EDITORIAL

Time to Reassess Tocilizumab's Role in COVID-19 Pneumonia

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In this issue of *JAMA Internal Medicine*, 3 important articles[1-3] explore the use of tocilizumab in coronavirus disease 2019 (COVID-19) pneumonia. Tocilizumab is a humanized monoclonal antibody that binds human interleukin 6 (IL-6) receptors. It is used routinely in inflammatory arthritis, giant cell arteritis, and cytokine release syndrome after chimeric antigen receptor T-cell therapy. Its use recently proliferated after early observations from China showed increased risk of death in patients with COVID-19 and elevated IL-6 levels,[4] and nonrandomized studies[5,6] suggested benefit from tocilizumab treatment. In many centers across the United States, off-label use of tocilizumab became standard of care for patients with COVID-19 and evidence of hyperinflammation. However, practice patterns have varied, and guidelines from the National Institutes of Health[7] and the Infectious Disease Society of America[8] now recommend against the use of tocilizumab except in the context of a clinical trial. Although an increasing number of observational studies[9-11] have suggested mortality benefit, data from randomized clinical trials (RCTs) of tocilizumab in COVID-19 are sorely needed to inform clinical practice.

Related articles

The studies reported by Salvarani et al for the RCT-TCZ-COVID-19 Study Group (RCT-TCZ-COVID-19)[1] and Hermine et al for the CORIMUNO-19 Collaborative Group (CORIMUNO-TOCI-1)[2] provide clinicians with their first look at peer-reviewed RCT results. In addition, preliminary results from COVACTA[12] and EMPACTA,[13] 2 multicenter, randomized, double-blind, placebo-controlled trials, have just been released. These studies, complemented by the largest observational study of tocilizumab in COVID-19 published to date, from the Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19 (STOP-COVID) investigators,[3] supply the raw material needed for a critical appraisal of tocilizumab use in COVID-19. For clinicians practicing on the front lines of the COVID-19 pandemic and weary of the deluge of research findings coming their way, now is the time to step back and reconsider the proper placement of tocilizumab in their COVID-19 treatment algorithms.

How should we interpret, and more importantly operationalize, findings from these studies? In the following discussion, several considerations that should influence our conclusions are highlighted.

Observational Studies and Residual Confounding

Even the best observational studies can be affected by residual confounding. With more than 60 000 COVID-19 publications listed in PubMed and multiple clinical trials under way, our choice of COVID-19 therapeutics can and should rely on the best possible evidence from randomized trials. In contrast to findings from STOP-COVID[3] and a growing number of observational studies,[9-11] none of the tocilizumab randomized trials reported mortality benefit at 28 or 30 days,[1-3,12,13] and only 2 of these[2,13] reported outcomes meeting predefined thresholds for clinical efficacy (**Table**).

The STOP-COVID tocilizumab study[3] stands out from other observational studies owing to its large size and focus on patients admitted to intensive care units (ICUs) at leading academic centers across the United States. The investigators used observational data from a large, multisite study and adjusted for confounding using a Cox proportional hazards model with inverse probability weighting. Reduced time to death and risk of death at 30 days were observed in patients treated with tocilizumab. However, there are potentially important differences in treatment groups at baseline (tocilizumab-treated patients were younger and had fewer comorbidities but were more likely to have hypoxemia and elevated levels of inflammatory markers). The authors appropriately acknowledge and attempt to adjust for these differences, but even careful statistical methods cannot completely overcome the risk of residual confounding in observational studies.

Despite their inherent limitations, carefully conducted retrospective clinical studies can provide critical insights into proper clinical management, especially when results of RCTs are unavailable. The STOP-COVID investigators[3] rapidly collected and analyzed data in the midst of a global pandemic and should be applauded for their efforts to establish a generalizable evidence base for COVID-19 management decisions. Nonetheless, randomized trials will ultimately determine tocilizumab's role in COVID-19.

Not All Randomized Trials Are Equal

The trials reported by the RCT-TCZ-COVID-19 Study Group[1] and the CORIMUNO-19 Collaborative Group[2] are similar in size, enrolled participants with similar clinical severity, and are strengthened by their multisite designs. Both are limited by the lack of blinding and placebo controls. However, the similarities stop there, because these trials included very different study populations that deserve careful consideration.

Salvarani et al[1] enrolled hospitalized patients in Italy with severe COVID-19 who required oxygen by nasal cannula but did not yet require ICU-level care. Their objective was to study the effect of early tocilizumab administration (≤8 hours of randomization). The trial was stopped early by the data and safety board for futility, after initial analyses did not find evidence of improvement in primary outcomes (development of a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen <150 mm Hg, ICU admission, or death). Two

Table. Comparison of Major Tocilizumab COVID-19 Studies Reported to Date

Study characteristic	Gupta et al[3] (STOP-COVID)	Salvarani et al[1] (RCT-TCZ-COVID-19)	Hermine et al[2] (CORIMUNO-TOCI-1)	COVACTA[12]	EMPACTA[13]
Design					
Type	Observational retrospective	Randomized prospective	Randomized prospective	Randomized prospective	Randomized prospective
Blinded	NA	No	No	Yes (double)	Yes (double)
Placebo-controlled	NA	No	No	Yes	Yes
Enrollment					
No. of sites	68	24	9	67	69
Countries	US	Italy	France	Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, United Kingdom, US	Brazil, Kenya, Mexico, Peru, South Africa, US
No. of participants	3924	126	131	450	389
No. tocilizumab treated	433	60[a]	63	225[b]	194[b]
Clinical severity[c]					
Moderate	No	No	No	No	No
Severe	Yes	Yes	Yes	Yes	Yes
Critical	Yes	No	No	Yes	No
Intervention					
Tocilizumab	Within 2 d of ICU admission	8 mg/kg ×2 Doses, 12 h apart	8 mg/kg ×1, Possible second dose on day 3	8 mg/kg ×1, Possible second dose	8 mg/kg ×1, Possible second dose
Comparator	Usual care	Usual care	Usual care	Usual care plus placebo	Usual care plus placebo
Outcomes[d]					
Primary, effect size	Time to death: Threshold for efficacy met; HR, 0.71 (95% CI, 0.56 to 0.92) 30-d mortality: Threshold for efficacy met; RD, 9.6% (95% CI, 3.1% to 16.0%)	Pao_2:Fio_2 <150 mm Hg, ICU admission, or death: Threshold for efficacy not met; RR, 1.05 (95% CI, 0.59 to 1.86)[e]	WHO-CPS score >5 on day 4: Threshold for efficacy not met; ARD, −9.0% (90% CrI, −21.0% to 3.1%); posterior probability of ARD <0 of 89.0% Survival without NIV or MV by day 14: Threshold for efficacy met; HR, 0.58 (90% CrI, 0.33 to 1.00), posterior probability of HR<1 of 95.0%	Difference in clinical status using a 7-category scale at day 28: Threshold for efficacy not met; OR, 1.19 (95% CI, 0.81 to 1.76)	Death or MV by day 28: Threshold for efficacy met; HR, 0.56 (95% CI, 0.32 to 0.97)
28- or 30-d mortality, tocilizumab vs comparator, effect size[f]	27.5% vs 37.1%; RD, 9.6% (95% CI, 3.1% to 16.0%)	3.3% vs 1.6%; RR, 2.10 (95% CI, 0.20 to 22.6)	11.1% vs 11.9%; aHR, 0.92 (95% CI, 0.33 to 2.53)	19.7% vs 19.4%; ARD, 0.3% (95% CI, −7.6% to 8.2%)	10.4% vs 8.6%; ARD, 2.0% (95% CI, −5.2% to 7.8%)
Trial registration	NCT04343898	NCT04346355	NCT04331808	NCT04320615	NCT04372186

Abbreviations: aHR, adjusted hazard ratio (HR); ARD, median absolute risk difference; CORIMUNO-TOCI-1, Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients-Tocilizumab Trial; CrI, credible interval; ICU, intensive care unit; MV, mechanical ventilation; NA, not applicable; NIV, noninvasive ventilation; OR, odds ratio; RCT-TCZ-COVID-19, Open-label Randomized Multicenter Study to Evaluate the Efficacy of Early Administration of Tocilizumab in Patients With COVID-19 (coronavirus disease 2019) Pneumonia; Pao_2:Fio_2, ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen; RD, risk difference; RR, rate ratio; STOP-COVID, Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19; WHO-CPS, WHO 10-point Clinical Progression Scale.

[a] Treatment assignment at enrollment. Crossover between treatment arms was permitted in the setting of clinical worsening.

[b] Numbers are derived from ClinicalTrials.gov and F Hoffman-La Roche Ltd.[12,13] Number of tocilizumab-treated participants is assumed based on planned 1:1 tocilizumab to placebo assignment.

[c] Definitions varied by study. This classification attempts to group by National Institutes of Health COVID-19 management categories.[7] Patients were or were not included with a given NIH severity scale.

[d] Efficacy estimated by the STOP-COVID investigators using an emulated target trial with observational data.

[e] Stopped early by the data and safety monitoring board for futility.

[f] Not a primary outcome for all studies; included here to facilitate comparison.

important characteristics of their population and treatment groups deserve extra attention.

First, the study population had very few deaths, with 2.4% overall mortality 30 days after randomization in the intention-to-treat analysis. This mortality rate is surprisingly low for a study of hospitalized patients with severe COVID-19, especially in Italy. Recent estimates indicate an overall case fatality rate of 13.2% among all comers (outpatients and hospitalized patients) with confirmed COVID-19 in Italy.[14] The trial's low mortality rate is likely driven by its exclusion criteria; participants were excluded if they were ineligible for ICU admission owing to comorbidities and clinical criteria that varied by site. The concept of ICU ineligibility will be unfamiliar to most US clinicians but was an unfortunate reality during Italy's pandemic response. Second, 14 of 60 patients assigned to the usual care treatment group ultimately received tocilizumab owing to clinical worsening. This

was permitted per study protocol, and per-protocol and intention-to-treat analysis results were similar, but treatment with tocilizumab in both the intervention and comparator groups complicates interpretation of the results. Although these 2 characteristics limit the trial's generalizability, the value of its prospective, randomized design cannot be understated.

The other prospective, randomized trial reported herein, CORIMUNO-19-TOCI-1,[2] enrolled hospitalized patients in France with moderate or severe COVID-19 pneumonia and oxygen requirement but who did not require high-flow oxygen by nasal cannula, noninvasive ventilation, or mechanical ventilation (World Health Organization clinical progression scale [WHO-CPS] score of 5). In layman's terms, they studied a population of patients with COVID-19 who were sick enough to require oxygen by low-flow nasal cannula and who would typically be managed on the floor (ie, not in the ICU) in US hospitals. The parent CORIMUNO trial also enrolled patients with more severe disease, but these patients were not included in the present study. Unlike the other randomized trials, the investigators used Bayesian statistical methods to assess efficacy.

One of 2 predefined thresholds for treatment efficacy was met; the posterior probability of improved survival without the need for noninvasive or mechanical ventilation by day 14 in the treatment group (their late outcome) was 95.05%, just exceeding the threshold of greater than 95%.[2] Reduced risk of a WHO-CPS score of greater than 5 at day 4 (their early outcome) was not observed. In contrast to the study by Salvarini et al,[1] the overall 28-day mortality rate was 11.5% and more in line with what might be expected in well-resourced hospitals in the global North. The narrow focus of CORIMUNO-19-TOCI-1 and its more representative patient population make its findings easier to generalize. Its findings suggest that tocilizumab may improve outcomes at 14 days, but the significance of this finding is unclear in light of newly released preliminary results from the COVACTA[12] and EMPACTA[13] trials.

COVACTA[12] and EMPACTA[13] are double-blind, placebo-controlled RCTs sponsored by F Hoffman-La Roche Ltd, tocilizumab's manufacturer, and conducted at sites worldwide. Peer-reviewed analyses are not yet available, but early press releases reported mixed results. The COVACTA study,[12] conducted across North America and Europe, reported failure to meet predefined efficacy thresholds and no mortality difference at day 28. Tocilizumab-treated patients had reduced hospital lengths of stay, but other secondary outcomes were negative. The EMPACTA study of patients largely from minority racial and ethnic groups across the Americas and Africa[13] reported efficacy in its primary end point, reduction of mechanical ventilation or death by day 28. However, secondary outcomes were negative, and no difference in mortality was observed at day 28.

Aware that the antiviral remdesivir has been widely adopted without clear evidence of mortality benefit, one might ask, "Is reduced risk of mechanical ventilation in some patient populations enough to motivate tocilizumab use?" Findings from the CORIMUNO-TOCI-1[2] and EMPACTA[13] studies suggest that tocilizumab may reduce the need for mechanical ventilation and, by extension, ICU-level care in some patients with severe COVID-19. However, the answer will depend on in-depth analysis of results from COVACTA,[12] EMPACTA,[13] and other studies nearing completion.

Things May Change

As with everything in the COVID-19 era, things may change. At least 5 other RCTs of tocilizumab in COVID-19 are under way.[15-19] These include double-blinded, randomized, placebo-controlled trials, as well as the massive, pragmatic Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial[17] being conducted across the United Kingdom. Studies focused on different patient populations and outcomes will better define tocilizumab's role in COVID-19 management.

For now, however, findings from the randomized trials described herein do not support routine tocilizumab use in COVID-19. Differences in mortality attributable to tocilizumab at day 28 or 30 were not observed across all randomized trials. Only 2 of the 4 trials reported evidence of efficacy, one based on a single primary outcome measure that barely met its predefined efficacy threshold. Although observational studies by the STOP-COVID investigators[3] and others[9-11] report mortality benefit and other positive outcomes, priority should be given to the randomized trial results when developing clinical algorithms.

There is an important caveat relevant to these and other therapeutic trials in COVID-19: longer-term outcomes may tell a different story. We know that the hyperinflammatory state induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in some patients is a major driver of COVID-19 morbidity and mortality. Prolonged hospitalization and rehabilitation are common among patients hospitalized with severe COVID-19. It is possible that blunting the immune response with tocilizumab will reduce morbidity and mortality over the long haul. It is also possible that treatment-related adverse events and secondary infections will become more apparent over time, although these were rare in the studies described herein.

Conclusions

Newly released randomized trials suggest a potential role for tocilizumab in COVID-19 but do not show clear evidence of efficacy, in contrast to observational studies. Their findings do not support the routine use of tocilizumab for COVID-19 in most settings. I plan to wait out the torrent of positive observational studies and reconsider tocilizumab's use in COVID-19 if, and only if, more compelling data from randomized trials emerges.

ARTICLE INFORMATION

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