Cost-effectiveness of tocilizumab in severe COVID-19: to see or not to see

Lauren Pischel, M.D.[1,2] and George Goshua, M.D.[3,4]

[1]Section of Infectious Diseases, Yale School of Medicine, New Haven, Connecticut, USA

[2]Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, Connecticut, USA

[3]Section of Hematology, Yale School of Medicine, New Haven, Connecticut, USA

[4]Department of Health Policy and Management, Harvard T.H. Chan School of Public Health Boston, Massachusetts, USA

Corresponding Author Contact:

Full Name: George Goshua

333 Cedar Street, New Haven CT 06520

Email: george.goshua@yale.edu

The hyperinflammatory phase that can be seen in patients hospitalized with SARS-CoV-2 infection, characterized in part by plasma cytokine profiling and autopsy studies early in the COVID-19 pandemic, spurred investigation into the potential therapeutic effects of immunomodulation. Contemporaneous studies of the cellular mediators of this hyperinflammation demonstrated the involvement of activated peripheral $CD4^+$ and $CD8^+$ T lymphocytes.[1,2] Concomitant induction of pro-inflammatory $CD14^+CD16^+$ monocytes with high expressions of interleukin-6 (IL-6) was thought to further potentiate an immune response that can result in severe lung pathology.[1] Clinical use of selective cytokine blockade, such as the IL-6 receptor antagonist tocilizumab, in treating such patients by physicians in China[2] paved the way for dozens of clinical trials globally examining this strategy. In parallel with study of IL-6 receptor antagonist therapy at that time were investigations into interleukin-1 and Janus kinase inhibition, initially due to some overlapping clinical features of severe COVID-19 with secondary hemophagocytic lymphohistiocytosis and macrophage activation syndrome.[3]

Earlier randomized clinical trials of tocilizumab therapy showed conflicting results, affected by the heterogeneity introduced with different inclusion criteria, timing of medication administration, imbalance in baseline characteristics such as dexamethasone use, and in some cases underpowered to detect a mortality benefit. This landscape changed with the remarkable work of investigators in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) Collaborative Group, which conducted by far the largest clinical trial of tocilizumab therapy in the treatment of adult patients hospitalized with COVID-19 who were suffering from hypoxia and systemic inflammation. The RECOVERY trial reported a mortality benefit with the use of tocilizumab, when added to therapy with dexamethasone.[4]

In this issue of *Clinical Infectious Diseases,* Sinha and Linas examine the cost-effectiveness of tocilizumab from the perspective of the United States' (US) health system, given its expense alongside a noted mortality benefit when tocilizumab therapy is added to usual care that includes dexamethasone for hospitalized patients with severe COVID-19.[5] A major strength of their analysis lies in abrogating a criticism of the RECOVERY trial by modeling both a higher baseline mortality scenario as reported in the trial and additionally modeling a separate lower mortality scenario that is more representative of the clinical reality in the United States. Moreover, although some centers have successfully utilized lower tocilizumab dosing, Sinha and Linas account for the cost of up to two 800mg doses of tocilizumab administration per patient in both scenarios, an important practical point in the care of hospitalized patients with COVID-19. The authors report their modeling results for both scenarios in US dollar (USD) costs per quality-adjusted life-year (QALY), finding the incremental cost effectiveness ratio (ICER) for combination therapy as compared to dexamethasone alone to be $16,520 [95% credible interval $10,760-51,350] and $26,840 [95% credible interval $14,800-101,030] in the higher and lower mortality scenarios, respectively. Utilizing a commonly accepted US willingness-to-pay (WTP) of $100,000 USD, the probability analyses in the two mortality scenarios show tocilizumab being cost-effective in more than 98% and 76% of 10,000 simulations each.

Accounting for additional secondary outcomes in the RECOVERY trial would have allowed for a more precise ICER calculation. These would be more favorable towards tocilizumab, given the decreased median hospital length-of-stay and need for invasive mechanical ventilation in the tocilizumab group in the RECOVERY trial. To overly focus on these details would be to miss the bare beauty of the authors' work, whose goal in this report was to inform clinicians of the cost-effectiveness of combination therapy with tocilizumab and dexamethasone, as they design their own treatment protocols. With this in mind, Sinha and Linas needed only a mortality benefit derived from the addition of tocilizumab

therapy in the treatment of patients with severe COVID-19 to convincingly demonstrate that the addition of tocilizumab is cost-effective in most circumstances in the US.

Sinha and Linas also correctly note that in lower and middle income countries, where WTP thresholds are lower than that in the US, price reductions for tocilizumab would likely be necessary. A more granular analysis utilizing patient-level data from RECOVERY, unavailable to the authors, may show additional QALY benefit from mitigating clinical sequelae of immune dysregulation in COVID-19 survivors. For example, we now know that the hyperinflammatory phase of COVID-19 brings with it significant endothelial dysfunction while disruption of the Ang-Tie2 axis may be directly tied to chronic lung disability, reported so far at a median follow-up of 3 months.[6] Additionally, dysregulated immunothrombosis in the setting of COVID-19 is reinforced by multiple hypercoagulable mechanisms and is clinically characterized by any one or a combination of venous, arterial, and microvascular thrombosis. Depending on thrombotic severity, these can also have lifelong consequences for patients who survive. Now that tocilizumab should be an accepted inclusion in the treatment paradigm of select hospitalized patients with COVID-19 where resources allow, an opportunity exists to prospectively evaluate the effects of combination therapy with tocilizumab and dexamethasone on the accompanying crescendo of these vascular and hematologic effects.

The authors are to be commended for showing that a mortality benefit seen with combination therapy in severe COVID-19 is largely sufficient to justify tocilizumab expense, from a health system perspective in the United States. We are hopeful that our colleagues taking care of patients with COVID-19 the world over will also stand to benefit from the authors' work by borrowing the mortality benefit seen in RECOVERY and applying it to their own health systems in a similar analysis as conducted by Sinha and Linas.

Author Contribution Statement: LP and GG wrote and edited the invited editorial commentary.

Funding Information: No funding to report.

Conflict of Interest Disclosure: The authors declare no conflicts of interest.

Citations

1. Zhou Y, Fu B, Zheng X, et al. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. *Natl Sci Rev* **2020**; 7(6): 998-1002.
2. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A* **2020**; 117(20): 10970-10975.
3. Ingraham NE, Lofti-Emran S, Thielen BK, et al. Immunomodulation in COVID-19. *Lancet Respir Med* **2020**; 8(6): 544-546.
4. 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.
5. Sinha P and Linas B. Combination therapy with tocilizumab and dexamethasone cost-effectively reduces Coronavirus disease 2019 mortality. *Clin Infect Dis* **2021** [Epub ahead of print].
6. Villa E, Critelli R, Lasagni S. Dynamic angiopoietin-2 assessment predicts survival and chronic course in hospitalized patients with COVID-19. *Blood Adv* **2021**; 5(3): 662-673.