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BRIEF REPORT

Combination Therapy With Tocilizumab and Dexamethasone Cost-Effectively Reduces Coronavirus Disease 2019 Mortality

Pranay Sinha and Benjamin P. Linas

Section of Infectious Diseases, Department of Internal Medicine, School of Medicine, Boston University, Boston, Massachusetts, USA

(See the Editorial Commentary by Pischel and Goshua on pages 2119–20.)

Recent randomized trials suggest that interleukin-6 inhibitors reduce mortality due to severe coronavirus disease 2019. Using a decision tree model, we found that tocilizumab is cost-effective with an estimated incremental cost-effectiveness ratio of $16 520 per quality-adjusted life year gained (95% credible interval, 10 760–51 530).

Keywords. tocilizumab; COVID-19; IL-6 inhibitors; cost-effectiveness; health economics.

Although compelling observational data suggested that interleukin-6 (IL-6) inhibitors such tocilizumab and sarilumab reduce mortality and morbidity associated with severe coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2), this effect was not seen in early randomized clinical trials [1–3]. Recently, 2 large randomized controlled trials demonstrated a meaningful mortality benefit. The number needed to treat to prevent mortality was 12 and 16, respectively, in the REMAP-CAP and RECOVERY studies [4, 5]. IL-6 inhibitors are now recommended for patients with severe or critical COVID-19 by the UK COVID-19 guidelines as well as the Infectious Diseases Society of America. To inform use of IL-6 inhibitors, we developed a decision tree model to investigate the cost-effectiveness of adding tocilizumab to dexamethasone for severe COVID-19.

METHODS

Analytic Overview

We incorporated data from the RECOVERY group titled, "Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open–label, platform trial," in Britain into a decision tree model to project the quality-adjusted life years (QALYs), discounted lifetime medical costs, and incremental cost effectiveness ratio (ICER) of 3 strategies for managing severe COVID-19 (Supplementary Figure 1) [4]: dexamethasone, both dexamethasone and tocilizumab (combination therapy), and supportive care alone.

Given the higher COVID-19 mortality in the United Kingdom compared with the United States, we also considered a scenario where the relative risks for death after receiving dexamethasone or combination therapy are the same as reported in the RECOVERY trial, but mortality with supportive care alone is similar to that of US cohorts.

Model structure: The decision tree model simulates progression from severe COVID-19 to survival or death.

Costs: We obtained the cost of dexamethasone ($12 for 6 mg orally for 10 days) and tocilizumab ($5304 for 800 mg intravenous single dose) from goodrx.com [6]. As suggested by the Second Panel on Cost–Effectiveness in Health and Medicine, we also factored in annual health expenses for COVID-19 survivors ($6929 per year) based on the 2016 Medical Expenditure Panel Survey [7, 8]. We calculated present value of costs assuming a 3% discount rate:

$$Cost\ of\ Living = Annual\ Cost\ of\ Living \times \frac{1-(1+Discount\ Rate)^{-Life\ expectancy\ at\ age}}{Discount\ Rate}$$

QALYs: We projected years of life saved using the mortality data from the RECOVERY trial. Of participants who received combination therapy, 457 of 1664 (27.4%) died. Of those who received corticosteroids alone, 565 of 1721 (32.8%) died. Finally, 127 of 367 (34.6%) of individuals who only received supportive care died. We estimated age-specific life expectancy from the Social Security actuarial table [9]. Subsequently, we discounted the life expectancy using the following formula:

$$Years\ of\ Life\ Saved = 1 \times \frac{1-(1+Discount\ Rate)^{-Life\ expectancy\ at\ age}}{Discount\ Rate}$$

To adjust years of life gained for quality of life lost due to chronic lung disease, we calculated the n-weighted mean of post–COVID-19 forced vital capacity (FVC) reported in a systematic review (95.8% expected; range, 82.4–108.8; Supplementary Figure 2) [10]. We estimated QALYs by multiplying years of life saved by the QALY weight corresponding to the FVC of survivors as listed in the Tufts cost-effectiveness analysis registry [11] (Supplementary Table 1).

Base Case Parameters

We assumed the mean age of the cohort to be 63 years based on trial data. We calculated probabilities of mortality in each strategy from reported clinical trial data (Supplementary Table 1).

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Correspondence: P. Sinha, 801 Massachusetts Ave, Crosstown Building, Suite 2021A, Boston, MA 02118 (Sinha.Pranay@pm.me).

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Lower Mortality Scenario

Based on observed data from New York City, we simulated a lower absolute mortality rate (14.6%) without treatment and assumed the same relative risks of death for dexamethasone and combination therapy that were observed in RECOVERY [12].

Sensitivity Analyses

To assess the robustness of our results, we conducted both deterministic and probabilistic sensitivity analyses. To conduct deterministic sensitivity analysis, we defined a priori feasible ranges around core parameter values and then repeated the analysis multiple times, each time ranging 1 parameter value through its feasible interval. We present the results of 1-way sensitivity analyses in tornado diagrams. Next, we conducted 2-way sensitivity analyses in which we simultaneously varied the cost of tocilizumab ($2652–$10 608) and the mortality associated with combination therapy at the same time. We used a wider range of mortality for both the base case (0.219–0.329) and low mortality scenarios (0.092–0.138). We present the results of 2-way sensitivity analyses in standard 2-dimensional arrays.

Lastly, we performed probabilistic sensitivity analysis (PSA). We defined uncertainty in parameter values using probability density functions (PDFs) around each parameter value. We then used Monte Carlo simulation to repeat the analysis 10 000 times, each time drawing the value of all model parameters from their PDF. We assumed beta distribution for survival probabilities and gamma distributions for costs. The result is 10 000 model outcomes, each one incorporating simultaneous uncertainty from all model parameters. We present the results of PSA using cost-effectiveness acceptability curves. In addition, we represent uncertainty around base case results using 95% credible intervals (CI) from PSA.

RESULTS

Base Case Analysis

Use of combination therapy resulted in 9.36 (95% CI 2.19–15.44) QALYs saved as compared to 8.66 (95% CI:2.00–14.11) QALYs with dexamethasone alone, and 8.43 (95% CI: 1.97–14.11) QALYs with supportive care alone. Costs associated were $83 130 (95% CI, $23 700–$124 390) with the combination therapy, $71 630 (95% CI, $16 300–$109 720) with dexamethasone therapy, and $69 700 (95% CI, $15 880–$107 350) with the supportive care strategy. The ICER for combination therapy compared with dexamethasone alone was $16 520/QALY (95% CI, 10 760–51 530; Table 1).

Low Mortality Scenario

The ICER for combination therapy compared with dexamethasone alone was $26 840/QALY (95% CI, $14 800–$101 030; Table 1).

1-Way Sensitivity Analysis

For both scenarios, 1-way sensitivity analyses found that the 2 parameters with the greatest impact on the ICER were age (baseline assumption, 63.3 years; range, 37.9–91.8) and mortality associated with dexamethasone (baseline assumption, 0.328; range ±10%). The ICER of combination therapy compared with dexamethasone alone increased with increasing age and decreasing mortality rate on dexamethasone. At the upper bound of age, the ICER was $42 730/QALY, and at the lower bound of dexamethasone mortality rate, it was $29 290/QALY (Supplementary Figure 3).

2-Way Sensitivity Analysis

In 2-way sensitivity analysis for both the base case and lower mortality scenarios, the dexamethasone and tocilizumab combination remained cost-effective over most combinations of the cost of tocilizumab and benefits associated with combination

Table 1. Base Case Analyses

Strategy	Cost, $	Incremental Cost, $	QALYs	Incremental Effect (QALYs Gained)	Incremental Cost-Effectiveness Ratio,[a] $
Base model					
Supportive care alone	69 700 (15 880–107 350)	Ref	8.43 (1.97–14.11)	Ref	Ref
Dexamethasone	71 630 (16 300–109 720)	1930 (–3910–8740)	8.66 (2.00–14.11)	0.23 (–0.48–1.12)	8320 (6760–8870) [b]
Dexamethasone and tocilizumab	83 130 (23 700–124 390)	11500 (5950–17670)	9.36 (2.19–15.44)	0.70 (0.13–1.44)	16520 (10760–51530)[c]
Lower mortality scenario					
Supportive care alone	91 020 (21 070–140 370)	Ref	11.01 (2.62–18.40)	Ref	Ref
Dexamethasone	91 780 (21 350–140 500)	760 (–5750–8630) [b]	11.10 (2.64–18.30)	0.09 (–0.73–1.09) [b]	8400 (6710–8870) [b]
Dexamethasone and tocilizumab	100 080 (21 350–150 230)	9060 (4850–12030) [c]	11.41(2.71–18.87)	0.31 (0.06–1.09) [c]	26840 (14800–101030) [c]

Abbreviation: QALY, quality-adjusted life year.

[a]Incremental cost-effectiveness ratio.

[b]Incremental cost-effectiveness ratio of dexamethasone compared with supportive care alone.

[c]Incremental cost-effectiveness ratio of dexamethasone and tocilizumab compared with dexamethasone alone.

therapy. The analysis did identify combinations, however, that resulted in combination therapy not being cost-effective. In the base case, when we assumed that the mortality associated with combination therapy was ≥0.323 and the cost of tocilizumab was ≥$5516, the ICER of combination therapy was >$100 000/QALY. In the low mortality scenario, when mortality with combination therapy was ≥0.131 and the cost of tocilizumab was ≥$9490, the ICER was >$100 000/QALY (Supplementary Figure 4).

Probabilistic Sensitivity Analysis

Cost-effectiveness conclusions were highly robust to uncertainty. As seen in the cost-effectiveness acceptability curve, dexamethasone and tocilizumab combination was favored at a willingness to pay (WTP) of $100 000 in >98% of iterations in the base case scenario and >76% in the lower mortality scenario (Supplementary Figure 5).

DISCUSSION

Our model suggests that the addition of tocilizumab to dexamethasone is likely a cost-effective intervention to reduce mortality from severe COVID-19 based on data from the RECOVERY trial. Combination therapy remained cost-effective in a lower mortality scenario, similar to observed rates in the United States. However, probabilistic sensitivity analyses suggest that the favorability of combination therapy would be less certain if the mortality rate among patients with severe COVID-19 was reduced through secular means.

We assumed a large range of tocilizumab costs in sensitivity analyses given regional variations in costs and dosing. While the RECOVERY and REMAP-CAP trials advocated for an 800-mg dose with provisions for a second dose, other centers have reported encouraging results with a single 400-mg dose [1]. If future studies validate the lower dose, the cost-effectiveness would increase considerably. These analyses were made from the perspective of the United States. In lower- and middle-income countries, price reductions in tocilizumab would likely be necessary given lower willingness-to-pay thresholds.

This analysis has limitations. The ICERs we report are likely underestimates, as we did not have access to primary trial data and were therefore unable to account for reductions in mechanical ventilation, length of hospitalization, or severity of chronic lung disease in those receiving combination therapy. However, the goal of this analysis was to assess cost-effectiveness, which we were able to demonstrate with the mortality benefit alone. Inclusion of additional benefits of combination therapy would strengthen our conclusions.

Furthermore, this model cannot reconcile the contradictory findings of earlier studies of tocilizumab for COVID-19 that did not demonstrate mortality benefit. This may be because earlier studies included individuals with less severe disease, individuals who received tocilizumab after inflammatory damage had occurred, and differences in corticosteroid use [1, 3]. To avoid overestimation of mortality benefit, we used data from the RECOVERY study to parameterize our model as it reported a lower estimate for mortality benefit compared with REMAP-CAP. We also used probabilistic sensitivity analysis as well as scenario analysis to thoroughly explore the uncertainty in mortality benefit. We conclude that unless the RECOVERY trial committed sizable type 1 errors, tocilizumab is almost certainly cost-effective, even in settings with lower expected mortality.

In conclusion, tocilizumab in addition to dexamethasone is a cost-effective intervention for individuals severely ill with COVID-19.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The funders had no role in study design, analysis, or reporting.

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