Tocilizumab in patients hospitalized with COVID-19 pneumonia: systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Tocilizumab is an interleukin receptor inhibitor that has been used in patients with COVID-19 pneumonia. There are recent randomized controlled trials (RCTs) that evaluated the efficacy and safety of tocilizumab in hospitalized patients with COVID-19 pneumonia. We performed a systematic review and meta-analysis of RCTs that evaluated the effectiveness of tocilizumab in hospitalized patients with COVID-19 not requiring mechanical ventilation. RCTs comparing tocilizumab with the standard of care treatment in hospitalized patients with COVID-19 pneumonia not requiring mechanical ventilation at the time of administration were included for analysis. The primary outcome was a composite of mechanical ventilation or 28-day mortality and the secondary outcomes were 28-day mortality and major adverse events. A total of 6 RCTs were included for the analysis. Tocilizumab was associated with a statistically significant reduction in the primary composite outcome of mechanical ventilation or 28-day mortality (risk ratio (RR): 0.83 (95% CI: 0.74 to 0.92, I^2=0, tau^2=0). Treatment with tocilizumab did not show a statistically significant reduction in 28-day mortality (RR: 0.90 (95% CI: 0.76 to 1.07), I^2=0, tau^2=0) and rate of serious adverse events (RR: 0.82 (95% CI: 0.62 to 1.10), I^2=0, tau^2=0). Tocilizumab was associated with a decrease in the incidence of primary outcome, that is, mechanical ventilation or death at 28 days in hospitalized patients with COVID-19 pneumonia.

Significance of this study

What is already known about this subject?

► A review of ClinicalTrials.gov revealed that as of April 2021, there are currently 18 clinical trials underway that attempt to study the effect of tocilizumab alone or in combination with other medications in patients with COVID-19.

What are the new findings?

► Tocilizumab use improved the composite primary outcome of mechanical ventilation or 28-day mortality without an increase in the rate of serious adverse events.

How might these results change the focus of research or clinical practice?

► Our review concluded that there is enough evidence to advocate for the routine clinical use of Tocilizumab in patients with COVID-19 pneumonia who are not on mechanical ventilation.

INTRODUCTION

Tocilizumab is a humanized monoclonal antibody that competitively inhibits the interleukin-6 (IL-6) receptor. The Food and Drug Administration first approved tocilizumab for the treatment of rheumatoid arthritis in 2008. Since then, it has been further approved for the treatment of multiple inflammatory conditions, including juvenile idiopathic arthritis, giant cell arteritis, and cytokine release syndrome (CRS).[1]

COVID-19 infection leads to a dysregulated inflammatory state in patients. There is increased release of pro-inflammatory cytokines, including IL-6, IL-1 beta, tumor necrosis factor, and granulocyte monocyte colony-stimulating factor. This CRS leads to an inflammatory cascade and downstream tissue damage despite downtrending viral load.[2] It is the CRS that is responsible for the development of acute respiratory distress syndrome in patients with COVID-19 pneumonia and not the virus itself. There is increasing evidence to suggest that elevated levels of IL-6 and other pro-inflammatory cytokines can predict the severity of the disease and prognosis in patients with COVID-19 pneumonia. Patients with IL-6 levels higher than 55 pg/mL are at higher risk of developing severe disease, and levels higher than 80 pg/mL are associated with a higher risk of mortality.[3] Hence, interleukin blockade can be employed as a strategy to prevent worsening disease in patients with COVID-19 pneumonia.[4]

In our study, we aimed to perform a systematic review and meta-analysis of randomized controlled trials (RCTs) that evaluated the effectiveness of tocilizumab in hospitalized patients with COVID-19 not requiring mechanical ventilation

METHODOLOGY

Literature search

We carried out an electronic search in Medline (PubMed), Embase, Google Scholar, and Cochrane database using the keywords/Medical Subject Heading (MeSH) terms: "Tocilizumab", "IL-6 inhibitor", "coronavirus", and 'COVID-19' until April 19, 2021 (online supplemental file 1). The search also included unpublished articles and conference abstracts. The search included articles in all languages.

Selection of studies

We applied the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement to the methods of this study. After duplication was removed, the title and abstracts were independently screened by 2 authors (SG and RPP). RCTs comparing tocilizumab with the standard of care treatment (steroids, antibiotics, and antivirals) in hospitalized patients with COVID-19 pneumonia not requiring mechanical ventilation at the time of administration were included for secondary analysis. Meta-analyses, systematic reviews, observational studies, single-arm trials, non-randomized trials, RCTs studying a combination of tocilizumab with other drugs, and RCTs performed in patients <18 years of age were excluded. RCTs not reporting primary outcome (incidence of mechanical ventilation/death within 28 days), RCTs with the primary outcome reported at less than 28 days, and RCTs not reporting primary outcome separately in non-mechanically ventilated patients were excluded from the analysis. Full texts of the included studies were then reviewed independently by the 2 authors (SG and RPP) and the data were extracted. Any discrepancies were resolved by the consensus of the authors. To ensure that no potentially important studies were missed, the reference lists from the retrieved articles were also checked. Quality assessment of the selected studies was performed by 2 authors separately (SG and AB) using V.2 of the Cochrane risk-of-bias tool for RCTs (RoB 2) and was categorized into either 'low risk of bias' (high quality) or 'high risk of bias' (low quality).[5]

Data extraction

The following data variables were collected: median age, gender, C reactive protein level, D-dimer level, ferritin level, IL-6 level, percentage of patients receiving systemic steroids, and percentage of patients receiving antiviral medications. The primary outcome was chosen to be a composite of mechanical ventilation or 28-day mortality. The secondary outcomes were selected to be 28-day mortality and major adverse events.

Statistical analysis

We used the Mantel-Haenszel method with Paule-Mandel estimator for tau^2, Hartung-Knapp adjustment for the random-effects model, and Q-profile method for the CI of tau^2 and tau to calculate risk ratio (RR) with 95% CI. The I^2

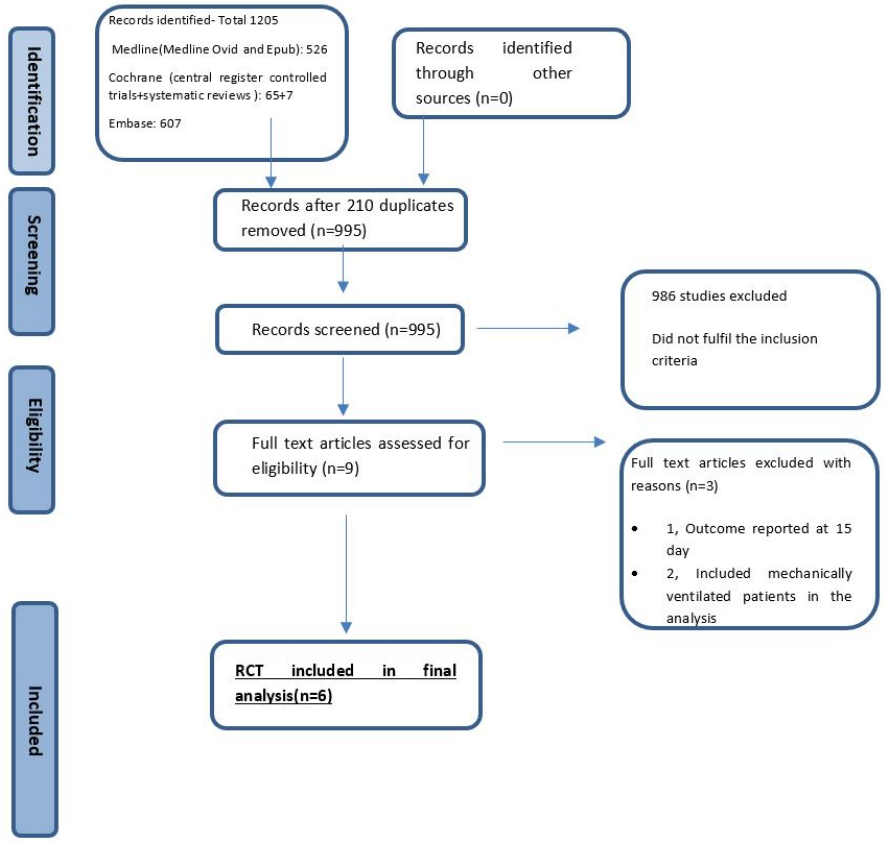

Figure 1 PRISMA flow chart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial.

Table 1 Baseline characteristics and outcomes of the patient population included in the trials

Characteristics	Salama *et al*[9]	Stone *et al*[10]	Hermine *et al*[11]	Salvarani *et al*[12]	Horby *et al*[13]*	Rosas *et al*[14]*
Type of study	Double blinded	Double blinded	Open label	Open label	Open label	Double blinded
Country	USA	USA	France	Italy	UK	USA
Sample size (T/C)	377 (249/128)	242 (161/81)	130 (63/67)	123 (60/63)	4116 (2022/2094)† 1868 (935/933) (without ventilation)	438 (294/144)† 183/90 (without ventilation)
Population distribution	Hispanic—56% Others—3.7%	Hispanic—45% Non-Hispanic—49% Others-—6%	NA	NA	NA	White—59.9 (T)/52.8 (C) Black—13.6 (T)/18.1 (C)
Mean/median age (years)	T—56.0±14.3 C—55.6±14.9	T—61.6 (46.4–69.7) C—56.5 (44.7–67.8)	T—64.0 (57.1–74.3) C—63.3 (57.1–72.3)	T—61.5 (51.5–73.5) C—60.0 (54.0–69.0)	T—63.3 C—63.9	T—60.9±14.6 C—60.6±13.7
Gender (female %)	T—39.8, C—43	T—40, C—45	T—30, C—34	T—33.3, C—43.9	T—34, C—31	T—30.3, C—29.9
Body mass index (BMI)	T—32.0±7.9 C—33.1±7.2	T—29.9 (26.0–34.2) C—30.2 (25.7–33.8)	T—27.9 (23.3–30.8) C—27.4 (24.5–31.3)	T— ≥30–38 (32.2%) C —≥30–16 (28.1%)	NA	NA
Non-smoker (%)	T—77.1, C—77.3	T—61, C—59	T—90, C—93	NA	NA	NA
CRP (mg/L)	T—124.50 (2.5–2099.0) C—143.40 (9.0–3776.0)	T—116.0 (67.1–190.6) C—94.3 (58.4–142.0)	T—119.5 (74.5–219.5) C—127.0 (84.0–171.0)	T—10.5 (5.0–14.6) C—6.5 (3.2–11.8)	T—143 (107–203) C—144 (106–205)	T—157.2 (1.1–446.6) C—150.3 (1.6–499.6)
D-dimer (ng/mL)	T—800 (100–4,436,000) C—605 (100–5,192,000)	T—857 (536–1695) C—980 (500–1739)	T—869 (524–1380) C—1250 (780–1812)	T—756 (480–1070) C—455 (326–0810)	NA	NA
Ferritin (mg/L)	T—623 (13–17,491) C—615 (49–55,603)	T—723 (413–1212) C—686 (382–1228)	T—1292 (424–2484) C—1070 (563–1790)	T—646.0 (289.2–1107.5) C—533.5 (351.0–1184.0)	T—947 (497–1599) C—944 (507–1533)	T—1023.59 (0.0–737,427.68) C—979 (44.5–228,749.44)
IL-6 (ng/L)	NA	T—23.6 (14.0–49.9) C—25.4 (14.6–40.3)	NA	T—50.4 (28.3–93.2) C—34.3 (19.0–59.3)	NA	T-—88.1 (3.1–4020) C—71.2 (3.1–2810)
Patient % who received systemic steroids	80.3 (T), 87.5 (C)	11 (T), 6 (C)	30 (T), 55 (C)	Yes	82 (T), 82 (C)	36.1 (T), 54.9 (C)
Patient % who received anti-viral	78.7 (T) 78.9 (C)	33 (T) 29 (C)	2 (T) 6 (C)	Yes	3 (T) 3 (C)	29.6 (T) 35.4 (C)
Follow-up (days)	60	28	28	30	28	28
MV/death at 28 day (HR, 95% CI), p value	0.56 (0.33 to 0.97), 0.04	0.66 (0.28 to 1.52), 0.64	0.58 (0.26 to 1.23), 0.80	1.05 (0.59 to 1.86), 0.87	0.85 (0.78 to 0.93), 0.0005	0.614 (0.40 to 0.94), 0.03
Death n/N, %	T—26/249, 10.4 C—11/128, 8.6 Weighted difference, 2.0 percentage points; 95% CI: –5.2 to 7.8	T—9/161, 5.6 C—3/81, 3.8 HR 1.52 (0.41 to 5.61)	T—7/63, 11.1 C—8/67, 11.9 , HR 0.92; 95% CI: 0.33 to 2.53	T—3/60, 3.3 C—1/63, 1.6 Rate ratio (95% CI) 2.10 (0.20 to 22.6)	T—571/1754, 33 C—687/1800, 38 RR (95% CI) 0.84 (0.69 to 1.03)	T—58/294, 19.7 C—28/144, 19.4 0.3 (–7.6 to 8.2) 0.94
Overall risk of bias	Low	Low	Low	Low	Low	Low
Quality of evidence (grade)	High	High	Moderate	Moderate	Moderate	High

*RCTs included population with or without mechanical ventilation, reported baseline characteristics and inflammatory markers including all patients; however, reported outcome of MV/death and mortality in last two rows include only non-intubated patients.
†Total population including intubated and non-intubated.
C, control group; CRP, C reactive protein; IL-6, interleukin 6; MV, mechanical ventilation; NA, not available; n/N, number of events/total number; T, treatment group.

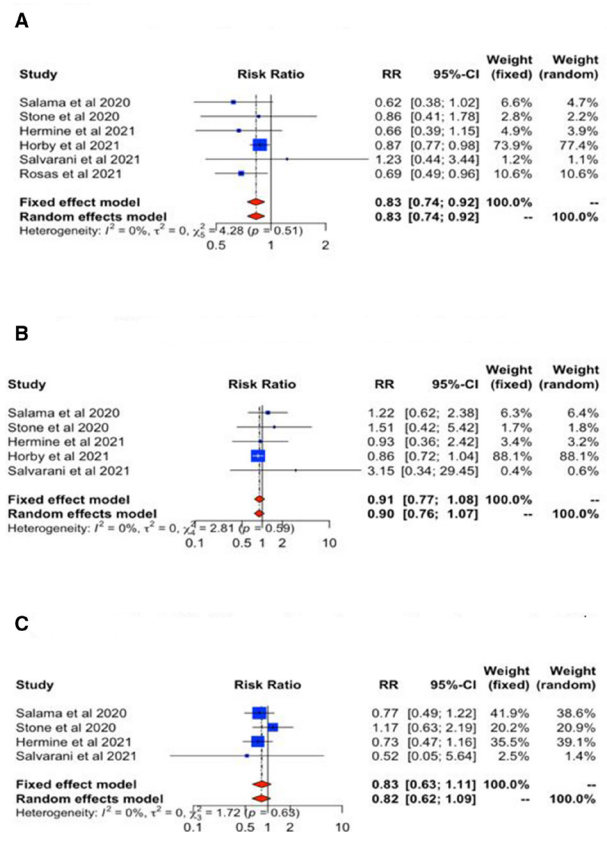

Figure 2 (A) Forest plot of the primary outcome, mechanical ventilation/death at 28 days; (B) forest plot of the secondary outcome, death at 28 days; (C) forest plot of the secondary outcome, serious adverse events at 28 days.

statistic was used to assess the heterogeneity between studies with values 0%–30%, more than 30%–60%, and more than 60% corresponding to low, moderate, and a high degree of heterogeneity, respectively. Funnel plots and Egger's regression test were used to assess publication bias. All statistical analyses were performed using R V.4.0.3.

RESULTS

A total of 1205 studies was compiled from all the sources. Duplicate references were removed and 995 citations were reviewed for abstract screening. Subsequently, 986 studies were excluded and 9 RCTs fulfilled the above inclusion criteria and underwent full-text screening. Three RCTs (REMAP-CAP, COVINTOC, TOCIBRAS) were excluded.[6–8] REMAP-CAP and COVINTOC trials did not report outcomes separately for non-mechanically ventilated patients and were excluded from the analysis. TOCIBRAS reported outcomes at day 15 and was thus excluded (figure 1). A total of 6 RCTs comparing tocilizumab with the standard treatment (steroids, antibiotics, and antivirals) in hospitalized patients with COVID-19 pneumonia not requiring mechanical ventilation at the time of administration of the medication were selected for final analysis. All 6 studies were categorized into low risk of bias as per the Cochrane RoB 2.

Four of the 6 trials were done exclusively in hospitalized patients with COVID-19 pneumonia not requiring mechanical ventilation.[9–12] Two trials were done in all patients hospitalized with COVID-19 pneumonia, irrespective of their mechanical ventilation status. However, in these trials, outcomes were reported separately for patients not requiring mechanical ventilation, and this specific subgroup was included in the review.[13 14]

A total of 3013 (1651 and 1362 in treatment and control groups, respectively) patients were included in the analysis, from 6 RCTs. Clinical characteristics and outcomes of the patients for the included studies are summarized in table 1. On analyzing the data from all 6 RCTs, the incidence of mechanical ventilation or death at 28 days was 25.9% (429 of 1651) and 33.4% (456 of 1362) in the treatment and control groups, respectively. Furthermore, the mortality at 28 days was 14.98% (220 of 1468) and 17.68% (225 of 1272) in the treatment and control group, respectively. Tocilizumab was associated with a statistically significant reduction in the primary composite outcome of mechanical ventilation or 28-day mortality (RR: 0.83 (95% CI: 0.74 to 0.92, I^2=0, tau^2=0) (figure 2A). However, treatment with tocilizumab did not show a statistically significant reduction in 28-day mortality (RR: 0.90 (95% CI: 0.76 to 1.07), I^2=0, tau^2=0) (figure 2B).There was no significant difference in the rate of serious adverse events between the two groups (RR: 0.82 (95% CI: 0.62 to 1.10), I^2=0, tau^2=0) (figure 2C). For all the included outcomes, there was no heterogeneity across studies. Visual inspection of the funnel plot for the primary outcome (ie, mechanical ventilation or all-cause mortality) (figure 3A) showed no significant publication bias, which was confirmed using Egger's regression test (p=0.385). The funnel plots for the secondary outcome are depicted in figure 3B,C.

DISCUSSION

Prior attempts at systematic reviews to determine the safety and efficacy of tocilizumab in hospitalized patients with COVID-19 were limited by the availability of high-quality RCTs and had to resort to including data from retrospective studies. Hence, due to these limitations, the conclusions have been heterogeneous. Our systematic review including 6 large multicenter RCTs demonstrates a clinically significant benefit to using tocilizumab in hospitalized patients with COVID-19 pneumonia, with a number needed to treat of 13 for the reduction of the primary outcome, that is, composite of mechanical ventilation or 28-day mortality. There was no distinct benefit to the reduction of 28-day mortality in our analysis. Our efforts were limited by the small sample sizes of some of the studies as well as the heterogenicity of the control group where the interventions in the control group were not standard across the board. This reduces the validity of head-to-head comparisons. However, improvements in the primary outcome in the pooled analysis remain valid, and with this, we propose the use of tocilizumab in hospitalized patients with COVID-19 pneumonia who are not on mechanical ventilation.

Our study is limited by the fact that the primary outcome measures of all the trials were not uniform across the board. There was heterogeneity in the sampled groups and outcomes. There was only limited availability of subgroup-specific data (for example, mechanical ventilation or not) for some of the trials hence they had to be excluded. Besides,

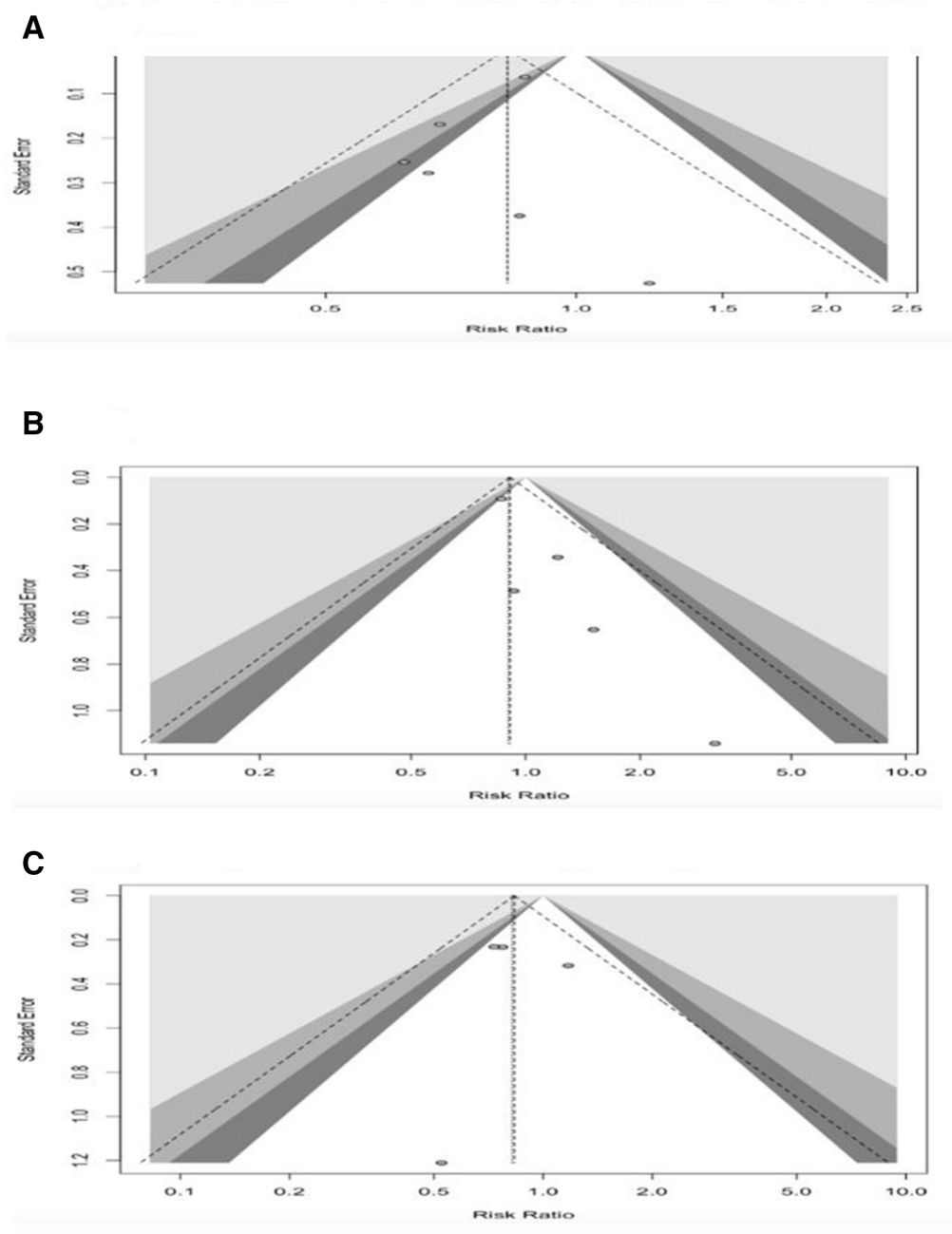

Figure 3 (A) Funnel plot for mechanical ventilation/death at 28-day, Egger's test, p=0.385; (B) funnel plot for 28-day mortality, Egger's test, p=0.040; (C) funnel plot for serious adverse events, Egger's test, p=0.990.

it can be argued that our selected primary composite outcome of mechanical ventilation or 28-day mortality, even though is clinically relevant, may not be an accurate representation of all of the downstream effects of blocking a cytokine-mediated inflammatory pathway. We need more long-term follow-ups of patients to see how the development of long-term sequelae of COVID-19 infection, such as multisystem inflammatory syndrome in adults, lung fibrosis, etc, are affected by the medication. Also, cytokine-mediated inflammation is not the sole reason for the morbidity and mortality in COVID-19 infections. There is a definite contribution from COVID-19-related coagulopathy, which can be specially compounded by immobilization and prolonged hospitalization. The difference in mortality from these conditions may not be truly reflected in a one-time outcome measure of 28-day mortality, which has been suggested as being not a valuable outcome measure in critical illnesses.[15]

Even though our review did not reveal a significant change in the rate of adverse events across patients who received tocilizumab as compared with placebo, it should be assumed that blocking an inflammatory cascade will increase the propensity of the patient to develop infections. There are concerns of super-added infections in patients with COVID-19, especially if they are also on concomitant steroid therapy. The attributable risk to these super-added

infections may not be evident during the analysis of a disease condition like COVID-19 pneumonia which by itself has a high mortality rate. Hence, the rates of secondary infections will need to be followed over a longer period of time.

A single 600 mg infusion of tocilizumab (at the Centers for Disease Control and Prevention-recommended dose of 8 mg/kg) for the average person costs US$3624.[16] Hence, advocating the routine clinical use of tocilizumab requires a major financial commitment from the health system. There may be a role in patient stratification and reserving the medication only for those patients who are at higher risk of worsening. Some experts propose the selection of patients with elevated IL-6 levels for administration of tocilizumab.[17] Even though this conclusion has a strong pathophysiological basis, there are practical implications for routine clinical use of IL-6 levels, due to high laboratory turnaround time, and the fact that treatment for this CRS is time-sensitive, and early intervention is crucial.

CONCLUSION

A review of ClinicalTrials.gov revealed that as of April 2021, there are currently 18 clinical trials underway that attempt to study the effect of tocilizumab alone or in combination with other medications in patients with COVID-19. As more evidence becomes available, the question of patient selection and adverse events will become clearer. However, our present analysis with available data so far demonstrates a definite benefit to suggest routine clinical use of tocilizumab in patients with COVID-19 who are not on mechanical ventilation.

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