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Systematic Review

Role of tocilizumab therapy in COVID-19 patients: a systematic review

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ABSTRACT

Coronavirus disease 2019 (COVID-19) caused by the Severe acute respiratory syndrome coronavirus-2 (SARS CoV 2) virus has created a global threat to the entire human population. The medical and scientific community are striving hard to find an effective therapeutic strategy to overcome this crisis. There are few studies showing the efficacy of tocilizumab against COVID-19, but they many of them lack reliability due to their small sample size or sample population not representative of the general population. This meta-analysis aims to elucidate the role of tocilizumab in the management of COVID-19, its efficacy and safety profile. A comprehensive search of databases including PubMed, Medline, Cochrane, Lancet, Google Scholar, WHO, Embase, Elsevier and other modalities of search like website searching and citation tracking was carried out through which 1061 articles were identified. Among them, 10 articles that fitted the inclusion criteria and qualitatively good were taken up for the meta-analysis. Out of the 10 studies selected, the results of 9 studies were in favour of the efficacy of tocilizumab therapy, while 1 study was against the efficacy of tocilizumab. The result of our statistical analysis was that OR=0.5569 (95% CI; 0.2289 to 0.9332) for the effect of tocilizumab on mortality reduction in COVID-19 patients. Among critically ill patients with COVID-19, the in-hospital mortality was significantly reduced in patients treated with tocilizumab during the first 2 days of ICU admission compared to patients those who were not administered with tocilizumab in the early phase. Treatment with tocilizumab significantly reduces the mortality rate, increases the survival rate and lowers the risk of requiring invasive mechanical ventilation.

Keywords: Corona virus disease, IL-6 receptor antagonist, Pharmacotherapy, SARS CoV 2, Tocilizumab

INTRODUCTION

The Corona virus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome virus (SARS CoV 2) is an ongoing global crisis that has created an adversity for the entire human community. The medical community suffer even more with the indispensable need to manage the situation.[1] With numerous studies conducted to understand the pathogenic mechanisms of the disease, it was discovered that not all COVID-19 patients were critical. The heterogenous clinical presentation varies from majority of those infected being asymptomatic or with mild symptoms and the vulnerable population like the elderly, patients with comorbidities and immunosuppressed patients getting highly affected to an extent of requiring mechanical ventilation or even death.[2-4] The process that occurs in them making the disease a fatal one is called the 'cytokine storm'. It is the gushing of inflammatory mediators like cytokines and interleukins, especially the interleukin 6 to the infected cells to elicit the immune response. Ironically, the overt immune response is what harms the patient more.[5]

The next snag was to identify a therapeutic measure to subside the chaos. Alongside the trial of various antivirals and corticosteroids, tocilizumab, a humanized monoclonal antibody was also attempted. Tocilizumab is an interleukin 6 (IL-6) receptor antagonist. It is potent enough to bind both the membrane and soluble IL-6 receptors, thereby blocking IL-6 signalling and reducing inflammation.6

There are several small studies showing the efficacy of tocilizumab, but their results were vacillating due to their smaller sample size. The objective of this meta-analysis is to project the role of tocilizumab in the management of COVID-19 patients.

METHODS

This systematic review was performed in strict compliance with the Preferred Reporting Items of the Systematic review and Meta-Analysis (PRISMA) checklist. All steps were conducted in concordance with the Cochrane Handbook of Systematic Review and Meta-Analysis.

Search strategy

A comprehensive literature review by searching the databases like PubMed, Google scholar, Lancet, WHO, Elsevier, Medline, Cochrane was done. The following search terms were used: 'Tocilizumab', 'Pharmacotherapy', 'Drug trials', 'randomized control trials'. The search also included probing references from quality articles, website searching and citation tracking.

Inclusion criteria

For the systematic review and meta-analysis, the following were set as the inclusion criteria: studies on COVID-19 published between April 2020 and July 2021; studies involving sample size >100; studies on pharmacotherapy for COVID-19 specially focussing Tocilizumab; studies with effective methodologies; studies with efficacy and safety points of Tocilizumab well outlined.

Exclusion criteria

The following were set as exclusion criteria: Studies on COVID conducted before 2020; studies discussing in-vitro effects of tocilizumab; abstract only articles where full texts were not available; articles with only protocol /guidelines; articles that were not in English.

Data extraction

The eligible studies were identified and the data was extracted from them. The data was cross-checked by glancing the same chosen articles in several other systematic reviews of multiple authors to ensure the reliability of the data. The odds ratios (ORs) or the proportions of patients for primary outcome variables with 95% confidence intervals (CIs) were estimated using a generic inverse variance method (random-effects model). Adjustments and propensity score matching was done to the results to eliminate 'Selection bias'.

Statistical analysis

The odds ratio with 95% confidence intervals of the individual studies were compiled. The data were analysed using the Statistical Package for the Social Sciences (SPSS) software version 20.0.

RESULTS

Study selection

A total of 1061 articles were identified via database searches, website searching and reference chaining. After eliminating duplicate studies (147), articles that were inappropriate to the study topic (133) and articles that did not fit the eligibility criteria (755), 26 articles were eligible. After quality assessment, 10 articles were taken for the meta-analysis, of which 3 were Randomized control trials and 6 were Cohort studies (Figure 1).

Study characteristics

The studies were chosen based on the following factors: date of publication, study design, country where the study was conducted, sample size, number of patients in the intervention group - treated with tocilizumab, combination of drugs if given, number of deaths, length of hospital stay, number of ICU admissions, invasive mechanical ventilation, viral clearance time, comorbidities and number of patients in the control group who received standard care of treatment/placebo.

Synthesis of results

In our meta-analysis, the following parameters were evaluated: improved survival, need for mechanical ventilation, mortality rate reduction.

Data of 17,789 patients collected from 10 studies conducted in different parts of the world are shown in Table 1.

Out of the 10 studies selected, the results of 9 studies were in favour of the use of tocilizumab, while 1 study was against the efficacy of tocilizumab. The result of our statistical analysis was that the odds ratio (Figure 2) for mortality reduction of tocilizumab in COVID-19 patients is 0.5569 (95% CI; 0.2289 to 0.9332).

Risk of bias assessment

We assessed the risk of bias ('low risk', 'unclear', or 'high risk') for the studies included in the meta-analysis using version 2 of the Cochrane risk of bias assessment tool for randomised control trials (Figure 3) and The New Castle Ottawa scale for non-randomised controlled trials (Figure 4). Disagreements aroused during this process were resolved through discussion. The grading of recommendations assessment, development and evaluation (GRADE) approach was utilised to assess the quality of the evidence obtained from various studies.

Table 1: Summary of studies analysed in the meta-analysis.

Study ID	Country	Study design	Sample size	Experimental group	Comparative group	Results	Description
Gupta et al (2020) [7]	US	Multicentre cohort study	3924	Patients treated with tocilizumab in the first 2 days (433)	Patients not treated early with tocilizumab (3491)	HR=0.71 for death of patients treated early with tocilizumab compared with those not treated.	Administration of tocilizumab in the first 2 days of ICU admission showed significantly lowered in-hospital mortality when compared with patients who were not on early use.
Horby et al (2020) [8]	UK	Open-label, platform RCT	4116	Patients who received tocilizumab (2022)	Patients who received usual care (2094)	RR=0.84 for patients treated with tocilizumab to require invasive mechanical ventilation or death than those given usual care (p<0·0001).	In hospitalised patients with hypoxia and systemic inflammation, tocilizumab significantly improved survival and clinical outcomes.
Narain et al (2020)[9]	US	Retrospective observational cohort study	3098	Patients who received Tocilizumab alone (60) + combination of tocilizumab and corticosteroids (304)	Patients who received standard care (1505)	HR=0.459 for improved hospital survival in patients receiving a combination of tocilizumab and corticosteroids compared to those receiving standard care (p<0·0001).	Patients treated with a combination of tocilizumab and corticosteroids had lowered in-hospital mortality.
Sanz et al (2020) [10]	Spain	Multicentre Cohort Study	1229	Patients treated with tocilizumab (260)	Patients on standard care (969)	aHR=0.34 (p=0.005) and 0.38 (p=0.011) for decreased risk of death and ICU admission respectively among patients treated on tocilizumab with CRP >150 mg/L.	In patients with high CRP levels, tocilizumab was associated with a significantly lower risk of death or ICU admission.
Andrew et al (2020)[11]	New Jersey	Retrospective Observational Multicentre cohort	2512	Patients who received tocilizumab (134)	Patients who never received tocilizumab (413)	aHR=0.76 for improved survival in patients treated with tocilizumab	Tocilizumab showed significantly reduced mortality rates among patients admitted in ICU.

Continued.

Study ID	Country	Study design	Sample size	Experimental group	Comparative group	Results	Description
						than those who were not.	
Gordon et al (2021)[12]	UK	REMAP-CAP trial	895	Patients on Tocilizumab (353) + Sarilumab (48)	Patients on standard care (402)	Median adjusted OR=1.64 for improved survival in patients on tocilizumab when compared to the control group.	Tocilizumab or Sarilumab improved clinical outcomes and survival in ICU patients with severe COVID-19.
Guaraldi et al (2020)[13]	Italy	Retrospective observational cohort study	544	Patients treated with tocilizumab (179)	Patients on standard care (365)	aHR=0.61 for invasive mechanical ventilation or death in patients treated with tocilizumab compared to those treated with standard group (p=0.020).	There was reduced risk of invasive mechanical ventilation or death when tocilizumab was administered in patients with severe COVID-19 pneumonia.
Biran et al (2020) [14]	US	Retrospective observational cohort study	630	Patients who received tocilizumab (210)	Patients who did not receive tocilizumab (420)	HR=0.64 for hospital-related mortality in patients who received tocilizumab when compared to those who did not (p=0.0040).	Tocilizumab significantly reduced the mortality in severe COVID-19 patients who required ICU support.
Rosas et al (2021)[15]	Europe, North America	RCT	452	Patients on Tocilizumab (294)	Patients on placebo (144)	Mortality rates were 19.7% and 19.4% at day 28 in the tocilizumab group and placebo group, respectively.	Tocilizumab did not result in clinical improvement or lower mortality in mild COVID-19 patients.
Salama et al (2020)[16]	US, Mexico, Kenya, South Africa, Peru, Brazil	Double blinded placebo-controlled RCT	389	Patients treated with Tocilizumab (249)	Patients treated with placebo (128)	HR=0.56 for mechanical ventilation or death in the tocilizumab group when compared to placebo group.	In hospitalized patients, tocilizumab reduced the likeliness of progression to severe outcomes like mechanical ventilation or death.

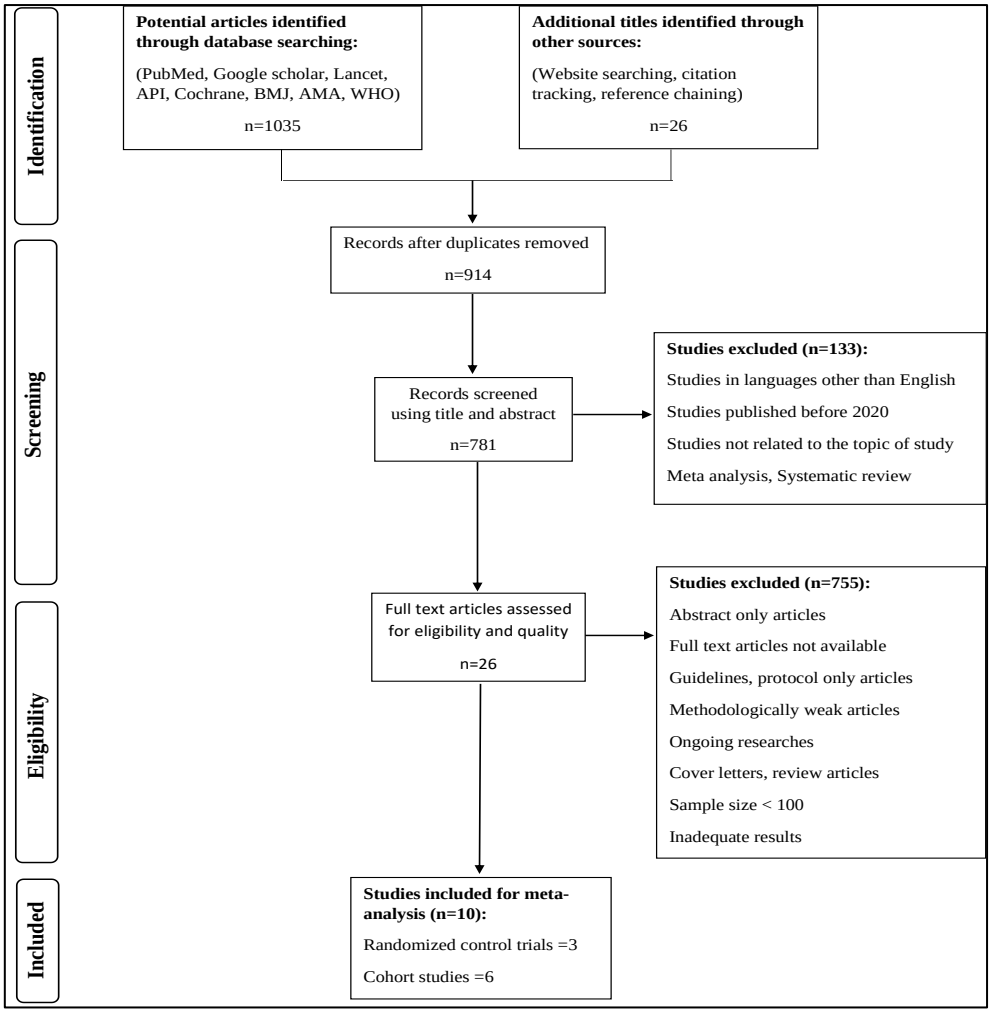

Figure 1: Prisma flowchart showing study selection.

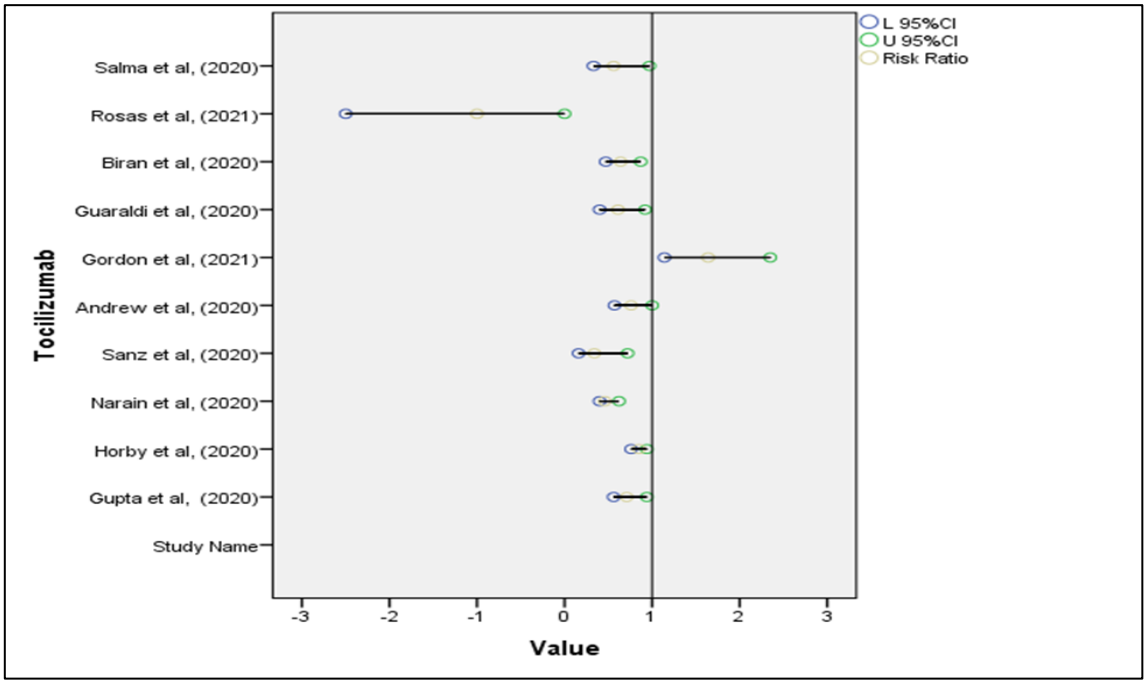

Figure 2: Risk ratio of mortality reduction of tocilizumab as per the analysed studies.

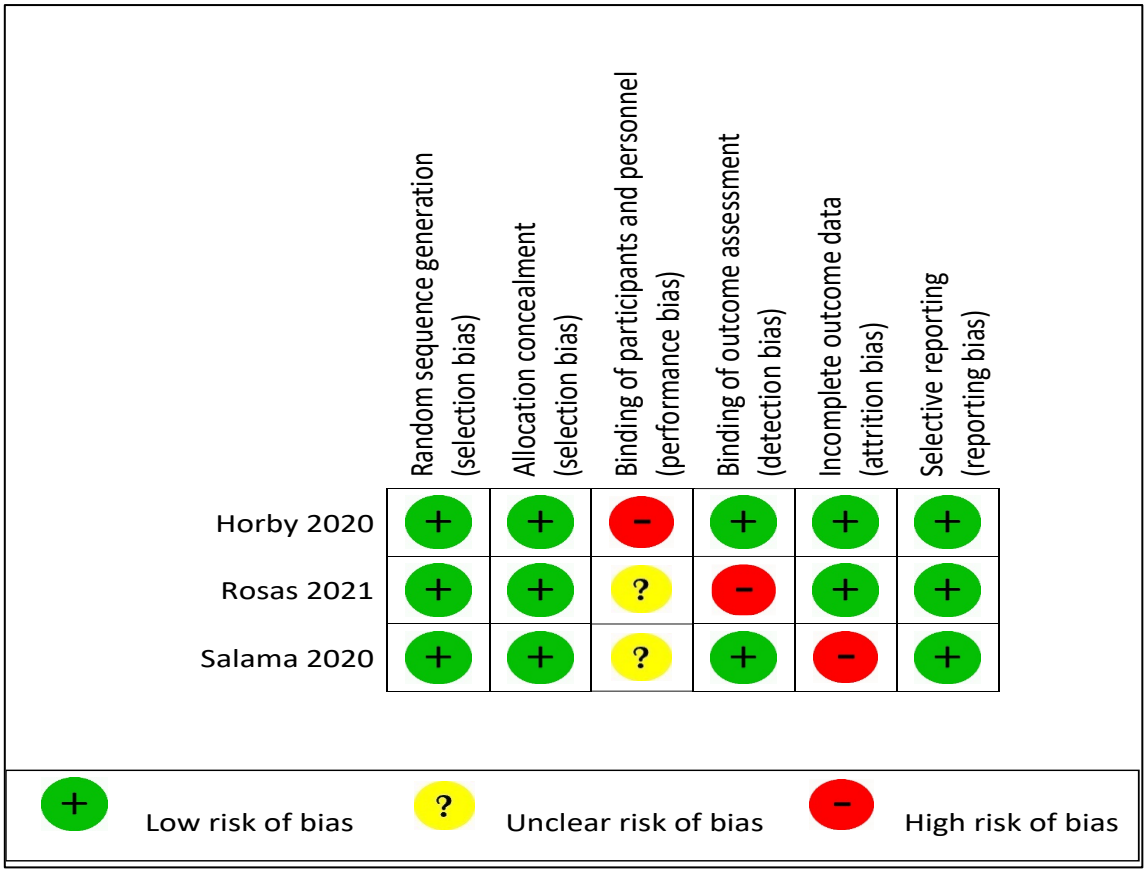

Figure 3: The Cochrane risk of bias assessment for randomised control trial studies analysed.

Study ID	Selection			Comparability*	Outcome		Total (7★)
	Representativeness of exposed cohort (★)	Selection of non-exposed cohort (★)	Ascertainment of exposure (★)	(★★)	Assessment of outcome (★)	Adequacy of follow up (★)	
Gupta 2020	-	★	-	★★	★	★	★★★★★ (5)
Narain 2020	★	★	★	★ -	★	-	★★★★★ (5)
Sanz 2020	★	★	★	★★	★	-	★★★★★★ (6)
Ip 2020	★	★	★	★★	★	-	★★★★★★ (6)
Gordon 2021	★	★	★	★★	★	-	★★★★★★ (6)
Guaraldi 2020	-	★	★	★ -	★	-	★★★★ (4)
Biran 2020	-	★	★	★ -	★	-	★★★★ (4)

Figure 4: The New Castle Ottawa scale for non-randomised controlled trial studies analysed.

DISCUSSION

SARS CoV 2 is a positive-sense single-stranded RNA virus belonging to the Coronaviridae family.[17] The entry of the pathogen into the host (human) causes activation of the immune system and release of lymphocytes at the target site. Majority of the population are cured at this level of immunity. Only the vulnerable population who are unable to tolerate the infection due to existing comorbidities are badly affected.[18] When infection is not controlled by the antiviral immunity alone, the patients enter a hyperinflammatory phase with dysregulation of

immune responses, resulting in release of massive amounts of inflammatory mediators by the body. The mediators released are pro-inflammatory cytokines including interleukins (IL) 2, 6, 7 and 10, granulocyte-colony stimulating factor (G-CSF), interferon-gamma-inducible protein-10 (IFN-gamma, IL-10) and tumor necrosis factor alpha (TNF-alpha). This cytokine storm creates a pro-thrombotic milieu, increasing the risk of cardiomyopathy and ultimately multi-organ failure. These mediators not only evade the virus, but may also cause damage of the lung tissues.[19,20]

Therapies targeting the cytokine release were experimented. Tocilizumab is one such attempt. Tocilizumab is a recombinant humanised monoclonal antibody of the IgG1 class.[21] It is directed against both the soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor. Several studies suggest that it is found to dampen the hyperactivated immune responses in COVID-19 patients.[22-24] Tocilizumab is also found to be effective in hospitalised COVID-19 patients who have hypoxia and CRP ≥75 mg/L, indicating the evidence of inflammation.[25,26]

Improved survival

In a study conducted by Gupta et al1 involving 3924 patients from US, 433 patients were treated with tocilizumab in the first 2 days and 3491 patients received standard care of treatment. Patents in the Steroids + Tocilizumab group had significantly improved survival compared to the Standard care of treatment group (Hazard Ratio (HR): 0·459, 95% confidence interval (CI): 0·295--0·714; p<0·0001). In the study conducted by Sanz et al involving 1229 patients from Spain, 260 patients were treated with tocilizumab and 969 patients were treated with standard care.[10] The adjusted odds ratios for in-hospital survival were 1.64 (95% credible interval, 1.14 to 2.35) for the patients treated with tocilizumab. The study conducted by Gordon et al with 895 patients from the United Kingdom also showed similar results.[12] For patients receiving tocilizumab, the overall survival from time of admission was not reached even at 23 days in contrast to the patients who did not receive tocilizumab, it was 19 days (HR=0.71, 95% CI 0.56–0.89; p=0.0027). The results from the study conducted by Biran et al including 630 patients from US were also in accordance with those of the above studies.[14] The time to improvement in clinical status in patients taking tocilizumab over 28 days period was 6 days (95% CI, 6.0 to 7.0) and in those taking placebo was 7 days (hazard ratio HR=1.15; 95% CI, 0.90 to 1.48).

Need for mechanical ventilation

In a study conducted by Horby et al involving 4116 patients from the United Kingdom, 2022 patients received tocilizumab while 2094 patients received usual care.[8] The risk ratio was 0.79 (95% CI: 0·69–0·92, p=0.0019) for the receipt of invasive mechanical ventilation and 0.91 (95% CI: 0·79–1·04, p=0.15) for non-invasive ventilation. In the study conducted by Guaraldi et al involving 544 patients from Italy, patients who received tocilizumab showed a significant reduction in need of invasive mechanical ventilation or death when compared with those receiving standard care only.[13] The adjusted hazard ratio was 0.61 for risk of invasive mechanical ventilation or death in patients treated with tocilizumab compared to those treated with standard group (p=0.020).

Mortality rate reduction

In the study conducted by Gupta et al involving 3924 patients from the United States, patients treated with tocilizumab had a lower adjusted risk of death compared with patients not treated with tocilizumab.[7] The hazard ratio was 0.71 (95% CI, 0.56-0.92). The 30-day mortality rate in the tocilizumab-treated patients was 27.5% (95%CI, 21.2%-33.8%) and 37.1% (95% CI, 35.5%-38.7%) in the non-tocilizumab treated patients. The risk difference was 9.6% (95%CI, 3.1%-16.0%). In the study conducted by Horby et al including 4116 patients from the United Kingdom, the risk ratio was 0.85 (95% CI: 0·76–0·94, p=0.0028) for 28 days mortality.[8] In the study conducted by Sanz including 1229 patients from Spain, patients who received tocilizumab and had baseline CRP levels above 150 mg/L experienced lower rates of death (adjusted Hazard Ratio=0.34, 95% CI; 0.17- .71, p=0.005) and ICU admission/death (aHR=0.39, 95% CI 0.19–0.80, p=0.011) than those who did not receive tocilizumab.[10] Similar results were seen in the study conducted by Andrew et al involving 2512 patients from New Jersey.[11] The adjusted Hazard Ratio for 30-day mortality rate was 0.76 (95% CI: 0.57-1.00, p=0.053). In Guaraldi's study, a significant reduction in the death rate was found in patients on tocilizumab treatment compared with standard of care treatment.[13] The adjusted Hazard Ratio was 0.38 (95% CI: 0.17–0.83; p=0.015). In Biran's study, among the propensity score matched population who required mechanical ventilation, patients who received tocilizumab had reduced mortality.[14] The hazard ratio was 0.63 (95% CI 0.46–0.85; p=0.0029). The results of Salama's study was also in accordance with the above studies.[16] The percentage of patients who had received mechanical ventilation or who had died by day 28 was significantly lower in the tocilizumab group than in the placebo group. The hazard ratio was 0.56 (95% CI, 0.33 to 0.97; p=0.04).

Limitations

Our study had two limitations. One, not all studies were randomised controlled trials, which paves for the risk of bias. Two, in some studies taken, tocilizumab was used in combination with other drugs like corticosteroids, antivirals. Hence the results of such studies could not be solely attributed to tocilizumab. Further studies in future overcoming these limitations will benefit with even more accurate results.

CONCLUSION

Among critically ill patients with COVID-19, the in-hospital mortality was significantly reduced in patients treated with tocilizumab during the first 2 days of ICU admission compared to patients those who were not

administered with tocilizumab in the early phase. Treatment with tocilizumab significantly reduces the mortality rate, increases the survival rate and lowers the risk of requiring invasive mechanical ventilation in all hospitalized COVID-19 patients.

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REFERENCES

1. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, et al. Immunology of COVID-19: Current State of the Science. Immunity. 2020;52(6):910-41.
2. Zhou F, Yu T, Du R. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-62.
3. Guan W-J, Ni Z-Y, Hu Y. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20.
4. Nicastri E, D'Abramo A, Faggioni G. Coronavirus disease (COVID-19) in a paucisymptomatic patient: epidemiological and clinical challenge in settings with limited community transmission, Italy, February 2020. Euro Surveill. 2020;25:2000230.
5. Srikumar S, Perumal S. A systematic review of immune pathogenesis of SARS-COV-2 infection. Int J Adv Med. 2021;8:978-83.
6. Hennigan S, Kavanaugh A. Interleukin-6 inhibitors in the treatment of rheumatoid arthritis. Ther Clin Risk Manag 2008;4: 767–75.
7. Gupta S, Wang W, Hayek SS. Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19 [published correction appears in JAMA Intern Med. 2021;181(4):570.
8. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637-45.
9. Narain S. Comparative Survival Analysis of Immunomodulatory Therapy for COVID-19 'Cytokine Storm': A Retrospective Observational Cohort Study. Northwell COVID-19 Research Consortium.
10. Martínez-Sanz J, Muriel A, Ron R. Effects of tocilizumab on mortality in hospitalized patients with COVID-19: a multicentre cohort study. Clin Microbiol Infect. 2021;27(2):238-43.
11. Ip A, Berry DA, Hansen E. Hydroxychloroquine and tocilizumab therapy in COVID-19 patients-An observational study. PLoS One. 2020;15(8):e0237693.
12. Gordon AC, Mouncey PR. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021;384(16):1491-502.
13. Guaraldi G, Meschiari M, Cozzi-Lepri A. Tocilizumab in patients with severe COVID-19: a retrospective cohort study [published correction appears in Lancet Rheumatol. 2020;2(10):e591.
14. Biran N, Ip A, Ahn J. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. Lancet Rheumatol. 2020;2(10):e603-12.
15. Rosas IO, Bräu N, Waters M. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 2021;384(16):1503-16.
16. Salama C, Han J, Yau L. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021;384(1):20-30.
17. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses—drug discovery and therapeutic options. Nature Rev Drug Disc. 2016;15(5):327-47.
18. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Møller R, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell. 2020;181(5):1036-45.
19. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39:529-39.
20. Huang C, Wang Y, Li X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
21. Swerdlow DI, Holmes MV, Kuchenbaecker KB. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. Lancet. 2012;379:1214-24.
22. Toniati P, Piva S, Cattalini M. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure. Autoimmun Rev. 2020;19(7):102568.
23. Guaraldi G, Meschiari M, Cozzi-Lepri A. Tocilizumab in patients with severe COVID-19. Lancet Rheumatol. 2020;2(8):e474-84.
24. Xu X, Han M, Li T. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad SciUSA. 2020;117(20):10970-5.
25. Morena V, Milazzo L, Oreni L. Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. Eur J Intern Med. 2020;76:36-42.
26. Capra R, De Rossi N, Mattioli F. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med. 2020;76:31-5.

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