International Journal of Infectious Diseases 104 (2021) 671–676

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Remdesivir and systemic corticosteroids for the treatment of COVID-19: A Bayesian re-analysis

Todd C. Lee[a,b,c,*], Emily G. McDonald[b,d], Guillaume Butler-Laporte[c], Luke B. Harrison[a], Matthew P. Cheng[a], James M. Brophy[c,e]

[a] Division of Infectious Diseases, Department of Medicine, McGill University, Montréal, Canada
[b] Clinical Practice Assessment Unit, Department of Medicine, McGill University, Montréal, Canada
[c] Department of Epidemiology, Occupational Health, and Biostatistics, McGill University, Montréal, Canada
[d] Division of General Internal Medicine, Department of Medicine, McGill University, Montréal, Canada
[e] Division of Cardiology, Department of Medicine, McGill University, Montréal, Canada

ARTICLE INFO

Article history:
Received 24 November 2020
Received in revised form 25 January 2021
Accepted 26 January 2021

Keywords:
Remdesivir
Corticosteroids
Dexamethasone
COVID-19
Mortality
Bayesian meta-analysis

ABSTRACT

Background: The global death toll from coronavirus disease 2019 (COVID-19) has exceeded 2 million, and treatments to decrease mortality are needed urgently.
Objectives: To examine the probabilities of a clinically meaningful reduction in mortality for remdesivir and systemic corticosteroids.
Design, setting and participants: This was a probabilistic re-analysis of clinical trial data for corticosteroids and remdesivir in the treatment of hospitalized patients with COVID-19 using a Bayesian random effects meta-analytic approach. Studies were identified from existing meta-analyses performed by the World Health Organization.
Main outcomes and measures: Posterior probabilities of an absolute decrease in mortality compared with control patients, by subgroups based on oxygen requirements, were calculated for corticosteroids and remdesivir. Probabilities of ≥1%, ≥2% and ≥5% absolute decrease in mortality were quantified.
Results: For patients needing mechanical ventilation, the probability of ≥1% absolute decrease in mortality was 4% for remdesivir and 93% for corticosteroids. For patients needing supplemental oxygen without mechanical ventilation, the probability of ≥1% absolute decrease in mortality was 81% for remdesivir and 93% for dexamethasone. Finally, for patients who did not need oxygen support, the probability of ≥1% absolute decrease in mortality was 29% for remdesivir and 4% for dexamethasone.
Conclusions and relevance: Using a Bayesian analytic approach, remdesivir had low probability of achieving a clinically meaningful reduction in mortality, except for patients needing supplemental oxygen without mechanical ventilation. Corticosteroids were more promising for patients needing oxygen support, especially mechanical ventilation. While awaiting more definitive studies, this probabilistic interpretation of the evidence will help to guide treatment decisions for clinicians, as well as guideline and policy makers.

Background

The public health crisis caused by coronavirus disease 2019 (COVID-19) has led to unparalleled international scientific collaboration to find a safe and effective treatment, particularly for hospitalized patients. With close to 2 million deaths, treatments that can reduce mortality are needed urgently. Large multicentre clinical trials are underway, led by groups such as the US National Institutes of Allergy and Infectious Diseases (Adaptive COVID-19 Treatment Trial), the University of Oxford's Nuffield Department of Population Health (RECOVERY trial) and the World Health Organization (WHO) and participating countries (SOLIDARITY trial). While the pace of discovery may feel slow under the stress of the pandemic, the speed of accomplishment of groups such as these has been remarkable.

Two of the most promising treatments to date are systemic corticosteroids and remdesivir. Dexamethasone has been established as life-saving by reducing mortality in patients needing supplemental oxygen [rate ratio 0.82, 95% confidence interval (CI)

* Corresponding author at: Royal Victoria Hospital, 1001 Decarie Blvd, Room E5.1820, Montréal, QC H4A3J1, Canada.
E-mail address: todd.lee@mcgill.ca (T.C. Lee).

https://doi.org/10.1016/j.ijid.2021.01.065

0.72–0.94] and mechanical ventilation (rate ratio 0.64, 95% CI 0.51–0.81) (RECOVERY Collaborative Group, 2020). However, an effect was not demonstrated among those who did not need oxygen support (rate ratio 1.19, 95% CI 0.91–1.55). A subsequent meta-analysis of seven trials of critically ill patients conducted by WHO [WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, 2020] included the RECOVERY trial, and arrived at a similar conclusion in this subgroup (summary odds ratio 0.66, 95% CI 0.53–0.82).

In contrast, an absolute decrease in mortality has been more difficult to demonstrate with remdesivir. The first clinical trial to be published did not show an absolute decrease in mortality (Wang et al., 2020). Subsequently, the ATCC-1 trial (Beigel et al., 2020) did not conclusively demonstrate a benefit (hazard ratio 0.73, 95% CI 0.52–1.03). A third open label trial (Spinner et al., 2020) involving moderate-risk patients had low mortality overall (<2%), and did not provide further insight. Finally, data from the SOLIDARITY trial, the largest remdesivir trial to date with 5451 patients (WHO Solidarity Trial Consortium, 2021), did not show a significant decrease in mortality for remdesivir alone (rate ratio 0.95, 95% CI 0.81–1.11) or in their embedded meta-analysis of all available trials (rate ratio 0.91, 95% CI 0.79–1.05).

While failing to reach statistical significance, the point estimate and 95% CI of the pooled remdesivir results include the potential for an important decrease in mortality. Therefore, it could be premature to abandon remdesivir based on statistical significance alone. The remdesivir results were re-analysed using Bayesian methods (Spiegelhalter et al., 1999) to estimate the posterior probability that remdesivir could lead not only to a reduction in mortality, but also to a clinically meaningful reduction in mortality compared with usual care. These probabilities were then contextualized against the same analysis performed for systemic corticosteroids, including dexamethasone. The purpose of doing so was to help clinicians contextualize the high-quality evidence and practice sensible medicine through Bayesian thinking (Seymour et al., 2020).

Methods

Study design

Bayesian methods were used to estimate the absolute reduction in mortality of remdesivir and systemic corticosteroids based on data available from systematic reviews and meta-analyses performed by WHO in September [WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, 2020] and December (WHO Solidarity Trial Consortium, 2021). PubMed was searched on 10 January 2021, which confirmed that no additional randomized controlled trials were available; however, two corticosteroid trials with additional patient data had been published since the WHO analysis, so those data were used instead (Jeronimo et al., 2020; Tomazini et al., 2020). The primary outcome was overall reduction in mortality compared with control patients, and three non-overlapping subgroups were pre-specified which matched those pre-specified for the largest trials (RECOVERY and SOLIDARITY trials): patients who needed mechanical ventilation; patients who needed supplemental oxygen without mechanical ventilation; and patients who did not need oxygen support.

Bayesian meta-analysis provides several advantages over frequentist approaches, including more rigorous assessment of overall uncertainty, especially between-study heterogeneity; more reliable analyses of smaller sample sizes; and the ability to provide direct probability statements conditional on current and prior data.

Data sources

Two authors (TCL and JMB) extracted the trial results available from each of the four controlled trials for remdesivir (Table 1). However, two noteworthy decisions were made as some of the outcomes were not reported with sufficient granularity. For the trial by Wang et al. (2020), the inclusion criteria required the use of oxygen; however, three patients in the placebo group were not receiving oxygen at the time of the first dose. Further, there was one mechanically ventilated patient in the placebo group. This study was included in the 'supplemental oxygen without mechanical ventilation' group as this represented most patients. For the trial by Spinner et al. (2020), oxygen requirement was an exclusion criterion; however, 14% and 19% of remdesivir and control patients, respectively, developed the need for supplemental oxygen between screening and the first dose, but the results did not separate mortality by oxygen requirement on day 1. As most patients did not receive oxygen support and due to the overall low mortality rate in both arms, this study was included in the 'no oxygen support' group.

For corticosteroids, results were extracted for patients from the RECOVERY (RECOVERY Collaborative Group, 2020), METCOVID (Jeronimo et al., 2020) and CODEX (Tomazini et al., 2020) trials, and the remainder of the data were extracted from the WHO meta-analysis of corticosteroids [WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, 2020]. For the REMAP-CAP (Writing Committee for the REMAP-CAP Investigators, 2020) trial, data from the WHO meta-analysis were used because 70 patients were included in their final paper who were enrolled at

Table 1
Twenty-eight-day mortality for all remdesivir trials.

Study	Remdesivir died	Remdesivir total	Control died	Control total
Mechanical ventilation	126	385	100	387
WHO SOLIDARITY (NEJM 2020)	98	254	71	233
ACTT-1 (NEJM 2020)	28	131	29	154
Supplemental oxygen without mechanical ventilation	242	2313	274	2190
WHO SOLIDARITY (NEJM 2020)	192	1828	219	1811
ACTT-1 (NEJM 2020)	28	327	45	301
Wang et. al (Lancet 2020)[a]	22	158	10	78
No oxygen support	19	1120	20	927
WHO SOLIDARITY (NEJM 2020)	11	661	13	664
ACTT-1 (NEJM 2020)	3	75	3	63
Spinner et al. (JAMA 2020)[b]	5	384	4	200

WHO, World Health Organization; ACTT, Adaptive COVID-19 Treatment Trial; NEJM, New England Journal of Medicine; JAMA, Journal of the American Medical Association.
[a] Three patients included in the placebo arm were not on oxygen at enrolment and one patient was on mechanical ventilation.
[b] Includes 55 and 38 patients, respectively, who went on oxygen between eligibility and receipt of first dose.

centres where care without corticosteroids was not available, and data excluding these subjects were not available with sufficient granularity.

Statistical analysis

To estimate the final (posterior) probability of differences in outcomes between the remdesivir and control groups, as well as the corticosteroid and control groups, objective data (binomial likelihood) for each study must be combined with previous beliefs according to Bayes' theorem (Spiegelhalter et al., 1999). The estimates of interest were absolute risk differences, which are easier for clinicians to conceptualize than hazard or risk ratios, and have more meaning for public health decisions.

The binary outcome data from each trial were transformed to logarithmic odds ratios (and their associated standard errors), which were subsequently analysed assuming a normal–normal hierarchical model. Under this model, individual trial outcomes and standard errors are modelled via normal distributions, using their means and standard errors as sufficient statistics. The second hierarchy level treats between-trial heterogeneity as an additive normal variance model. This provides a random-effects model to estimate two parameters: the overall effect (μ, the risk difference); and the positive heterogeneity τ between trials. Vague proper informative priors were used: μ centred at 0 (standard deviation = 4), which corresponds to no effect; and heterogeneity τ assumed to be half-normal prior (to ensure positive values), with a scale of 0.03. Sensitivity analyses were performed using different prior distributions (e.g. varying μ and/or using a half-Cauchy distribution for τ) to confirm the estimates were stable. This was operationalized with the bayesmeta package (Röver, 2020) in the R environment (R Core Team, 2019). For comparison, a random-effects meta-analysis for risk ratio is presented in the online supplementary material.

Next, figures of posterior density vs. absolute difference in mortality between treatment and control patients were generated. From these, simulations were used to calculate the posterior probability of any decrease in mortality, and whether the decrease in mortality exceeded 1 in 100 (1%), 1 in 50 (2%) and 1 in 20 (5%), graphically equivalent to the area under the posterior probability density curves.

Results

In total, data from four remdesivir trials including 7322 patients (Table 1) and eight corticosteroid trials including 7557 patients (Table 2) were included. Figures 1 and 2(a–c) show posterior density as a function of risk difference for mortality for remdesivir and corticosteroids vs. control patients, respectively, for the three subgroups. Table 3 shows the probabilities that remdesivir or corticosteroids reduce mortality at all, and by at least 1%, 2% and 5%. Remdesivir had a low probability of a clinically meaningful decrease in mortality in subgroups other than patients needing supplemental oxygen without mechanical ventilation, where the probabilities of a decrease in mortality overall and of at least 1%, 2% and 5% were 92%, 81%, 61% and 10%, respectively. Conversely, corticosteroids (predominantly dexamethasone) showed a high probability of a decrease in mortality (≥93% exceeding 1%) in all subgroups except patients who did not need oxygen support, where the probability of any decrease in mortality was only 7%.

Discussion

Remdesivir clinical trial results were evaluated by performing a Bayesian meta-analysis to provide estimates of the probability of a clinically meaningful effect. Remdesivir was found to be unlikely to benefit critically ill patients needing mechanical ventilation, with a 93% chance of no effect or increased mortality. In comparison, corticosteroids demonstrated strong evidence of benefit in patients needing advanced respiratory support or supplemental oxygen without mechanical ventilation. A potential benefit of remdesivir was found for patients needing supplemental oxygen without mechanical ventilation; however, using the analytic approach, the probability of a small meaningful effect on mortality (>1%) was only 81%. Finally, patients who did not need oxygen support were unlikely to benefit from either therapy, with the probability of ≥1% absolute decrease in mortality of 29% for remdesivir and 4% for corticosteroids.

In line with these findings, the National Institutes of Health (NIH) COVID-19 guidelines [as of 3 December 2020 (COVID-19 Treatment Guidelines Panel, 2020)] recommend dexamethasone without remdesivir for patients needing mechanical ventilation or extracorporeal membrane oxygenation. The NIH panel

Table 2
Twenty-eight-day mortality for all corticosteroid trials.

Study	Corticosteroid died	Corticosteroid total	Control died	Control total
Mechanical ventilation	277	697	469	1038
RECOVERY	95	324	283	683
DEXA-COVID	2	7	2	12
CoDEX	85	151	91	148
CAPE COVID[a]	10	61	17	59
COVID STEROID	4	7	0	6
REMAP-CAP[b]	18	68	10	49
Steroids-SARI	10	13	9	14
METCOVID	53	66	57	67
Supplemental oxygen without mechanical ventilation	330	1447	729	2768
RECOVERY	298	1279	682	2604
CAPE COVID[a]	1	14	3	14
COVID STEROID	2	8	2	8
REMAP-CAP[b]	8	37	19	43
Steroids-SARI	3	11	4	9
METCOVID	18	98	19	90
No oxygen support	90	531	145	1076
RECOVERY	89	501	145	1034
METCOVID	1	30	0	42

[a] Mortality at 21 days.
[b] Only includes patients who could have received usual care.

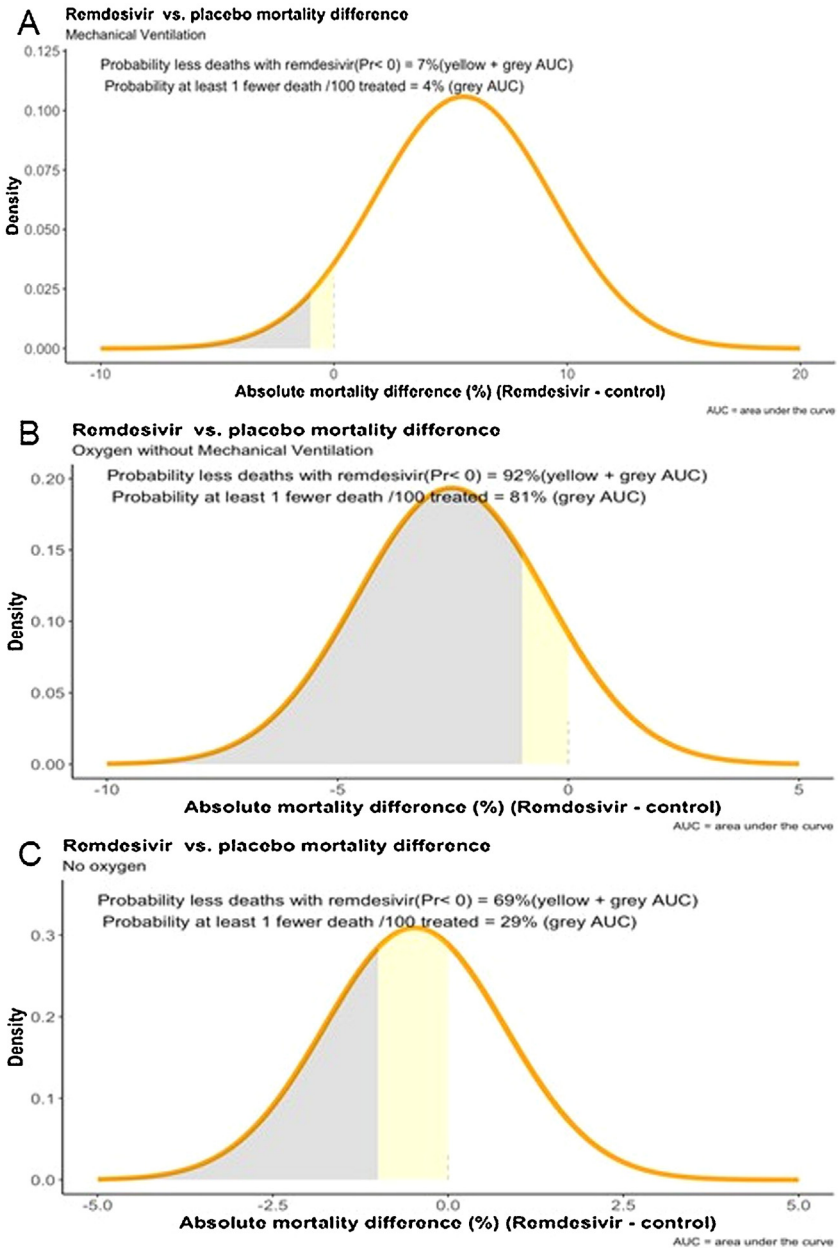

Figure 1. Probability density functions for combined posterior distributions of the included remdesivir trials. (a) Mechanical ventilation. (b) Supplemental oxygen without mechanical ventilation. (C) No oxygen support.

recommends dexamethasone either with remdesivir or alone for patients with high flow or non-invasive ventilation requirements and for those who are hospitalized and need oxygen without advanced support, remdesivir monotherapy with a lesser recommendation for combination therapy with dexamethasone or dexamethasone monotherapy. The present analysis suggests that the probability that dexamethasone and remdesivir will reduce mortality by >1% in this population is 93% and 81%, respectively. The estimates for dexamethasone are limited by lack of a large replication trial. However, given that dexamethasone is inexpensive, has a well-established safety record and is generally well tolerated, it seems reasonable to proceed with the treatment of hypoxic patients without such a confirmatory trial. Whether or not there is additional benefit from giving remdesivir in combination with corticosteroid treatment is unknown. In the SOLIDARITY trial, there was no evidence of effect modification of remdesivir for patients (approximately 50%) who also received corticosteroids (WHO Solidarity Trial Consortium, 2021). The role of remdesivir in this population would be a good target for a rapid and focused randomized controlled trial, and stratifying by the intensity of oxygen requirement would provide further clarity. Finally, among patients who do not need oxygen support, the NIH guidelines recommend against the use of dexamethasone and give a contextual recommendation for remdesivir. The present findings indicate that neither dexamethasone nor remdesivir are likely to benefit patients in this subgroup, if one accepts that a 1% mortality reduction is a reasonable threshold for clinically significant impact.

This analysis has several limitations. Firstly, the absence of individual patient data limits the ability to stratify for important subgroups including age, ethnicity, medical comorbidities and duration of illness. Such an analysis, although post-hoc, might better define which patients would gain the greatest benefit from remdesivir, or which groups would be best represented in confirmatory trials. Secondly, the authors were required to make

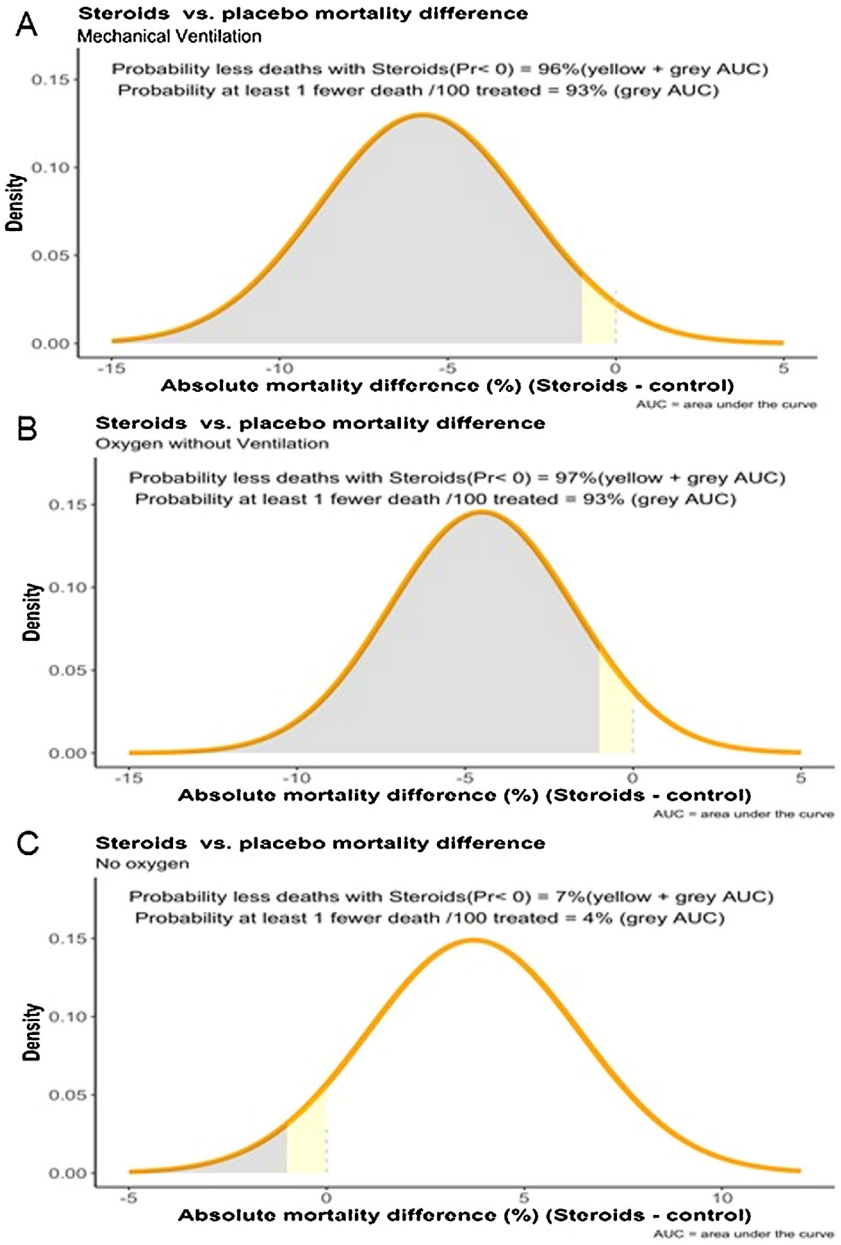

Figure 2. Probability density functions for combined posterior distributions of the included corticosteroid trials. (a) Mechanical ventilation. (b) Supplemental oxygen without mechanical ventilation. (C) No oxygen support.

Table 3
Probability of ≥1% absolute decrease in mortality by drug and subgroup.

Drug and subgroup	Probability of decrease in mortality			
	Any	≥1%	≥2%	≥5%
Mechanical ventilation				
Remdesivir	7%	4%	2%	0%
Corticosteroids	96%	93%	89%	62%
Supplemental oxygen without mechanical ventilation				
Remdesivir	92%	81%	61%	10%
Corticosteroids	97%	93%	85%	37%
No oxygen support				
Remdesivir	69%	29%	9%	1%
Corticosteroids	7%	4%	2%	0%

some assumptions in the subgroups because granular data were not available. However, the number of patients who may have been misclassified was small and/or mortality was unlikely in both control and treatment groups. Thirdly, in terms of contextualizing the effect size of remdesivir with corticosteroids, data for corticosteroid use outside of severe illness were limited and highly influenced by the RECOVERY trial (RECOVERY Collaborative Group, 2020). Importantly, this was not a network meta-analysis, but some indirect comparisons were made between corticosteroids and remdesivir. These treatments may not be directly comparable, and the authors' objective in doing so was only to contextualize the effect size of remdesivir compared with the only other currently proven effective therapy. Finally, the benefit in terms of time to 'recovery' or 'fitness to discharge' was not evaluated; this was reduced in the ATCC-1 trial and is an important

consideration given constraints on the availability of hospital beds. In the more generalized practice environment of SOLIDARITY sites, and with the limitations of an open label design, remdesivir did not accelerate time to recovery. For example, a higher proportion of patients remained in hospital on day 7 in the treatment group compared with the usual care group (69/2743 vs. 59/2708), and approximately equal numbers of patients in both treatment groups progressed to mechanical ventilation (295 vs. 284) (WHO Solidarity Trial Consortium, 2021). Notwithstanding these limitations, it is believed that this analysis provides a richer and complementary interpretation of the data to help guide clinicians to make appropriate use of remdesivir and corticosteroids in various subgroups of hospitalized patients.

Conclusions and relevance

Based on a Bayesian meta-analysis, the results of remdesivir and corticosteroid clinical trials were contextualized in terms of the probability of a meaningful impact on inpatient mortality. When viewed alongside the data for corticosteroids, particularly dexamethasone, the probability of a meaningful effect for remdesivir was lower. Remdesivir was found to be unlikely to reduce mortality in critically ill patients and those who do not need oxygen support; however, remdesivir may reduce mortality by $\geq$1% in patients needing non-invasive oxygenation. At an estimated cost of US$2340–3120 per 5-day course (O'Day, 2020), investment in a moderate probability of a 1% absolute reduction in mortality requires a substantial global commitment of funds. In the future, a cost-effectiveness analysis examining the potential for reduced length of hospital stay with 5 days of remdesivir would be a meaningful addition to the discussion. In addition, the added benefit of remdesivir in hypoxic patients needing non-invasive supplemental oxygen and treated with dexamethasone would be a good target for a rapid and focused randomized controlled trial. While awaiting such a definitive study, this probabilistic interpretation of the evidence may help guide treatment decisions for clinicians, as well as guideline and policy makers.

Conflict of interest

Drs Lee, Harrison and Cheng were co-investigators on CATCO, the Canadian arm of the WHO SOLIDARITY trial.

Funding

Drs Lee, McDonald and Brophy receive research salary support from the Fonds de Recherche Québec - Santé. Dr Butler-Laporte is supported by a scholarship from the Fonds de Recherche Québec - Santé and the Ministère de la Santé et des Services sociaux. The funders had no influence on the conduct or content of this article.

Ethical approval

Not required.

Acknowledgements

The authors wish to thank all the patients who volunteered for the included studies, and the investigators and research teams who performed and published them.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2021.01.065.

References

Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of COVID-19 – final report. N Engl J Med 2020;383:1813–36.
COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. Bethesda, MD: National Institutes of Health; 2020. Available at: https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/ [accessed 15.10.20].
Jeronimo CMP, Farias MEL, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomised, double-blind, phase IIb, placebo-controlled trial. Clin Infect Dis 2020;, doi:http://dx.doi.org/10.1093/cid/ciaa1177.
O'Day D. An open letter from Daniel O'Day, Chairman & CEO, Gilead Sciences 2020. Available at: https://www.gilead.com/news-and-press/press-room/press-releases/2020/6/an-open-letter-from-daniel-oday-chairman–ceo-gilead-sciences [accessed 15.10.20].
R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2019. Available at: https://www.R-project.org [accessed 08.02.21].
RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19 – preliminary report. N Engl J Med 2020;, doi:http://dx.doi.org/10.1056/NEJMoa2021436.
Röver C. Bayesian random-effects meta-analysis using the bayesmeta R package. J Stat Softw 2020;93:1–51.
Seymour CW, McCreary EK, Stegenga J. Sensible medicine – balancing intervention and inaction during the COVID-19 pandemic. JAMA 2020;324(18):1827–8.
Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR. An introduction to Bayesian methods in health technology assessment. BMJ 1999;319:508.
Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA 2020;324:1048–57.
Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA 2020;324:1307–16.
Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569–78.
WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) 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.
WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19 – interim WHO SOLIDARITY trial results. N Engl J Med 2021;384:497–511.
Writing Committee for the REMAP-CAP Investigators. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. JAMA 2020;324:1317–29.