Compiling Observational Research During a Pandemic: A Necessary Bridge

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Coronavirus disease 2019 (COVID-19) has altered the scientific landscape, upending a great many things we had wrongly assumed were immutable. Gone are the days, if indeed they ever existed, when studies came out at a deliberate pace, with a pause for reflection and synthesis. Press releases and nonreviewed preprints offer the sneak peeks that were once the purview of abstracts at scientific meetings. And the pace is torrential—all occurring at a time when practicing clinicians are stretched thin managing high clinical volumes and the associated burnout. As of early June 2020, there were an astonishing 674 active interventional COVID-19 trials, of which 21 were randomized, controlled trials (RCTs) with tocilizumab [1]. In fact, this editorial became a striking example of this phenomenon. We submitted it on 14 October 2020. In the week that followed, 3 tocilizumab RCTs were published, along with another large observational cohort [2–5]. In the face of such rapid churn, it is tempting to question whether there is value in compiling retrospective, observational cohorts at all. Maybe we should just sit back and bide our time until the RCTs arrive.

Two principal factors argue against this wait-and-see approach, however.

First, the recent surge of tocilizumab RCTs aside, coordinated, multicenter, adequately powered COVID trials are the exception [6, 7]. Many studies will fail to achieve goal enrollment before pandemic dynamics shift, leaving researchers unable to offer definitive conclusions due to small sample size. Such was the fate, for example, of an early remdesivir trial [8]. Second, with no sign that the pandemic is abating, clinicians and patients need the best answers today that the scientific literature can provide. As a bridge to the randomized trials, the exercise of rapidly compiling and analyzing information from the deluge of emerging observational data is the sturdiest foundation we can build [9].

In this issue of *Clinical Infectious Diseases*, Malgie et al take on this challenge in a methodologically clear and well-written systematic review and meta-analysis that aggregates information from 10 observational studies of interleukin 6 (IL-6) receptor antagonist therapy, including 1358 patients with COVID-19, of whom 554 (41%) received tocilizumab [10]. A 12% lower mortality rate was observed among patients who received tocilizumab compared with those who did not.

The headline results are tantalizing for clinicians and patients who are desperate for better therapies, particularly the suggestion that the number needed to treat to save a life may be as low as 11. However, as acknowledged by the authors, there are multiple known limitations to these observational data.

Patient-level information was not available, study heterogeneity was high, there was heavy use of concomitant COVID-19 therapeutics, and there were baseline differences in treatment groups. Definitions of the severity of COVID-19 illness were also diverse among studies, and investigators could not perform sensitivity analyses by disease severity or many other patient-level factors to account for confounding or selection biases. Therefore, the finding of a mortality benefit requires supportive evidence from RCTs.

Unfortunately, the limited information available from early RCTs of tocilizumab and other IL-6 receptor antagonists has, thus far, been either negative or mixed. The first 3 peer-reviewed trials, with 499 patients between them (285 assigned to tocilizumab treatment) did not provide compelling evidence of benefit [2–4, 11]. It is certainly possible that the next wave of trials will be more encouraging. However, a phase 3 RCT for sarilumab (Kevzara) was stopped early for futility and a slight imbalance in adverse events among treatment groups [12]. Preprint information for the COVACTA study of tocilizumab, which included 294 patients receiving tocilizumab and 144 receiving placebo, showed no significant effects in the primary outcome of improvement in ordinal score or in 28-day mortality [13]. Of note, a smaller proportion of patients in the tocilizumab group received corticosteroids than in the control group (36% vs 55%), which may have impacted study results. Faster time to hospital discharge and fewer days in the intensive care unit

were seen in the COVACTA tocilizumab group compared with controls. Top-line results from the EMPACTA study, which included 389 patients, reported meeting the primary endpoint of reduced likelihood of progression to mechanical ventilation or death, but the improvements seen were mostly related to the mechanical ventilation component [14]. The press release information did not report significant reductions in 28-day mortality, time to hospital discharge, or improvements in ordinal score compared with placebo. Detailed study results are not yet available, and neither of these studies has yet undergone peer review.

When results are mixed, one explanation may be that there is benefit for some patients but not all. Subgroup analyses from RCTs and information from observational cohorts may help identify clinical criteria for informed patient selection. Based on the data presented here and results from the early RCTs, group characteristics to further investigate include receipt of corticosteroids, baseline disease severity, timing of symptom onset to diagnosis and initiation of treatment, and perhaps additional markers of a dysregulated inflammatory response. Indeed, a critically important observation in this meta-analysis is that a mortality benefit of tocilizumab is not apparent when glucocorticoid coadministration is taken into account.

For IL-6 receptor antagonists to be incorporated into standard practice, we believe that future comparisons must include and rigorously control exposures to corticosteroids, especially in critically ill patients for whom trial data are strongest for a corticosteroid benefit. The devastating effects of a dysregulated inflammatory response are evident in acute COVID-19. We now know corticosteroid use impacts mortality [7, 15]. Thus, placebo or no-intervention comparisons for therapeutics that are targeting the immune response are less informative unless they can be put into the context of the known effects of corticosteroids. Whether to use steroids and long-acting immune

modulators together or separately is another important clinical management question, especially if some benefit is ultimately shown with placebo-controlled trials of IL-6 receptor antagonists.

In addition to showing definitive evidence of efficacy, IL-6 receptor antagonists must overcome additional barriers before incorporation into standard practice, including justification for higher costs and potential adverse effects from immune modulation. While use of short courses of steroids in acute infections is common and generally accepted in treating selected critically ill patients, use of a long half-life immune modulator would represent a larger shift in practice. In addition, IL-6 receptor antagonists are not the only immune modulators under investigation. Multiple other agents are under study, including interferon beta, IL-1 inhibitors, and multiple Janus kinase (JAK) inhibitors. JAK inhibitors are less selective in their target than tocilizumab, and early press release information reported benefit in recovery time among patients who received baricitinib in addition to remdesivir compared with remdesivir alone [16]. Indeed, it is worth celebrating that we are in a position that would have seemed enviable just a few months ago. There are multiple medications that have proven beneficial in the treatment of severe COVID, and trial results for additional antivirals and immunomodulatory agents are eagerly anticipated. Adaptive trial platforms have moved quickly to update standard-of-care comparator arms to enable meaningful comparisons [17, 18].

There is a lot we don't know about COVID-19, especially the inflammatory response. Malgie et al's meta-analysis used methods that combined observational data and produced a suggestive benefit from tocilizumab, particularly in patients who did not receive corticosteroids. In contrast, RCT data are emerging that, thus far, are inconclusive, without the reported mortality benefit. On balance, there is currently no clear role for tocilizumab or other IL-6 receptor

blockers in the management of severe COVID. Future comparisons to corticosteroids and other immunomodulators, either alone or in combination, will help determine tocilizumab's place, if any, in the hierarchy of effective COVID treatments.

Note

References

1. Kouzy R, Abi Jaoude J, Garcia Garcia CJ, El Alam MB, Taniguchi CM, Ludmir EB. Characteristics of the multiplicity of randomized clinical trials for coronavirus disease 2019 launched during the pandemic. JAMA Netw Open **2020**; 3:e2015100.
2. 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 clinical trial. JAMA Intern Med **2020**: E1–8. doi:10.1001/jamainternmed.2020.6820.
3. 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 Intern Med **2020**: E1–8. doi:10.1001/jamainternmed.2020.6615.
4. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med **2020**: 1–12. doi:10.1056/NEJMoa2028836.
5. Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. JAMA Intern Med **2020**: E1–E11. doi:10.1001/jamainternmed.2020.6252.
6. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—final report. N Engl J Med **2020**; 383:1813–26.
7. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19—preliminary report. N Engl J Med **2020**: 1–11. doi:10.1056/NEJMoa2021436.
8. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet **2020**; 395:1569–78.
9. Petkova E, Antman EM, Troxel AB. Pooling data from individual clinical trials in the COVID-19 era. JAMA **2020**; 324:543–5.
10. Malgie J, Schoones JW, Pijls BG. Decreased mortality in COVID-19 patients treated with tocilizumab: a rapid systematic review and meta-analysis of observational studies. Clin Infect Dis **2020**; ciaa1445:1–8 Available at: https://doi.org/10.1093/cid/ciaa1445.
11. Parr JB. Time to reassess tocilizumab's role in COVID-19 pneumonia. JAMA Intern Med **2020**: E1–E4. doi:10.1001/jamainternmed.2020.6557.

12. Press Release 2 July 2020. Sanofi and Regeneron provide an update on Kevzara (sarilumab) phase 3 U.S. trial in COVID-19 patients. Available at: https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00. Accessed 8 October 2020.

13. Rosas I, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. medRxiv **2020**. doi:10.1101/2020.08.27.20183442.

14. Press Release 17 September 2020. Genentech's phase III EMPACTA study showed Actemra reduced the likelihood of needing mechanical ventilation in hospitalized patients with COVID-19 associated pneumonia. Available at: https://www.gene.com/media/press-releases/14881/2020-09-17/genentechs-phase-iii-empacta-study-showe. Accessed 8 October 2020.

15. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA **2020**; 324:1330–41.

16. Press Release 14 September 2020. Baricitinib in combination with remdesivir reduces time to recovery in hospitalized patients with COVID-19 in NIAID-sponsored ACTT-2 trial. Available at: https://investor.lilly.com/news-releases/news-release-details/baricitinib-combination-remdesivir-reduces-time-recovery. Accessed 8 October 2020.

17. National Institutes of Health. Accelerating COVID-19 therapeutic interventions and vaccines (ACTIV). Available at: https://www.nih.gov/research-training/medical-research-initiatives/activ. Accessed 8 October 2020.

18. Adaptive COVID-19 treatment trial (ACTT). Available at: https://clinicaltrials.gov/ct2/show/NCT04280705. Accessed 8 October 2020.