001. PMID: 32387320; PMCID: PMC7202806.

27. Alattar R, Ibrahim TBH, Shaar SH, Abdalla S, Shukri K, Daghfal JN, et al. Tocilizumab for the treatment of severe Coronavirus Disease 2019. J Med Virol. 2020 Oct;92(10):2042-9. doi: 10.1002/jmv.25964. PMID: 32369191; PMCID: PMC7267594.

28. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. Autoimmun Rev. 2020 Jul;19(7):102568. doi: 10.1016/j.autrev.2020.102568. PMID: 32376398; PMCID: PMC7252115.

29. Sarhan RM, Madney YM, Abou Warda AE, Boshra MS. Therapeutic efficacy, mechanical ventilation, length of hospital stay, and mortality rate in severe COVID-19 patients treated with tocilizumab. Int J Clin Pract. 2021 Jun;75(6):e14079. doi: 10.1111/ijcp.14079. PMID: 33550688; PMCID: PMC7995153. Erratum in: Int J Clin Pract. 2021 Dec;75(12):e15015. doi: 10.1111/ijcp.15015. PMID: 34965665.

30. Karampitsakos T, Malakounidou E, Papaioannou O, Dimakopoulou V, Zarkadi E, Katsaras M, et al. Tocilizumab improves 28-day survival in hospitalized patients with severe COVID-19: an open label, prospective study. Respir Res. 2021 Dec 22;22(1):317. doi:10.1186/s12931-021-01914-6. PMID: 34937570; PMCID: PMC8692825.

31. Ip A, Berry DA, Hansen E, Goy AH, Pecora AL, Sinclaire BA, et al. Hydroxychloroquine and tocilizumab therapy in COVID-19 patients - an observational study. PLoS One. 2020 Aug 13;15(8):e0237693. doi: 10.1371/journal.pone.0237693. PMID: 32790733; PMCID: PMC7425928.

32. Menzella F, Fontana M, Salvarani C, Massari M, Ruggiero P, Scelfo C, et al. Efficacy of tocilizumab in patients with COVID-19 ARDS undergoing noninvasive ventilation. Crit Care. 2020 Sep 29;24(1):589. doi: 10.1186/s13054-020-03306-6. PMID: 32993751; PMCID: PMC7523258.