

MORTALITY COMPARISON OF USING ANTI INTERLEUKIN-6 THERAPY AND USING STANDARD TREATMENT IN SEVERE COVID-19

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ABSTRACT

Severe Coronavirus Disease 19 (COVID-19) can cause serious lung inflammation and death. COVID-19 has been characterized by a very high mortality rate. This severity is associated with the overproduction of proinflammatory cytokines called "cytokine storms". One of the cytokines that play a central role is Interleukin-6 (IL-6). High IL-6 levels are associated with mortality. It is hoped that the IL-6 blockade can reduce cytokine storms and thus reduce deaths in severe COVID-19 patients. The aim of this systematic review was to summarize the comparison of mortality from using anti-IL-6 therapy with using standard treatment in severe COVID-19 patients. We systematically searched the PubMed, ScienceDirect, and ProQuest database until 13 August 2020. After screening, twelve studies matched the inclusion criteria. The mortality of the anti IL-6 therapy group was lower than the standard treatment group without anti IL-6 therapy in COVID-19 patients in 10 of the 12 studies obtained. Four of the ten studies found a statistically significant difference in mortality between the anti IL-6 therapy group and the standard treatment group. Confirmation of anti IL-6 therapy effectiveness in reducing mortality in severe COVID-19 patients will require randomized controlled trials.

Keywords: covid-19; SARS-CoV-2; terapi anti IL-6; inhibitor IL-6; mortality

ABSTRAK

Coronavirus Disease 19 (COVID-19) yang parah dapat menyebabkan peradangan paru-paru berat hingga kematian. Kematian pada COVID-19 ini cukup tinggi. Tingkat keparahan ini terkait dengan produksi berlebihan sitokin proinflamasi yang disebut "badai sitokin". Salah satu sitokin yang berperan sentral adalah Interleukin-6 (IL-6). Kadar IL-6 yang tinggi berhubungan dengan kematian. Blokade IL-6 diharapkan dapat meredam badai sitokin sehingga mengurangi kematian pada pasien parah COVID-19. Tujuan dari systematic review ini adalah untuk merangkum perbandingan kematian pada penggunaan terapi anti IL-6 dengan penggunaan pengobatan standar pada pasien COVID-19 berat. Pencarian literatur secara sistematis di database Proquest, PubMed, dan Science Direct hingga 13 Agustus 2020. Setelah dilakukan screening, didapatkan dua belas studi yang sesuai dengan kriteria inklusi. Kematian kelompok terapi anti IL-6 lebih rendah daripada kelompok pengobatan standar tanpa terapi anti IL-6 pada pasien COVID-19 pada 10 dari 12 studi yang didapatkan. Empat dari sepuluh studi tersebut mendapatkan perbedaan kematian yang secara statistik signifikan antara kelompok terapi anti IL-6 dan kelompok pengobatan standar. Konfirmasi efektivitas terapi anti IL-6 dalam mengurangi kematian pada pasien COVID-19 yang berat memerlukan uji coba terkontrol secara acak.

Kata kunci: covid-19; SARS-CoV-2; terapi anti IL-6; inhibitor IL-6; mortalitas

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread widely around the world (Ge et al 2020). People with COVID-19 can have a wide range of symptoms, from mild symptoms to severe illness (CDC 2020). In severe cases, SARS-CoV-2 virus can cause serious lung inflammation, acute respiratory distress syndrome (ARDS), multi-organ failure, and death (Tufan et al 2020; Zhou et al 2020). COVID-19 has been characterized by a high mortality rate. The main cause of death was interstitial pneumonia with respiratory failure (De Rossi et al 2020).

The severity of COVID-19 patients associated with the excessive production of pro-inflammatory cytokines called "cytokine storms". The cytokine storm will cause shock, respiratory failure, multiple organ failure, and finally lead to death in severe COVID-19 cases. These pro-inflammatory cytokines are IFN- α , IFN- γ , IL-1 β , IL-2, IL-6, IL-12, TNF- α , and others (Tufan et al 2020, Li et al 2020). From these pro-inflammatory cytokine, interleukin-6 (IL-6) plays a key role in the pathogenesis of the COVID-19 related cytokine storm (Coperchini et al 2020).

High IL-6 levels are often found in severe COVID-19 patients (Antwi-Amoabeng et al 2020). Elevated serum IL-6 correlates with respiratory failure, ARDS, and adverse clinical outcomes (Moore & June 2020). Moreover, IL-6 is significantly associated with mortality (Klopfenstein T et al 2020). IL-6 blockade is a promising strategy for COVID-19 related cytokine storm (Liu et al 2020). Therefore, this study was conducted to review the comparison of mortality from using anti-IL-6 therapy with using standard treatment in severe COVID-19 patients.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We systematically searched the PubMed, ScienceDirect, and ProQuest database until 13 August 2020. The key terms searched were "Mortality" AND ("COVID-19" OR "SARS-CoV-2") AND ("Anti IL-6 therapy" OR "IL-6 inhibitor" OR "Tocilizumab" OR "Sarilumab").

We retrieved all the studies comparing the mortality of the anti IL-6 therapy and control group for severe COVID-19 patients. We excluded preprints that were yet to undergo peer-review, case reports, review, editorials, correspondences, and commentary types of

articles, studies that did not report mortality outcomes with anti IL-6 therapy in severe COVID-19, and studies that did not compare mortality outcomes for anti IL-6 therapy compared with placebo or control.

Furthermore, the extracted relevant data from all the retrieved studies were collected and tabulated using Microsoft Excel. The extracted information included the name of the first author, title, study design, study site, patients demographic characteristics, the regimen of anti IL-6 therapy and comparative agents, and mortality outcome.

RESULTS

Search Results

The search strategy initially resulted 1187 articles. After removing 78 duplicates, 1109 articles were subsequently screened by title and abstract. Finally, 37 articles were identified for full-text review for eligibility. Twelve retrospective studies were designed to compare the mortality outcome for anti IL-6 therapy and its comparators in the treatment of severe COVID-19 patients, thus were included in this systematic review (Figure 1).

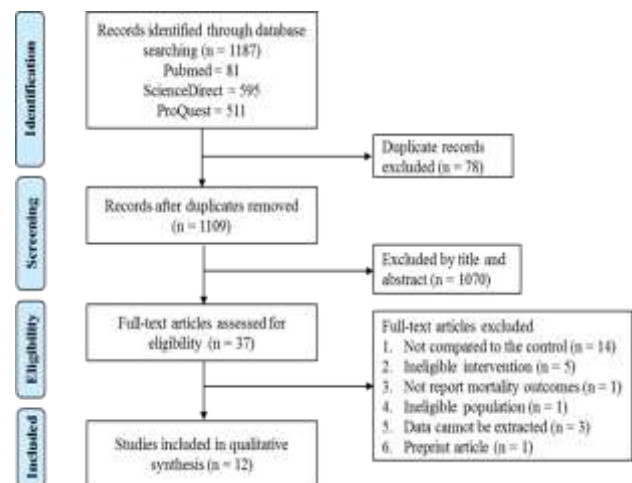


Figure 1. Flow diagram of study selection

Characteristics of the Involved Studies

The characteristics of the included studies are shown in Table 1. Six studies were conducted in Italy. The remaining 6 studies were from USA (n=3), France (n=2), and Spain (n=1). In addition, only 2 studies were multicenter and the remaining 10 studies were single-center. The included studies had a wide range of sample sizes from 45 to 544. The median/mean ages of subjects were above 50 years old in all studies. Except for one

study that used sarilumab, eleven studies used tocilizumab as an anti IL-6 regimen. Tocilizumab 400 mg or 8 mg/kg intravenously was the most commonly reported regimen of tocilizumab.

Mortality Outcome

The mortality data in the articles among severe COVID-19 patients are summarized in Table 1. The reported mortality of COVID-19 patients with anti IL-6 therapy from the included studies were very broad and ranged from 3.22% to 52%. While, the mortality in the control group ranged from 1.9% to 62%. In twelve retrospective studies, ten of the twelve studies found that mortality was lower in the anti IL-6 therapy compared to the control group. Four of the ten studies found a lower mortality in the anti IL-6 therapy which was statistically significant. This supports the reduction in mortality from the use of anti IL-6 therapy, especially in the study conducted by Guaraldi et al (2020) which had a large enough sample of 544 patients ($p = 0.0007$).

Meanwhile, in six of the ten studies, there were no significant differences in mortality. However, mortality was lower in the group receiving anti IL-6 therapy. Interestingly, the two Klopfenstein et al's (2020) study found that the combined primary endpoint (death and/or ICU admission; mortality and/or IMV requirement) was lower in the Tocilizumab group which was statistically significant even though the patients in the Tocilizumab group had a more severe condition. In addition, in the study by Rojas-Marte et al (2020), mortality was significant lower in the Tocilizumab group when the intubated patients were excluded. A study conducted by Canziani et al (2020) had a significant lower risk of invasive ventilation at 30 days in the Tocilizumab group.

Table 1. Characteristics of included studies

Reference	Study design (study site)	Age		Comorbidity		Inclusion criteria	Regimen		Findings
		Anti IL-6	Control	Anti IL-6	Control		Anti IL-6 (no. of patients)	Control (no. of patients)	
De Rossi et al. (Early use of low dose tocilizumab in patients with COVID-19: A retrospective cohort study with a complete follow-up)	Retrospective cohort study (Single center in Italy)	62.9 ± 12.5	71 ± 14.6	Hypertension (45.5%), heart disease (12.2%), DM (15.5%)	Hypertension (42.9%), heart disease (32.3%), DM (30.9%)	Bilateral pulmonary interstitial opacities, respiratory failure showing at least one of the following conditions: RR ≥ 30 x/min; SpO2 ≤ 93% while breathing ambient air, or; PaO2/FiO2 ≤ 300 mmHg (only patients with COVID-19 pneumonia in the early stages of respiratory failure)	Tocilizumab 400 mg i.v. (n = 43), 324 mg s.c. (n = 47) Hydroxychloroquine 400 mg daily, lopinavir 800 mg daily plus ritonavir 200 mg per day (n = 68)	>>The control group were older and with higher prevalence of comorbidities; whereas the Tocilizumab group were admitted to the hospital later during the disease course. >>Mortality was lower in the Tocilizumab group (7.7%) than in the control group (50%) which was statistically significant (p <0.001).	
Campochiaro et al. (Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study)	Retrospective cohort study (Single center in Italy)	64 [53-75]	60 [55-75.5]	Hypertension (37%), CAD (12%), DM (18%), COPD (3%), cancer (6%), CKD (9%), smoking (0%)	Hypertension (48%), CAD (18%), DM (18%), COPD (6%), cancer (3%), CKD (15%), smoking (6%)	Hyper-inflammation defined as elevation in either CRP, ferritin, or LDH; severe respiratory involvement defined by typical radiological findings at chest X-ray and/or CT scan, SpO2 ≤ 92% while breathing ambient air, or PaO2/FiO2 ≤ 300 mmHg	Tocilizumab 400 mg i.v. once (n = 23), second dose of 400 mg of tocilizumab was given after 24 hours in case of respiratory worsening (n = 9) Hydroxychloroquine 400 mg daily, lopinavir/ritonavir 400/100 mg twice daily, ceftriaxone 2 gr for 6 days, anti-coagulation prophylaxis with enoxaparin 4000 UI s.c. once a day (n = 33)	>>At day 28, mortality was lower in the Tocilizumab group (16%) than in the control group (33%), but not statistically significant (p = 0.150). >>In the Tocilizumab group, older age was a predictor of mortality, whereas a higher baseline PaO2/FiO2 was a predictor of clinical improvement.	
Moreno-Pérez et al. (Experience with tocilizumab in severe COVID-19 pneumonia after 80 days of follow-up: A retrospective cohort study)	Retrospective cohort study (Single center in Spain)	62 [53-72]	57 [44-70]	Hypertension (41.6%), cardiovascular disease (7.8%), DM (20.8%), chronic respiratory disease (14.3%), obesity (34.7%), immunosuppression (5.2%) CCI: 2 [1-3]	Hypertension (40.3%), cardiovascular disease (8.2%), DM (16.4%), chronic respiratory disease (16.5%), obesity (35.5%), immunosuppression (10.1%) CCI: 2 [0-4]	Maximum care population (ICU and intubation as needed)	Tocilizumab 600 mg, with a second or third dose (400 mg) in case of persistent or progressive disease (n = 77) Hydroxychloroquine, lopinavir/ritonavir, and azithromycin (n = 159)	>>Tocilizumab group clearly differed at admission in fever and dyspnea, worse respiratory function, higher inflammatory parameters, more frequent extensive lung opacities, and lower lymphocytes count. >>Mortality was lower in the control group (1.9%) than in the Tocilizumab group (12.8%) which was statistically significant (p = 0.0001).	
Capra et al. (Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia)	Retrospective observational study (Single center in Italy)	63 [54-73]	70 [55-80]	Hypertension (46%), heart disease (14%), DM (14%)	Hypertension (48%), heart disease (26%), DM (22%)	RR ≥ 30 x/min, SpO2 ≤ 93% while breathing ambient air, PaO2/FiO2 ≤ 300 mmHg	Tocilizumab 400 mg i.v. once (n = 33), 324 mg s.c. once (n = 27) atau 800 mg i.v. (n = 2) 23)	>>Mortality was lower in the tocilizumab group (3.22%) than in the control group (47.8%). >>The Tocilizumab group showed significantly greater survival rate compared to the control group, adjusting for age, comorbidities and PCR baseline levels (p = 0.0004).	

Table 1. Characteristics of included studies (continued)

Reference	Study design (study site)	Age		Comorbidity		Inclusion criteria	Regimen		Findings
		Anti IL-6	Control	Anti IL-6	Control		Anti IL-6 (no. of patients)	Control (no. of patients)	
Klopfenstein et al. (Impact of Tocilizumab on mortality and/or invasive mechanical ventilation requirement in a cohort of 206 COVID-19 patients)	Retrospective case-control study (Single center in France)	75.6 ± 11.3	74.3 ± 11	Hypertension (60%), cardiovascular disease (40%), DM (16.7%), COPD (10%), immunosuppression (10%), malignancy (13%), malnutrition (17%), obesity (13.3%)	Hypertension (51.1%), cardiovascular disease (47.7%), DM (28.4%), COPD (10.8%), immunosuppression (10.8%), malignancy (2.8%), malnutrition (6.8%), malnutrition (14.2%), obesity (11.9%)	Period since symptoms onset ≥ 5 days, oxygen therapy ≥ 4 L/min, ≥ 25% of lung damages on CT scan, and ≥ 2 parameters of inflammation or biological markers of mortality	Tocilizumab 8 mg/kg 1 doses (n = 3), or 2 doses (n = 27)	Hydroxychloroquine or lopinavir-ritonavir therapy or corticosteroids and antibiotics (n = 176)	>>The Tocilizumab group had worse biological findings (ferritin, D-dimer, LDH) and required a higher level of oxygen therapy than control group. >>Mortality was lower in the Tocilizumab group (27%) than in the control group (38%), but not statistically significant (p = 0.253). >>The combined primary endpoint (mortality and/or IMV requirement) was lower in the Tocilizumab group (27%) than in the control group (52%) which was statistically significant (p = 0.009).
Della-Torre et al. (Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study)	Retrospective cohort study (Single center in Italy)	56 (49-60)	57 (52-60)	Hypertension (21%), CAD (8%), type 2 diabetes (11%), COPD (4%), chronic renal failure (4%), dyslipidemia (14%), smoking (18%)	Hypertension (39%), CAD (14%), type 2 diabetes (21%), COPD (4%), chronic renal failure (8%), dyslipidemia (14%), smoking (18%)	Severe COVID-19 pneumonia (PaO ₂ /FiO ₂ < 300 mmHg) with hyperinflammation (elevated inflammatory markers and serum IL-6 levels)	Sarilumab 400 mg i.v. once (n = 28)	Hydroxychloroquine, lopinavir/ritonavir and azithromycin (n = 28)	>>Mortality was lower in the Sarilumab group (7%) than in the control group (18%), but not statistically significant (p = 0.42). >>The time to clinical improvement in patients with < 17% of consolidated lung was significantly shorter in the sarilumab group than in the control group.
Canziani et al. (Interleukin-6 receptor blocking with intravenous tocilizumab in COVID-19 severe acute respiratory distress syndrome: A retrospective case-control survival analysis of 128 patients)	Retrospective case-control study (Multicenter involving two hospitals in the Italy)	63 ± 12	64 ± 8	Hypertension (52%), active smoking (4%), coronary heart disease, type 2 diabetes, COPD CCI: 2.2 ± 1.4	Hypertension (52%), active smoking (7%), coronary heart disease, type 2 diabetes, COPD CCI: 2.7 ± 1.7	Clinical worsening in the previous 24 h with increasing need for oxygen or ventilatory support, elevated CRP, higher risk for mortality at blood tests, based on the odds ratios reported elsewhere	Tocilizumab 8 mg/kg i.v. once (n = 3), followed by a second dose 24 h later if no clinical worsening (n = 63)	Hydroxychloroquine 200 mg twice a day, lopinavir 400 mg + ritonavir 100 mg twice daily or danavir 800 mg + cobicistat 150 mg once a day, enoxaparin s.c. at prophylactic dosage, glucocorticoids, and antibiotics (n = 64)	>>The 30-day mortality rate was lower in the Tocilizumab group (27%) than in the control group (38%), but not statistically significant (p = 0.185). >>The risk of invasive ventilation at 30 days was lower in the Tocilizumab group (17%) than in the control group (48%) in patients who were not receiving this respiratory support at baseline (p = 0.017).
Rojas-Martel et al. (Outcomes in patients with severe COVID-19 disease treated with tocilizumab: a case-controlled study)	Retrospective case-control study (Single center in USA)	58.8 ± 13.6	62.0 ± 14	Hypertension (55.2%), heart failure (7.3%), atrial fibrillation (4.2%), diabetes (30.2%), COPD (8.3%), asthma (4.2%), stroke (4.2%), active smoker (2.1%)	Hypertension (52.6%), heart failure (11.3%), atrial fibrillation (7.2%), diabetes (39.2%), COPD (3.1%), asthma (9.3%), stroke (3.1%), active smoker (0%)	Requiring oxygen supplementation via face mask up to 10 L/min, a non-rebreather mask, high-flow nasal cannula, or intubation and mechanical ventilation to maintain an oxygen saturation of 95% or higher	Tocilizumab 1 doses (n = 96)	Hydroxychloroquine, azithromycin, corticosteroid, full-dose anticoagulation, remdesivir, antibiotics for suspected bacterial infection, vasopressors (n = 97)	>>More patients in the Tocilizumab group reported fever, cough, shortness of breath, and presented with lower oxygen saturation; while the control group had higher BUN (blood urea nitrogen). >>Mortality was lower in the Tocilizumab group (52%) than in the control group (62%), but not statistically significant (p = 0.09). >>When the intubated patients were excluded, mortality was lower in the Tocilizumab group (6%) than in the control group (27%) which was statistically significant (p = 0.024).

Table 1. Characteristics of included studies (continued)

Reference	Study design (study site)	Age		Comorbidity		Inclusion criteria	Anti IL-6 (no. of patients)	Regimen Control (no. of patients)	Findings
		Anti IL-6	Control	Anti IL-6	Control				
Somers EC et al. (Tocilizumab for treatment of mechanically ventilated patients with COVID-19)	Retrospective observational study (Single center in USA)	55 ± 14.9	60 ± 14.5	Hypertension (64%), congestive heart failure (21%), chronic pulmonary disease (10%), asthma (20%), sleep apnea (23%), diabetes (13%), CKD (35%), chronic liver disease (1%), solid organ transplant (9%)	Hypertension (68%), congestive heart failure (26%), chronic pulmonary disease (28%), apnea (30%), diabetes (20%), CKD (49%), chronic liver disease (1%), solid organ transplant (3%)	Severe COVID-19 pneumonia requiring invasive mechanical ventilation	Tocilizumab 8 mg/kg (max 800 mg) once (n = 74), followed by a second dose (n = 4)	Hydroxychloroquine 600 mg every twelve hours x2 doses, then 200 mg every 8 hours. After 26 March 2020, hydroxychloroquine was formally removed from their guidelines (n = 76)	>>The Tocilizumab group were younger, less likely to have either chronic pulmonary disease, and chronic kidney disease; while median PaO2/FiO2 ratios were lower in the tocilizumab group. >>The 28-day mortality was lower in the Tocilizumab group (18%) than in the control group (36%), which was statistically significant (p = 0.01).
Kewan et al. (Tocilizumab for treatment of patients with severe COVID-19: A retrospective cohort study)	Retrospective cohort study (Single center in USA)	62 [53-71]	70 [55-75]	Hypertension (68%), CAD (7%), DM (39%), COPD (11%), asthma (18%), smoking (50%), obstructive sleep apnea (21%), SLE (4%)	Hypertension (74%), CAD (30%), DM (35%), COPD (13%), asthma (17%), CKD (13%), smoking (30%), obstructive sleep apnea (13%), RA (0%), SLE (0%)	Requiring supplemental oxygen for saturation of less than 94% while on ambient air	Tocilizumab 400 mg as a 60 min single intravenous infusion (n = 28)	Hydroxychloroquine with a loading dose of 400 mg twice daily followed by 200 mg per day twice daily for additional five days and azithromycin 500 mg per day for five days (n = 23)	>>The Tocilizumab group was sicker because more patients required invasive mechanical ventilation (75% vs 48%, p = 0.046). >>Mortality in the tocilizumab group compared to the control group was 11% and 9% (p = 1).
Guaraldi et al. (Tocilizumab in patients with severe COVID-19: a retrospective cohort study)	Retrospective cohort study (Multicenter involving three tertiary care centres in the Italy)	64 [54-72]	69 [57-78]	At the Modena centre only (n = 132): Hypertension (44.7%), cardiovascular disease (5%), diabetes (3%), chronic renal insufficiency (3%), cancer (4%)	At the Modena centre only (n = 222): Hypertension (14%), cardiovascular disease (5%), diabetes (3%), chronic renal insufficiency (3%), cancer (4%)	Severe pneumonia, defined as at least one of the following: RR ≥ 30 x/min, SpO2 ≤ 93% in room air, PaO2/FiO2 ≤ 300 mm Hg in room air, and lung infiltrates of more than 50% within 24-48 h	Tocilizumab 8 mg/kg i.v. (up to a maximum of 800 mg) administered twice, 12 h apart (n = 88). 162 mg s.c. in two simultaneous doses, one in each thigh (n = 91)	Hydroxychloroquine (400 mg 2x on day 1, followed by 200 mg 2x/day on days 2-5), azithromycin (500 mg/day for 5 days), lopinavir-ritonavir (400/100 mg 2x/day) or darunavir-cobicistat (800/150 mg 1x/day) for 14 days, and low molecular weight heparin for prophylaxis (n = 365)	>>The control group were older, whereas the Tocilizumab group had a lower PaO2/FiO2 ratio and a higher SOFA score. >>Mortality was lower in the Tocilizumab group (7%) than in the control group (20%), which was statistically significant (p = 0.0007). >>After adjustment for sex, age, recruiting centre, duration of symptoms, and SOFA score, tocilizumab treatment was associated with a reduced risk of invasive mechanical ventilation or death (p = 0.020).
Klopfenstein et al. (Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients)	Retrospective case-control study (Single center in France)	76.8 ± 11	70.7 ± 15	Hypertension (55%), cardiovascular disease (70%), DM (25%), COPD (20%), malignancy (35%), CCI: 5.3 ± 2.4	Hypertension (44%), cardiovascular disease (68%), DM (32%), COPD (4%), malignancy (8%), CCI: 3.4 ± 2.6	Failure of standard treatment, time to symptom onset > 7 days, oxygen therapy ≥ 5 L/min, > 25% of lung damages on CT scan, and ≥ 2 parameters of inflammation or biological markers of mortality	Tocilizumab 1 or 2 doses (n = 20)	Hydroxychloroquine or lopinavir-ritonavir therapy and antibiotics, and less commonly corticosteroids (n = 25)	>>Patients with Tocilizumab had a higher Charlson comorbidity index, higher level of oxygen therapy, and poorer biological findings (severe lymphopenia and CRP level). >>Mortality was lower in the Tocilizumab group (25%) than in the control group (48%), but not statistically significant (p = 0.066). >>The combined primary endpoint (death and/or ICU admission) was lower in the Tocilizumab group (25%) than in the control group (75%) which was statistically significant (p = 0.002).

CAD = coronary artery disease; CCI = Charlson comorbidity index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CT = computed tomography; DM = diabetes mellitus; i.v. = intravenous; ICU = intensive care unit; IL-6 = interleukin-6; IMV = invasive mechanical ventilation; LDH = lactate dehydrogenase; PaO2/FiO2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen; PCR = polymerase-chain-reaction; RA = rheumatoid arthritis; RR = respiratory rates; s.c. = subcutaneous; SLE = systemic lupus erythematosus; SOFA = sequential organ failure assessment; SpO2 = peripheral capillary oxygen saturation

DISCUSSION

In this study, we review the effect of anti IL-6 therapy in reducing severe COVID-19 mortality. Our findings supported the effectiveness of anti IL-6 therapy in the prevention or treatment of COVID-19 induced cytokine storms that lead to death. Ten of the twelve studies we reviewed found lower mortality in the anti IL-6 therapy than control group although not all of them were statistically significant. The low number of patients in the study probably explains that the difference in mortality was not significant because of the lack of statistical power.

IL-6 is one of the most important cytokines involved in COVID-19 induced cytokine storms that cause acute respiratory disease syndrome (ARDS), multiple organ dysfunction, and death rapidly (Luo et al 2020, Tufan et al 2020). IL-6 blockade is a promising strategy for COVID-19 induced cytokine storms (Liu et al 2020). A retrospective observational study by Luo et al (2020) supported the effectiveness of Tocilizumab in the prevention or treatment of cytokine storms in COVID-19 patients. The gradual decrease in IL-6 reflects an improvement in the condition of most patients after Tocilizumab administration, although a persistent and dramatic increase in IL-6 was observed in some critically ill patients who failed treatment. There may exist an upper threshold beyond that cause this persistent increase in IL-6. Rapid control of hyperinflammation can result in clinical improvement in some of patients (Antwi-Amoabeng et al 2020). Therefore, early treatment with Tocilizumab, one of the anti IL-6 therapies, could be helpful to prevent excessive hyperinflammation and death in severe COVID-19 patients (Capra et al 2020, De Rossi et al 2020).

This systematic review had several limitations that must be considered. First, all studies in this systematic review were retrospective non-randomized studies. Second, the clinical characteristics of the anti IL-6 therapy group and the control group were not homogeneous. Third, the inclusion criteria for COVID-19 patients in each study were also different. This was related to the timing of anti IL-6 therapy which could affect the outcome of severe COVID-19 patients. Fourth, the treatment given to both standard treatment and anti IL-6 therapy was not the same in dose and frequency. Fifth, the low number of patients in most studies led to ambiguous results. Therefore, a larger randomized controlled study was needed to clarify the effectiveness of anti IL-6 therapy in reducing mortality in severe COVID-19 patients.

CONCLUSION

We found lower mortality on the use of anti-il-6 therapy compared with standard treatment in 10 of the 12 available studies, but a larger randomized controlled study was needed to clarify the effectiveness of anti IL-6 therapy in reducing mortality in severe COVID-19 patients.

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