# Tocilizumab in Severe and Critical COVID-19 Pneumonia: Streamlining the Mixed Signals

Four years since the start of the pandemic, the first lockdown in Manila happened on March 15, 2020 causing a pandemonium in the metro as the Filipinos gear up for the unexpected. As the suspected and confirmed cases grew, case numbers of unidentified patients soon became friends, relatives, and loved ones. As of May 2023[1], there have been more than 1.3 million confirmed COVID-19 cases in Metro Manila alone with almost 14,000 deaths from severe and critical cases.

The current knowledge about the disease as well as the explanation of its widely varied symptomatology continues to evolve.[2-4] At the center of the discussion for severe and critical COVID-19 requiring hospitalization is the hyperactivation of the inflammatory response resulting to simultaneous increase in multiple cytokines.[4,5] Such an inflammatory cascade results in nonspecific inflammatory reaction from damaged or dysfunctional virus-infected host cells making it difficult to identify a specific mediator of inflammatory response.[5,6] It is therefore not surprising that multiple therapeutic trials done targeting specific cytokines such as IL-6 and TNF-a have also led to mixed results.[7-10]

Since 2020, aggressive research has allowed both the development of new medications as well as repurposing of other molecules in the treatment of COVID-19. Antiviral drugs, monoclonal antibodies, IL-6R inhibitor/immune modulators, and systemic corticosteroids have become household names.[6] IL-6, an identified key propagator of the cytokine storm in severe and critical COVID, has been the focus of the noise as mechanistically, IL-6 blockers including tocilizumab and sarilumab theoretically disrupt the inflammatory cascade.[5-7]

If mechanistically, IL-6 blockers, particularly tocilizumab can block the inflammatory cascade, why are there mixed signals on its benefit based on real-world evidence?[7-10]

One of the largest and most recently published systematic review and meta-analysis of 15 randomized and two non-randomized clinical trials evaluating the effect of tocilizumab on the clinical outcomes of COVID-19 patients[11] showed a combined cumulative risk of death in COVID-19 patients of 0.93 (RR 0.93, 95% CI 0.86 – 1.00, $i^2$ 72.39%). The need for invasive ventilation, ICU admission was at 1.04 (RR 1.04, 95% CI 0.90 – 1.20, $i^2$ 0.00). These figures indicate a 7% decreased risk of death with a 4% increased risk of ICU admission and need for invasive ventilation, again indicating mixed signals on the perceived benefit of tocilizumab.[11] Limitations in the study results compared to controlled clinical trials are probably due to (1) heterogeneity of the patients with severe and critically ill COVID-19 patients potentially having different degrees of inflammatory activities; (2) timing of administration of tocilizumab; (3) different administrative and hospital policies in the management of more ill patients suffering from COVID-19; and (4) presence of multiple inflammatory cytokines aside from IL-6, making it difficult to pinpoint the specific key mediator of inflammatory response on a per-patient basis.

The local randomized controlled trial published by Amante et al.[12] agree with these mixed signals from the published literature in COVID-19. In both intention-to-treat and per-protocol-analysis, there was no statistical significance and clinical benefit of using tocilizumab for severe and critically ill patients.

Four years later, the picture is clearer now as real-world evidence coupled with carefully conducted clinical trials provide us a better understanding of the use of tocilizumab for current cases. However, back in 2020, when this mysterious respiratory illness is wreaking havoc, medications both newly developed and repurposed were offered as the medical research community was challenged by a pandemic in an unprecedented manner.

As COVID-19 becomes endemic, the search for the cure for severe COVID-19 remains to be discovered. Given its mixed signals, shared decision making (pending confirmation in further studies) between the patient, caregiver, and the physician remains the cornerstone of management.

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## REFERENCES


1. COVID-19 Tracker Philippines. Department of Health [Internet]. October 22, 2021 [cited 2024 Apr 11]. Available from: https://doh.gov.ph/diseases/covid-19/covid-19-case-tracker/
2. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. Clin Immunol. 2020 Jun;215:108427. doi: 10.1016/j.clim.2020.108427.
3. Parasher A. COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment. Postgrad Medl J. 2021 May; 97(1147):312-20. doi: 10.1136/postgradmedj-2020-138577. PMID: 32978337; PMCID: PMC10017004.
4. Chávez-Ocaña SDC, Bravata-Alcántara J.C, Cortés-Ortiz IA, Reyes-Sandoval A, García-Machorro J, Herrera-Gonzalez NE. Parameters to predict the outcome of severe and critical COVID-19 patients when admitted to the hospital. J Clin Med. 2023 Feb 7;12(4):1323. doi: 10.3390/jcm12041323. PMID: 36835858; PMCID: PMC9959673.
5. Zhu Y, Sharma L, Chang D. Pathophysiology and clinical management of coronavirus disease (COVID-19): a mini-review. Front Immunol. 2023 Aug 14:14:1116131. doi: 10.3389/fimmu.2023.1116131. PMID: 37646038; PMCID: PMC10461092.
6. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. Virol Sin. 2020 Jun;35(3):266–71. doi: 10.1007/s12250-020-00207-4. PMID: 32125642; PMCID: PMC7090474.
7. Godolphin PJ, Fisher DJ, Berry LR, Derde LPG, Diaz JV., Gordon AC, et al. Association between tocilizumab, sarilumab and all-cause mortality at 28 days in hospitalized patients with COVID-19: A network meta-analysis. PloS One. 2022 Jul 8;17(7):e0270668. doi: 10.1371/journal.pone.0270668. PMID: 35802687; PMCID: PMC9269978.
8. McKenzie MG, Lee YM, Mathew J, Anderson M, Vo AT, Akinyele S, et al. Tocilizumab for the critically ill with severe COVID-19: a community hospital case series. J Pharm Pract. 2022 Aug;35(4): 587-92. doi: 10.1177/08971900211002353. PMID: 33736526.
9. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. N Engl J Med. 2020 Dec 10;383(24):2333-44. doi: 10.1056/NEJMoa2028836. PMID: 33085857; PMCID: PMC7646626.
10. Kyriakopoulos C, Ntritsos G, Gogali A, Milionis H, Evangelou E, Kostikas K. Tocilizumab administration for the treatment of hospitalized patients with COVID-19: a systematic review and meta-analysis. Respirology. 2021 Nov;26(11):1027-40. doi: 10.1111/resp.14152. PMID: 34605114; PMCID: PMC8661720.
11. Ghaempanah F, Nikouei M, Cheraghi M, Jahangiri A, Moradi Y. Does tocilizumab have an effect on the clinical outcomes in COVID-19 patients? A meta-analysis of randomized control trials. J Pharm Policy Pract. 2023 Nov 20;16(1):151. doi: 10.1186/s40545-023-00662-w. PMID: 37986199; PMCID: PMC10658795.
12. Amante EJB, David-Wang AS, Tee ML, Punzalan FER, Añonuevo JC, Fernandez LC, et al. Intravenous tocilizumab versus standard of care in the treatment of severe and critical COVID-19-related pneumonia: a single center, double-blind, placebo-controlled, phase 3 trial. Acta Med Philipp. 2024;58(6):7-13. doi: 10.47895/amp.vi0.6175.