



Tocilizumab in patients with COVID-19: which patient, time, and dose?

Ahmed Hasanin¹ · Maha Mostafa¹

Received: 2 June 2021 / Accepted: 10 July 2021 / Published online: 15 July 2021
© Japanese Society of Anesthesiologists 2021

Abstract

Tocilizumab (TCZ) is a recombinant anti-interleukin-6 monoclonal antibody which showed uprising evidence as an anti-inflammatory agent which modulates the cytokine storm in patients with COVID-19. However, proper use of the drug requires selection of the appropriate patient and timing. The two main factors which might improve patient selection are the degree of respiratory failure and systemic inflammation. TCZ can decrease the mortality and progression to invasive mechanical ventilation in patients with severe COVID-19 who are not yet invasively ventilated. However, its use in invasively ventilated patients did not yet gain the same level of evidence especially when administered after > 1 day from mechanical ventilation. Being an anti-inflammatory and immunomodulatory drug, TCZ was mostly used in patients with COVID-19 who have clear signs of cytokine storm. However, the drug still showed positive response in some studies which did not strictly select patients with elevated markers of systemic inflammation. Thus, it is warranted to investigate and/or re-analyze the role of the drug in patients with severe COVID-19 and with no signs of systemic inflammation. TCZ is used in a dose of 8 mg/kg which can be repeated if there was no clinical improvement. However, there are no clear criteria for judgment of the success of the first dose. Being a drug with a major effect on gross outcomes in a serious pandemic with millions of mortalities, TCZ should be meticulously investigated to reach definitive indications and number of doses to avoid drug overuse, shortage, and side effects.

Keywords Tocilizumab · COVID-19 · SARS-CoV-2

Background

Coronavirus disease-2019 (COVID-19) represents a major health threat with \approx 3 million worldwide mortalities and with few effective drugs [1]. COVID-19 is characterized by an excessive host inflammatory response with a surge of proinflammatory cytokines such as interleukin-6 causing sepsis, acute respiratory distress syndrome and multiorgan failure [2]. Therefore, the use of immunomodulatory drugs was able to improve patient outcomes. Dexamethasone was the first immunomodulatory agent which decreased mortality in patients with COVID-19 [3]. Interlukin-6 has an important role in the cytokine storm by promoting helper T cell response and inhibit regulatory T cell [2]. Tocilizumab

(TCZ) is a recombinant anti-interleukin-6 monoclonal antibody that block interlukin-6 receptor; and is known to be effective in treating cytokine storm associated with B-cell chronic lymphocytic leukemia [2]. Hence, TCZ is believed to be able to modulate the cytokine storm in patients with COVID-19. The benefit of TCZ is nearly settled in patients with severe COVID-19; however, there is still lack of evidence about the proper choice of patients who would benefit from the drug as well as the proper timing of drug administration. The aim of this work is to provide a simplified comprehensive review for the relevant clinical data for the optimum patient, timing, and regimen for the use of TCZ in patients with COVID-19.

What is current evidence for TCZ in COVID-19?

There are nine randomized controlled trials (RCTs) which showed non-consistent results for the value of TCZ in COVID-19. The most probable reason for the variable response to the drug in the available studies is the

✉ Ahmed Hasanin
ahmedmohamedhasanin@gmail.com

Maha Mostafa
maha.mostafa@cu.edu.eg

¹ Department of Anesthesia and Critical Care Medicine,
Faculty of Medicine, Cairo University, 01 elsarayah street,
Elmanyal, Cairo, Egypt

heterogeneity of the outcomes, baseline characteristics, and the severity of respiratory failure in the participants as well as the concomitant use of steroids. Hence, in this review, we categorized the trials to a positive or a negative trial depending on the presence of any clinical benefit (improvement in survival and/or disease severity; or reduction in the need to respiratory support). Furthermore, we used the world health organization (WHO) clinical progression scale to describe the degree of respiratory support of the included patients in each trial. According to this scale, patients with COVID-19 are generally divided into ten categories according to the disease severity: uninfected (category 0), infected asymptomatic (category 1), symptomatic independent (category 2), symptomatic dependent (category 3), hospitalized without oxygen (category 4), hospitalized with oxygen by mask or nasal prongs (category 5), non-invasively ventilated or on high-flow nasal cannula (category 6), invasively ventilated up to extra-corporeal membrane oxygenation (categories 7–9), dead (category 10) [4].

Table 1 summarizes the type of patients, mortality, and progression of disease in each trial.

The positive studies

Five studies showed benefits for the use of TCZ in COVID-19. The RECOVERY [5] ($n=4116$) and REMAP-CAP [6] ($n=895$) trials included patients with severe COVID-19 on different levels of respiratory support (WHO categories 5–9). Two other smaller trials, namely the CORIMUNO-TOCI [7] ($n=131$) and EMPACTA [8] ($n=389$) trials, also included patients with severe COVID-19 who were on oxygen therapy but not on invasive mechanical ventilation (WHO category 5 [7] and categories 4–6 [8]). The COVINTOC study [9] ($n=179$) included a mix of moderate and severe patients (WHO categories 4–9) who were mostly not receiving invasive ventilation (only 5% of the participants were invasively ventilated at randomization).

The negative studies

On the other side, four RCTs with 933 total number of patients, which are smaller than the positive studies, showed no advantage for the use of TCZ compared to placebo on patient outcomes. The first two trials, the TOCIBRAS [10] ($n=129$) and COVACTA [11] ($n=438$) studies, included patients on various modes of respiratory support starting from simple O_2 therapy up to invasive mechanical ventilation (WHO categories 5–9). The BACC-Bay trial [12] ($n=243$) did not include patients requiring supplementary $O_2 > 10$ L/min and 15% of the participants were not receiving O_2 therapy (WHO categories 4,5). The RCT-TCZ-COVID-19 [13] study ($n=123$) included patients who require supplementary O_2 including high-flow oxygen but did not include

those who required other modes of non-invasive ventilation (WHO categories 5,6).

Which patient would benefit from TCZ?

Reaching the maximum benefit for TCZ depends on appropriate selection of the patient and the window of drug administration. The two main factors which impact the decision are the severity of respiratory failure as well as the extent of systemic inflammation.

The degree of respiratory failure

With exception of the REMAP-CAP study [6], the three positive studies shared a common feature which is the clear benefit of TCZ in patients with severe illness who did not receive invasive mechanical ventilation. The CORIMUNO-TOCI [7] and EMPACTA [8] trials strictly excluded patients who received any invasive ventilatory support (WHO categories 7–9). In the COVINTOC trial, despite including case-mix (WHO categories 4–9), the post hoc analysis revealed benefit in patients with severe disease (WHO category > 4) in addition only 5% of the participants were WHO categories 7–9 [9]. The RECOVERY trial [5], despite the presence of invasively ventilated participants (WHO categories 7–9), did not show positive results except in those who were not invasively ventilated (WHO categories 5,6). While those who were invasively ventilated (WHO categories 7–9) did not show improved survival nor reduced duration of ventilation after receiving TCZ. The REMAP-CAP [6] study is the only study which showed positive results in patients who were invasively ventilated (WHO categories 7–9); however, drug administration in this study was very early within 12 h from admission.

On the other hand, the most common feature in the negative studies is being small and the case-mix regarding the severity of the disease of the included patients (TOCIBRAS and COVACTA studies included patients with WHO categories 5–9 [10, 11], while the BACC-Bay [12] included severe and non-severe cases [WHO categories 4,5]). The only exception is the RCT-TCZ-COVID-19 trial [13] which included nearly a homogenous group of patients (WHO categories 5,6).

According to the available evidence, the patient category who would show maximum benefit from TCZ is category 6 and probably category 5. There are no data to support the use of TCZ in patients with no or low supplementary oxygen requirements (categories 1–4). The use of TCZ in invasively ventilated patients (categories 7–9) did not reduce mortality and did not improve weaning success in the RECOVERY trial [5]. In the REMAP-CAP study [6], TCZ was beneficial in invasively ventilated patients when

Table 1 Summary of patients' characteristics and outcomes in the trials

Trial name, no of patients	Patients	Mortality	Progression of disease	Infection-related adverse event in the TCZ group
RECOVERY [5], (<i>n</i> = 4116)	Respiratory support: From simple oxygen therapy to invasive ventilation (WHO categories* 5–9) Inflammatory markers: CRP \geq 75 mg/L	TCZ reduced 28-day mortality (1ry outcome) especially for those not receiving invasive ventilation	At 28 days, TCZ reduced the risk of receipt of invasive ventilation or death in patients not receiving invasive ventilation TCZ did not reduce the risk of receipt ventilatory support† in patients on simple oxygen therapy at the time of randomization	3 cases of bacterial infection
REMAP-CAP [6], (<i>n</i> = 865)	Respiratory support: from high-flow oxygen to invasive ventilation within 24 h of ICU admission (WHO categories 6–9) Inflammatory markers: not required	TCZ reduced 90-day mortality	TCZ reduced the risk of receipt of invasive ventilation or death in patients not receiving invasive ventilation at the time of randomization TCZ increased organ support-free days (1ry outcome)	One case of bacterial infection
CORIMUNO-TOCI [7], (<i>n</i> = 131)	Respiratory support: simple oxygen therapy 3–10 L/min (WHO category 5) Inflammatory markers: not required	In all patients, TCZ did not reduce the 14- or 90-day mortality TCZ reduced 90 mortality in patients with CRP > 150 mg/L (post hoc analysis)‡	Initially, TCZ reduced the risk of receipt of ventilatory support† or death at 14 days (1ry outcome) and was updated to be significant only in patients with CRP > 150 mg/L (post hoc analysis)‡	2 cases of bacterial sepsis 4 cases of neutropenia
EMPACTA [8], (<i>n</i> = 389)	Respiratory support: From Simple oxygen therapy to non-invasive ventilation 10% did not require oxygen therapy (WHO categories 4–6) Inflammatory markers: Not required	28- and 60-day mortality was indeterminate	TCZ reduced the risk of receiving invasive ventilation or death (1ry outcome)	13 cases of serious infection
COVINTOC [9], (<i>n</i> = 180)	Respiratory support: from simple oxygen therapy to invasive ventilation 11% did not require oxygen supplementation, and 5% were on invasive mechanical ventilation (WHO categories 4–9) Inflammatory markers: not required	TCZ is likely to reduce the 28-day mortality in patients with severe disease (SaO ₂ < 90% on room air) (post hoc analysis)	TCZ did not reduce the risk of progression of the disease (progression from moderate to severe, or from severe to death) at 14 days (1ry outcome) and 28 days	6 cases of infection 3 cases of sepsis

Table 1 (continued)

Trial name, no of patients	Patients	Mortality	Progression of disease	Infection-related adverse event in the TCZ group
TOCIBRAS [10], (n = 129)	Respiratory support: From simple O2 therapy to invasive ventilation (WHO categories 5–9) Inflammatory markers: CRP > 50 mg/L, ferritin > 300 mcg/L, D-dimer > 1000 ng/mL, or LDH > normal upper limit	TCZ did not reduce the risk of invasive ventilation or death (1ry outcome) regardless of the level of respiratory support (post hoc analysis) TCZ increased the risk of 15-day mortality and was indeterminable at 28 days	No separate analysis regarding the progression of disease in patients not receiving ventilatory support [†] However, TCZ reduced the hospital stay among the survivors	The cause of death was COVID-19-related ARDS and multiple organ dysfunction 10 cases of secondary infection 1 case of neutropenia
COVACTA [11], (n = 438)	Respiratory support: From simple oxygen therapy to invasive ventilation (WHO categories 5–9) Inflammatory markers: not required	TCZ effect on 28-day mortality was indeterminable	In patients not receiving invasive ventilation, TCZ did not reduce the risk of receiving invasive ventilation but reduced the risk of clinical failure* TCZ did not reduce the risk of invasive ventilation or death (1ry outcome) TCZ did not reduce the risk of receiving mechanical ventilation	7 cases of Septic shock 7 cases of pneumonia 6 cases of bacterial pneumonia 2 cases of bacteremia 3 cases of bacterial sepsis
BACC-Bay, [12], (n = 243)	Respiratory support: oxygen therapy no more than 10L/min, 15% of patients were not on oxygen therapy. (WHO categories 4,5) Inflammatory markers: CRP > 50 mg/L, ferritin > 500 mcg/L, D-dimer > 1000 ng/mL, or a LDH > 250 U/L	28-day mortality was indeterminable		13 cases of infection and were significantly lower than the control group 22 cases of neutropenia and were higher than the control group
RCT-TCZ-COVID-19 [13], (n = 126)	Respiratory support: from simple oxygen therapy to high-flow oxygen (WHO categories 5,6) Inflammatory markers: CRP ≥ 100 mg/L, or CRP > 2 X admission measurement	14- and 28-day mortality was indeterminable	TCZ did not reduce the risk of clinical worsening, receive mechanical ventilation, or death. (1ry outcome)	One case of urinary tract infection 3 cases of neutropenia

CRP C-reactive protein; ECMO extra-corporeal membrane oxygenation, ICU intensive care unit, LDH lactate dehydrogenase, SaO2 arterial oxygen saturation, TCZ tocilizumab, WHO world health organization

*According to WHO clinical progression scale to describe the degree of respiratory support; category 0: uninfected, category 1: infected asymptomatic, category 2: symptomatic independent, category 3: symptomatic dependent, category 4: hospitalized without oxygen, category 5: hospitalized with oxygen by mask or nasal prongs, category 6: non-invasively ventilated or on high-flow nasal cannula, categories 7–9: invasively ventilated up to extra-corporeal membrane oxygenation, category 10: dead

[†]Ventilatory support: include high-flow nasal oxygen, non-invasive mechanical ventilation, invasive mechanical ventilation, and ECMO

[‡]Data from the extended 90-day follow-up that were published later [17]

*Clinical failure, which was defined as death, discontinuation from trial participation during hospitalization, initiation of mechanical ventilation, or ICU transfer or a I-category worsening of clinical status in patients who were receiving mechanical ventilation or who were in the ICU at baseline

used early within 12 h from admission. The use of TCZ in invasively ventilated patients in the later phases of the disease required further investigation and/or subgroup analysis in future meta-analyses.

The severity of cytokine storm:

The benefit of TCZ in patients with COVID-19 is explained by its anti-inflammatory, immunomodulatory actions. However, inclusion of patients in the available RCTs did not strictly include patients with clear cytokine storm. C-reactive protein (CRP) was the most used biomarker for inflammation in the available RCTs. CRP is highly correlating with interleukin-6 level [14], widely available and is associated with the severity and prognosis of the disease [15, 16]. The RECOVERY [5], TOCIBRAS [10], BACC-Bay [12] and RCT-TCZ-COVID-19 trials clearly included patients with elevated CRP, being the most available marker (the inclusion criteria in those trials was CRP level > 75, 50, 50, and 100 mg/L, respectively). The presence of severe inflammation was not necessarily included in the other five RCTs.

The REMAP-CAP study [6] reported that the positive effect of TCZ was greatest in patients with the highest titer of CRP. The CORIMUNO-TOCI investigation group published updated results of the extended follow-up of their patients and showed that TCZ is beneficial in the subset of patients with CRP level ≥ 150 mg/L [17]. However, neither of the other studies found any association between the severity of inflammation and the effect TCZ. Therefore, we cannot reach a clear suggestion for the inflammatory criteria upon which drug administration should be decided. A patient with elevated CRP (> 75–150 mg/L) is very likely to benefit from TCZ, while patients with impaired oxygenation and low inflammatory markers require further subgroup analyses and/or new RCTs before declaring a similar benefit for TCZ.

The concomitant use of steroids with TCZ

Steroids are the most widely used and effective anti-inflammatory and immunosuppressive drugs. Steroids, namely dexamethasone, was the first immunomodulatory drug that reduced mortality in hospitalized patients with COVID-19 and since then, steroids were routinely used in the usual care of the hospitalized patients. The use of steroids was highly variable in the available RCTs mainly depending on the timing of the trial and local protocols. The use of steroids was high in both treatment and control arms in the RECOVERY (99%), REMAP-CAP (93%), COVINTOC (91%) and TOCIBRAS (70%), and was variable between the TCZ and control arms in the CORIMUNO-TOCI (44% Vs. 83%), EMPACTA (55% Vs. 67%), COVACTA (33% Vs. 52%), and was low in the BACC-Bay (11% Vs. 6%) and RCT-TCZ-COVID-19 (nearly 10% in both groups). There is a very clear evidence

that combination of TCZ and dexamethasone has a synergistic effect on patients' outcomes: (1) the studies whose most of the participants received the two drugs showed positive results (the only exception was the TOCIBRAS study) (2) the two studies with low use of steroids showed negative results (3) the subgroup analysis in the RECOVERY trial showed a potential positive effect of the concomitant use of steroid and TCZ. Hence, the proportion of patients receiving steroid drugs might contribute to the variable response to TCZ within the available RCTs.

Infection-related adverse events

One of the feared side effects of TCZ is exacerbation of infection and sepsis; however, TCZ did not increase the risk of infection or sepsis in comparison to the control arm of the current RCTs. However, it should be noted that patients with suspicion of active viral (other than SARS-CoV-2), bacterial or fungal infection were strictly excluded from the trials. The number of infection-related adverse events in TCZ arm in each trial is reported in Table 1.

Drug administration

Proper regimen for drug prescription requires selection of the right patient, dose, monitoring of patient response, and determination of patients who require an additional dose.

What is the dose of TCZ in patients with COVID-19?

With exception of the COVINTOC study [9] which used a dose of 6 mg/kg with a maximum up to 480 mg, nearly all the available studies used the same dose of TCZ which is 8 mg/kg with a maximum dose of 800 mg. (Table 2) However, there is lack of consistency in the number of doses of the drug. The BACC-Bay [12] and TOCIBRAS [10] studies used a fixed single dose regimen while the RCT-TCZ-COVID-19 [13] used a fixed double-dose regimen with a 12-h interval between the two doses. All the remaining six RCTs repeated the drug if the patient did not respond positively to the first dose. The second dose was administered within 8–24 h from the first dose in all studies except the CORIMUNO-TOCI study [7] which used 400 mg, 3 days after the first dose, and the COVINTOC study [9] which used the second dose within a period of 12 h–7 days from the first dose. It should be noted that the decision of the second dose was mostly left to the physician judgment with no solid definition for “which patient responded adequately to TCZ and did not require an additional dose”. The CORIMUNO-TOCI study [7] was the only RCT in which the authors clarified the indication of the second dose which is failure of

Table 2 Summary of drug regimen

Trial name	First dose	Second dose	
		Timing	Indication
RECOVERY [5]	800 mg if weight > 90 kg 600 mg if weight 65–90 kg 400 mg if weight 40–65 kg 8 mg/kg if weight ≤ 40 kg	After 12–24 h	If no improvement according to the attending clinician. 29% received a second dose
REMAP-CAP [6]	8 mg/kg, maximum of 800 mg	After 12–24 h	If no improvement according to the attending clinician. 29% received a second dose
CORIMUNO-TOCI [7]	8 mg/kg	Day 3	If oxygen requirement did not decrease by 50% 47% received a second dose
EMPACTA [8]	8 mg/kg, maximum of 800 mg	After 8–24 h	if no improvement or worsening of clinical state on a 7-point ordinal scale* 27.2% patients received a second dose
COVINTOC [9]	6 mg/kg maximum of 480 mg	Within 12 h to 7 days	If no improvement or worsening clinical state
TOCIBRAS [10]	8 mg/kg, maximum of 800 mg	NA	
COVACTA [11]	8 mg/kg, maximum of 800 mg	After 8–24 h	If no improvement or worsening clinical state on a 7-point ordinal scale* 22.1% patients received a second dose
BACC-Bay [12]	8 mg/kg, maximum of 800 mg	NA	
RCT-TCZ-COVID-19 [13]	8 mg/kg, maximum of 800 mg	After 12 h	To all patients in TCZ group

ECMO extra-corporeal membrane oxygenation, ICU intensive care unit, NA not applicable, TCZ tocilizumab

*7-point ordinal scale: 1: Discharged (or “ready for discharge” as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen); 2: Non-ICU hospital ward (or “ready for hospital ward”) not requiring supplemental oxygen; 3: Non-ICU hospital ward (or “ready for hospital ward”) requiring supplemental oxygen; 4: ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen; 5: ICU, requiring intubation and mechanical ventilation; 6: ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy); 7: Death

decreasing the oxygen requirements by $\geq 50\%$. It is to be noted that the first dose was effective without the need to a second dose in nearly 70% of the patients in the largest two study, namely the RECOVERY and REMAP-CAP studies [5, 6]. (Table 2) However, further research is warranted to compare the outcomes of patients who received one dose and those who received two doses of TCZ.

Conclusions and future perspectives

TCZ is a useful drug in decreasing mortality and progression to invasive mechanical ventilation in patients with severe COVID-19 who are not yet invasively ventilated. However, its use in invasively ventilated does not show a clear benefit especially when administered after > 1 day from mechanical ventilation. Thus, more research is warranted to explore the value of TCZ in severe cases who did not receive the drug early before- or within one day of invasive mechanical ventilation.

The main mechanism for TCZ in COVID-19 is modulation of the systemic inflammation; however, some studies reported positive response to the drug despite inclusion of patients who did not have documented cytokine storm.

Furthermore, even the studies which stipulated the presence of severe inflammation did not use the same cutoff values. Therefore, restricting the use of TCZ in patients with elevated inflammatory markers is not supported by strong evidence and it is warranted to investigate and/or re-analyze the role of the drug in patients with severe COVID-19 and no signs of systemic inflammation.

TCZ is used in a dose of 8 mg/kg which can be repeated if there was no clinical improvement. However, there are no clear criteria for judgment of the success of the first dose which was defined in one study by decrease of oxygen requirements by 50% and left to the physician judgment in all other studies. More analyses of the currently present data and new studies should compare the outcomes of single versus two doses of the drug.

Being a drug with a major effect on gross outcomes in a serious pandemic with millions of mortalities, TCZ should be meticulously investigated to reach definitive indications of administration of the first and second doses to avoid drug overuse, shortage, and side effects.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations

Conflict of interest The authors declare that they have no conflict of interest with this work.

References

- Hopkins J. COVID-19 Map - Johns Hopkins Coronavirus resource Center [Internet]. Johns Hopkins Coronavirus Resource Center. (2020). <https://coronavirus.jhu.edu/map>.
- Thepmankorn P, Bach J, Lasfar A, Zhao X, Souayah S, Chong ZZ, Souayah N. Cytokine storm induced by SARS-CoV-2 infection: the spectrum of its neurological manifestations. *Cytokine*. 2021;138:155404.
- RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384:693–704.
- WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):192–7.
- RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397:1637–45.
- REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, Bhimani Z, Bonten MJM, Bradbury CA, Brunkhorst FM, Buzgau A, Cheng AC, Detry MA, Duffy EJ, Estcourt LJ, Fitzgerald M, Goossens H, Haniffa R, Higgins AM, Hills TE, Horvat CM, Lamontagne F, Lawler PR, Leavis HL, Linstrom KM, Litton E, Lorenzi E, Marshall JC, Mayr FB, McAuley DF, McGlothlin A, McGuinness SP, McVerry BJ, Montgomery SK, Morpeth SC, Murthy S, Orr K, Parke RL, Parker JC, Patanwala AE, Pettilä V, Rademaker E, Santos MS, Saunders CT, Seymour CW, Shankar-Hari M, Sligl WI, Turgeon AF, Turner AM, van de Veerdonk FL, Zarychanski R, Green C, Lewis RJ, Angus DC, McArthur CJ, Berry S, Webb SA, Derde LPG. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384:1491–502.
- Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P, CORIMUNO-19 Collaborative Group. Effect of tocilizumab vs. usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2021;181:32–40.
- Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, Criner GJ, Kaplan-Lewis E, Baden R, Pandit L, Cameron ML, Garcia-Diaz J, Chávez V, Mekebeb-Reuter M, Lima Menezes F, Shah R, González-Lara MF, Assman B, Freedman J. Tocilizumab in patients hospitalized with Covid-19 pneumonia. *N Engl J Med*. 2021;384:20–30.
- Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, Govil D, Deswal V, Chaudhry D, Singh PK, Gupta A, Agarwal V, Kumar S, Sangle SA, Chawla R, Narreddy S, Pandit R, Mishra V, Goel M, Ramanan AV. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. *Lancet Respir Med*. 2021;9:511–21.
- Veiga VC, Prats JAGG, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, Machado FR, Lopes RD, Berwanger O, Azevedo LCP, Avezum Á, Lisboa TC, Rojas SSO, Coelho JC, Leite RT, Carvalho JC, Andrade LEC, Sandes AF, Pintão MCT, Castro CG, Santos S V., de Almeida TML, Costa AN, Gebara OCE, de Freitas FGR, Pacheco ES, Machado DJB, Martin J, Conceição FG, Siqueira SRR, Damiani LP, Ishihara LM, Schneider D, de Souza D, Cavalcanti AB, Scheinberg P, Coalition covid-19 Brazil VI Investigators. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ*. 2021;372:n84.
- Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, Skiest D, Aziz MS, Cooper N, Douglas IS, Savic S, Youngstein T, Del Sorbo L, Cubillo Gracian A, De La Zerma DJ, Ustianowski A, Bao M, Dimonaco S, Graham E, Matharu B, Spotswood H, Tsai L, Malhotra A. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. *N Engl J Med*. 2021;384:1503–16.
- Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM, Woolley AE, Nikiforow S, Lin N, Sagar M, Schrager H, Huckins DS, Axelrod M, Pincus MD, Fleisher J, Sacks CA, Dougan M, North CM, Halvorsen Y-D, Thurber TK, Dagher Z, Scherer A, Wallwork RS, Kim AY, Schoenfeld S, Sen P, Neilan TG, Perugino CA, Unizony SH, Collier DS, Matza MA, Yinh JM, Bowman KA, Meyerowitz E, Zafar A, Drobní ZD, Bolster MB, Kohler M, D’Silva KM, Dau J, Lockwood MM, Cubbison C, Weber BN, Mansour MK, BACC Bay Tocilizumab Trial Investigators. Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med*. 2020;383:2333–44.
- Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, Bruzzi P, Boni F, Braglia L, Turrà C, Ballerini PF, Sciascia R, Zammarchi L, Para O, Scotton PG, Inojosa WO, Ravagnani V, Salerno ND, Sainaghi PP, Brignone A, Codeluppi M, Teopompi E, Milesi M, Bertomoro P, Claudio N, Salio M, Falcone M, Cenderello G, Donghi L, Del Bono V, Colombelli PL, Angheben A, Passaro A, Secondo G, Pascale R, Piazza I, Facciolongo N, Costantini M, RCT-TCZ-COVID-19 Study Group. Effect of tocilizumab vs. standard care on clinical worsening in patients hospitalized With COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2021;181:24–31.
- Oberhoffer M, Karzai W, Meier-Hellmann A, Bögel D, Faßbinder J, Reinhart K. Sensitivity and specificity of various markers of inflammation for the prediction of tumor necrosis factor- α and interleukin-6 in patients with sepsis. *Crit Care Med*. 1999;27:1814–8.
- Ahnach M, Zbiri S, Nejari S, Ousti F, Elkettani C. C-reactive protein as an early predictor of COVID-19 severity. *J Med Biochem*. 2020;39:500.
- Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan. *China Intensive Care Med*. 2020;46:846–8.
- Mariette X, Hermine O, Tharaux P-L, Resche-Rigon M, Steg PG, Porcher R, Ravaud P. Effectiveness of tocilizumab in patients hospitalized With COVID-19: a follow-up of the CORIMUNO-TOCI-1 randomized clinical trial. *JAMA Intern Med*. 2021;384:1491–502.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.