Tocilizumab for the Treatment of Severe COVID-19 Pneumonia in Critically Ill Patients:
Trendy or Tried-and-True?

Background

SARS-CoV-2 and resulting COVID-19 pneumonia have been an evolving global crisis since their emergence in December 2019. While most individuals experience minor or modest pulmonary and gastrointestinal symptoms, a substantial minority are afflicted with severe disease leading to critical illness characterized by prolonged mechanical ventilation and possible multi-organ failure.[1] One of the earliest characteristics noted in COVID-19 positive patients was a marked elevation in inflammatory markers. A three-stage model has been proposed to describe the progression of COVID-19 pneumonia and associated severity of illness (Fig 1).[2] The hyperinflammatory stage (III) is characterized by surges of pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-8, interleukin-1β, granulocyte-macrophage colony stimulating factors, reactive oxygen species, as well as acute phase reactants: C-reactive protein (CRP), d-Dimer, ferritin, and lactate dehydrogenase.[3-4] Studies have since demonstrated a positive correlation between certain inflammatory markers and negative outcomes in the COVID-19 population, including thrombosis (d-Dimer) and increased mortality (IL-6 and CRP).[5-6] As a result of this understanding, controlling inflammation became a primary therapeutic target.

The race to prevent, treat, and cure COVID-19 has been one of the greatest medical gauntlets of the last century. Early treatments included repurposed anti-viral and anti-inflammatory medications such as hydroxychloroquine and the combination of lopinavir and ritonavir, but these therapies did not prove effective. The next major wave of treatments included remdesivir and tocilizumab, followed by dexamethasone. These three agents have remained in the spotlight throughout the pandemic, with tocilizumab occupying a particularly debated place in COVID-19 therapy.

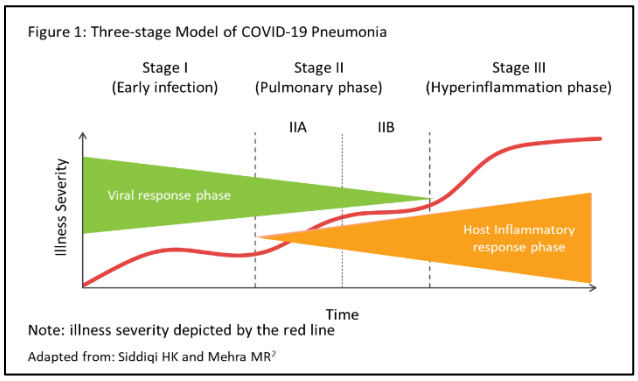

Figure 1: Three-stage Model of COVID-19 Pneumonia
Note: illness severity depicted by the red line
Adapted from: Siddiqi HK and Mehra MR[7]

Tocilizumab is a recombinant humanized monoclonal antibody, selective for both membrane and circulating IL-6 receptors. It is FDA-approved for the treatment of rheumatoid arthritis, giant cell arteritis, systemic sclerosis-associated interstitial lung disease, and cytokine-release syndrome associated with anti-cancer treatments.[7] Early in the pandemic, small case series emerged suggesting mortality benefit with tocilizumab treatment in patients presumed or demonstrated to fall within the hyperinflammatory stage of the disease.[8-9] These data were used to support the frequent use of tocilizumab and its fervent evaluation in clinical trials. Tocilizumab treatment subsequently fell out of favor when data from the RCT-TCZ-COVID-19 and CORIMUNO-19-TOCI-1 randomized controlled trials were published in addition to preliminary results from the COVACTA randomized controlled trial demonstrated no clinical benefit in heterogeneous patient groups given tocilizumab.[10-12] In addition to mounting doubts of benefit, wide-spread use of tocilizumab was further discouraged by growing concerns for significant adverse reactions, including increased bacterial or fungal infections, hepatotoxicity, secondary hemophagocytic lymphohistiocytosis, and bowel perforations.[7,13-14] Interest in continued investigations remained as previously published data, though limited by flawed methodology and uncontrolled confounding, hinted at potential subgroups of patients with severe COVID-19 who could benefit from tocilizumab.

More than one year into the pandemic, large, randomized controlled trials evaluating tocilizumab, including the RECOVERY (tocilizumab arm), COVACTA, REMAP-CAP, and EMPACTA trials, have published results. These reports have been highly influential, leading to guideline updates and strongly informing clinical practice. Despite the strength of each trial's design, questions remain about the optimal place in therapy for tocilizumab and the nature of potential clinical benefits. This review highlights key differences in trial, patient, and concomitant therapy characteristics that affect the interpretation of these studies and subsequent application to patient care.

Jessica A. Ward, Pharm.D.
April 2021

Tocilizumab for the Treatment of Severe COVID-19 Pneumonia in Critically Ill Patients: Trendy or Tried-and-True?

Table 1: Randomized Controlled Trials of Tocilizumab Treatment for COVID-19 Pneumonia

Trial		RECOVERY (Tocilizumab arm) [15]	COVACTA[16]	REMAP-CAP[17]	EMPACTA[18]
Study Design		Multi-center, open-label, adaptive platform RCT	Multi-national, phase III, placebo-controlled RCT	International, adaptive platform RCT	Global, randomized, double-blind, placebo-controlled, phase III RCT
Patients		n=4,116 Hospitalized adults with hypoxia (SpO2% <92%) and hyperinflammation (CRP ≥7.5 mg/dL)	n=452 Hospitalized adults with hypoxia (SpO2% ≤93% or P:F <300 mmHg)	n=803 Critically ill patients requiring respiratory or cardiovascular support in the ICU*	n=388 Hospitalized patients with hypoxia (SpO2% <94% on ambient air)
Baseline Characteristics	Oxygen Support	MV: 14% Non-invasive: 41%	MV: ~37%	MV: ~29% Non-invasive: ~42% PaO_2:FiO_2: 116.5 mmHg	MV: 0% Non-invasive: 0%
	ICU-level care	Not reported	70.4% vs 65.3%	100% Vasoactive use: ~20%	≤26.5%
	CRP	14.3 mg/dL	~17 mg/dL	13.6 mg/dL	13.6 mg/dL
	Glucocorticoid use	82% (dexamethasone)	19.4% vs 28.5%	>93% (dexamethasone)	55.4% vs 67.2% (dexamethasone)
Intervention		Standard of care +/- Toci 400-800 mg IV once. Optional second dose after 12-24 hrs, if no improvement	Standard of care + placebo or Toci 8 mg/kg (max 800 mg) IV once. Optional second dose after 8-24 hrs, if no improvement	Standard of care +/- Toci 8 mg/kg (max 800 mg) IV once. Optional second dose after 12-24 hrs, if no improvement	Standard of care + placebo or Toci 8 mg/kg (max 800 mg) IV once. Optional second dose after 8-24 hrs, if no improvement
Patients given second toci dose		29%	22.1%	29%	27%
Primary Outcome		28-day ACM: 29% vs 33% RR 0.86 (0.77-0.96)	Day 28 clinical status: 1 vs 2; NSS	Day 21 respiratory and CV organ support-free days: 10 vs 0; NSS	28 day MV or mortality: 12% vs 19.3% HR 0.56 (0.33-0.94)
Secondary Outcomes		Intubation: 12% vs 15%; p<0.001 Time to hospital discharge: 20 vs 28 days; p<0.001 Hospital discharge alive: 54% vs 47%; p<0.001 Cessation of MV: 34% vs 32%; NSS	Mortality: 19.7% vs 19.4%; NSS Day 14 clinical status: 3 vs 4; NSS Days to hospital discharge: 20 vs 28; NSS ICU transfer: 21.3% vs 35.9%; NSS Clinical failure‡: 29% vs 42.2%; NSS	Probability of efficacy†: >99.9% Hospital mortality: 28% vs 36% OR 1.64 (1.14 to 2.35) Survival probability: HR 1.59 (1.24-2.05) ICU discharge probability: HR 1.42 (1.18-1.70) Hospital discharge probability: HR 1.41 (1.18-1.70)	Mortality: 10.4% vs 8.6%; NSS MV: 8% vs 12.5% Time to hospital discharge: NSS Time to clinical improvement: NSS Time to clinical failure: NSS
Safety and Adverse effects (AE)		Serious AE: 3 events vs NR No excess infection-related mortality Cardiac arrhythmias: NSS Tocilizumab: 2 invasive infections 1 non-invasive infection	Serious AE: 34.9% vs 38.5% Serious infection, abnormal LFTs, any bleeding: NSS	Serious AE: ~2.5% vs ~2.7% Tocilizumab: 1 secondary infection	Serious AE: 5.2% vs 7.1%

Abbreviations: ACM = All-cause mortality | CRP = C-reactive protein | CV = cardiovascular |HR = Hazard ratio | ICU = Intensive care unit | LFTs = Liver function tests | LOS = Length of stay | MV = Mechanical ventilation | NSS = Not statistically significant | OR = Odds ratio |RCT = Randomized controlled trial |RR = Relative risk | SpO2% = Oxygen saturation

For all comparisons: Tocilizumab vs control

*Respiratory support defined as oxygen requirements of high-flow nasal cannula at >30 L/min or greater (including mechanical ventilation); Cardiovascular support defined as any use of vasoactive agents

**Categories on a seven-category ordinal scale as follows: 1, discharged or ready for discharge; 2, non-ICU hospitalization without supplemental oxygen; 3, non-ICU hospitalization with supplemental oxygen; 4, ICU or non-ICU hospitalization with noninvasive ventilation or high-flow oxygen; 5, ICU hospitalization with mechanical ventilation; 6, ICU hospitalization with extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; and 7, death

‡Clinical failure was defined as death, withdrawal from the trial during hospitalization, transfer to the ICU, or the initiation of invasive mechanical ventilation by 28 days

†Efficacy defined as results from a model fit by a Markov chain Monte Carlo algorithm which resulted in a calculated posterior probability (odds ratio) of >99% that the intervention was superior to control

Jessica A. Ward, Pharm.D.
April 2021

Tocilizumab for the Treatment of Severe COVID-19 Pneumonia in Critically Ill Patients:
Trendy or Tried-and-True?

Clinical Trial Review

The tocilizumab arm of the RECOVERY trial identifies a key patient group who benefit from treatment with tocilizumab: severely ill, hospitalized patients with oxygen requirements and evidence of inflammation. The trial also confirms the safety of combined use with glucocorticoids with, 82% of patients receiving dexamethasone during tocilizumab treatment. The combination appeared synergistic as the patients receiving both agents experienced substantially less mortality than patients treated with glucocorticoids as part of standard care. Seventeen percent of patients randomized to tocilizumab did not receive treatment for unspecified reasons which may translate to an underestimated magnitude of benefit in the current report. Importantly, RECOVERY includes one of the longest time frames for patient enrollment (10 months) of any available RCT and the largest sample size to date. Though the results are preliminary, 92% of patients had completed follow-up and were included for analysis reducing the likelihood of significant changes to outcomes or conclusions being published with the full report. [15]

In the COVACTA trial, tocilizumab use in a critically ill population was not associated with improvements in clinical status or mortality. Despite this, notable benefits were observed in secondary outcomes including the rate of ICU transfer, time to symptom improvement, and time to discharge or readiness which align with findings in the RECOVERY trial. Additionally, COVACTA collected data for only eight weeks, in the early stages of the pandemic, from April through May 2020. Possibly a result of the early time frame, glucocorticoid treatment was incompletely characterized and infrequent in both groups. With the incorporation of dexamethasone as standard of care for severe and critical COVID-19, observing the interaction of tocilizumab and glucocorticoids is critical as this would best elucidate both benefits and risks of incorporating tocilizumab into current practice. Finally, patients were intubated for an average of three days prior to randomization and potential tocilizumab treatment. It is likely that differences in duration or severity of illness and lack of glucocorticoid treatment affected the results of COVACTA and contributed to the concerning rate of serious adverse events in tocilizumab- and placebo-treated groups. [16]

In opposition to observations in COVACTA, REMAP-CAP demonstrated benefit with tocilizumab treatment in critically ill patients with COVID-19 pneumonia and evidence of hyperinflammation who have been receiving organ support for a short period of time (~24 hours). Sensitivity analyses revealed an additive effect for patients treated with tocilizumab and glucocorticoids compared to either intervention alone which affirms the findings of RECOVERY and strengthens support for earlier treatment with the combination. One of the key differences between REMAP-CAP and COVACTA is the duration of critical illness allowed to precede tocilizumab treatment which may allow tissue damage to progress and reduce the potential benefits of anti-inflammatory treatment. The divergent results of these studies emphasize the importance of early consideration of tocilizumab in eligible patients.[17]

EMPACTA demonstrated that tocilizumab treatment is associated with reductions in a composite outcome of mechanical ventilation or death in severely ill, hypoxic patients with COVID-19. Notably, though all patients were treated in ICUs, the prevalence of mechanical ventilation suggests a less critically ill population than is represented in RECOVERY and REMAP-CAP. Secondary endpoints in which improvement was demonstrated in previously reviewed trials did not reveal any benefit associated with tocilizumab treatment. EMPACTA included a 60-day follow-up period for adverse effects, longer than published counterparts. It is possible that the wide variation in healthcare systems represented in this and other multi-national trials could limit the generalizability of these results to specific populations. Similarly, the inconsistent use of dexamethasone may have affected observed outcomes, as is supported by the results of RECOVERY and REMAP-CAP. Importantly, EMPACTA addresses COVID-19 in vulnerable and underrepresented populations, including those identifying as Alaska Native, American Indian, Asian, Black, and Hispanic. The disproportionate effect of COVID-19 on these and other underserved and minority groups is well documented.[18-19]

Jessica A. Ward, Pharm.D.
April 2021

Tocilizumab for the Treatment of Severe COVID-19 Pneumonia in Critically Ill Patients: Trendy or Tried-and-True?

Guideline Recommendations

The Infectious Diseases Society of America (IDSA) currently recommends the use of dexamethasone 6 mg IV or PO for 10 days (or until discharge), or an equivalent dose of another glucocorticoid, for critically ill patients with COVID-19. They suggest use in hospitalized patients with severe COVID-19 experiencing hypoxemia and against use in hospitalized patients without evidence of hypoxemia. IDSA recommendations for tocilizumab use have been updated to incorporate the results of the newly published RCTs previously reviewed. Tocilizumab is now suggested as a potential adjunct to the standard of care, particularly in patients who have not improved with glucocorticoid treatment. For those patients who are concerned for potential tocilizumab-related adverse effects or who have improved with glucocorticoid treatment, the use of tocilizumab may be "reasonably declined." Both of these suggestions are noted to have a very low quality of evidence. Though the greatest benefit of tocilizumab was seen among patients who had a proven hyperinflammatory state identified by CRP or IL-6 levels, current guidelines do not require the use of an objective laboratory threshold to guide therapy.[20]

The Society of Critical Care Medicine (SCCM) Guidelines for the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU do not address the use of tocilizumab.[21] The National Institutes of Health (NIH) released a statement regarding tocilizumab use in March 2021 to address the findings of these recent studies. The Guideline Panel moderately recommends tocilizumab in combination with dexamethasone for critically ill patients with COVID-19 admitted to the ICU within the last 24 hours and requiring respiratory support and in non-critically ill patients with "rapidly increasing" oxygen requirements and elevated inflammatory markers. This statement also uniquely includes recommendations for patients who may be at higher risk for adverse effects related to tocilizumab therapy, including (1) significant immunosuppression; (2) alanine transaminase >5 times the upper limit of normal; (3) high risk of gastrointestinal hemorrhage; (4) uncontrolled, serious non-SARS-CoV-2 infection; (5) absolute neutrophil count <500 cells/µL; or (6) platelet count <50,000 cells/µL.[22]

Conclusions

The use of tocilizumab for the treatment of COVID-19 has been debated throughout the pandemic. Recently published randomized controlled trial data support tocilizumab use in severe or critically ill patients with hypoxia and hyperinflammation. Several important patient characteristics have emerged as potentially strong influences on treatment success and should inform treatment decisions: the requirement of respiratory support, duration of illness, presence of hyperinflammation, and use of glucocorticoids. Though mortality benefit was not consistently reported amongst the trials, the data suggest the presence of other benefits, including reduced time to clinical recovery, rates of intubation, escalation of care, and time to ICU discharge. Preventing progression to intensive care or mechanical ventilation could contribute significantly to better patient outcomes over time and improvements in health-systems' capacity to care for COVID-19 patients, particularly during surges. Surges in COVID-19 cases have placed enormous strain on health-systems to provide care to a number of critically ill patients that exceed existing capacity. Situations requiring rationing of equipment including ventilators early in the pandemic, emphasize the importance of identifying treatments and supportive strategies that preserve healthcare resources.

The results of the tocilizumab arm of RECOVERY, COVACTA, REMAP-CAP, and EMPACTA trials are encouraging, and treatment guideline recommendations have been updated to incorporate these results at an unprecedented speed. Despite these positive results, the optimal place in therapy for tocilizumab is not fully defined. Following more than fourteen months of rapid gains and losses in treatment popularity and expected benefit, there remains room for skepticism. Further evaluations of tocilizumab in different patient populations and potentially different regimens are warranted and underway. If tocilizumab is utilized for severe or critical COVID-19, patient-specific factors should be considered to weigh the potential benefits and risks of treatment.

Jessica A. Ward, Pharm.D.
April 2021

Tocilizumab for the Treatment of Severe COVID-19 Pneumonia in Critically Ill Patients: Trendy or Tried-and-True?

References

1. Huang C, Want Y, Li C, RenL, Zhao J, Hu Y, Zhang L, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan China. Lancet. 2020;395(10223):497-506.
2. Siddiqi HK and Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Heart Lung Transplant. 2020;39:405-407.
3. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607-613.
4. 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;46:846-848.
5. Lavillegrand J-R, Garnier M, Spaeth A, Mario N, Hariri G, et al. Elevated plasma IL-6 and CRP levels are associated with adverse clinical outcomes and death in critically ill SARS-CoV-2 patients: inflammatory response of SARS-CoV-2 patients. Ann Intensive Care. 2021;11(1):9. [online ahead of print].
6. Iba T, Levy TH, Levi M, Connors JM, Thachil J. Coagulopathy of Coronavirus Disease 2019. Crit Care Med. 2020;48(9):1358-1364.
7. Tocilizumab. In: Lexi-Drugs. UpToDate, Inc. Updated 2021. Accessed 19 April 2021.
8. Klopfenstein T, Zayet S, Lohse A, Balblanc J-C, Badie J, Royer P-Y, et al. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. Med Mal Infect. 2020;50(5):397-400.
9. Somers EC, Eschenauer GA, Troost JP, Golob JL, Gandhi TN, Wang L, et al. Clin Infect Dis. 2020. PMID: 32651997. [online ahead of print]
10. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: A randomized clinical trial. JAMA Int Med. 2021;1818(1):24-31. [online ahead of print]
11. Hermine O, Mariette X, Tharaux P-L, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: A randomized controlled trial. JAMA Int Med. 2021;1818(1):32-40. [online ahead of print]
12. "Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia." Roche, 29 Jul. 2020. Roche, https://www.roche.com/investors/updates/inv-update-2020-07-29.htm. Press release. Accessed 20 April 2021.
13. Radbel J, et al. Use of tocilizumab for COVID-19-induced cytokine release syndrome: A cautionary case report. Chest. 2020;158(1):e15-19.
14. Vikse J and Henry BM. Tocilizumab in COVID-19: Beware the risk of intestinal perforation. Int J Antimicrob Agents. 2020;56(1):106009.
15. Horby PW, Pessoa-Amorim G, Peto L, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. medRxiv 2021: Available at: https://doi.org/10.1101/2021.02.11.21249258. Accessed 10 April 2021.
16. Rosas I, Brau N, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. N Engl J Med 2021;384:1503-1516.
17. Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19 . N Engl J Med 2021;384(16):1491-1502.
18. Salama C, Han J, Yau L, Reiss WG, Kramer B, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. N Engl J Med; 384:20-30.
19. Tai DBGT, Shah A, Doubeni CA, Sia IG, Weiland ML. The disproportionate impact of COVID-19 on racial and ethnic minorities in the United States. Clin Infect Dis. 2021;72(4):703-706.
20. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 4.2.0. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 19 April 2021.
21. SCCM Guidelines: Alhazzani W, Evans L, Alshamsi F, Moller MH, Ostermann M, et al. Surviving Sepsis Campaign guidelines on the management of adults with Coronavirus Disease 2019 (COVID-19) in the ICU: First update. Crit Care Med. 2021;49(3):e219-e234. Accessed [21 April 2021].
22. NIH Guidelines: COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 21 April 2021.

Jessica A. Ward, Pharm.D.

April 2021