Statistical Review and Evaluation

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1. Summary

This addendum to the statistical review of remdesivir discusses results from the SOLIDARITY treatment trial[1] conducted by the World Health Organization. The previously submitted statistical review briefly noted that this trial was meant to conclusively determine whether remdesivir provides a mortality benefit. The study was not discussed in any further detail because results were not yet known.

At the time of this writing the results are available[2] from a preprint. However, no additional materials or datasets have been reviewed.

The SOLIDARITY trial was a randomized, open label, multinational, large simple trial. The active treatments were remdesivir (intravenously administered at 200 mg on the first day and then 100 mg for the next 9 days), hydroxychloroquine, lopinavir-ritonavir, and interferon beta-1a. The hydroxychloroquine and lopinavir-ritonavir groups were previously dropped from the trial for futility due in part from results found in other clinical trials of these agents. When a patient was eligible for one or more active treatments that were locally available, he or she was randomized with equal probability to these groups or to an open-label standard of care control group. Results discussed in this review restrict to those participants concurrently randomized to remdesivir versus standard of care. This approach was considered statistically valid and yielded the same information for the (remdesivir – control) comparisons as a 1:1 randomization trial.

[1] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments. Accessed October 20, 2020.
[2] https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1. Accessed October 20, 2020.

The SOLIDARITY trial had a large sample size with 5451 patients randomized to remdesivir or the concurrent control group. This was a pragmatic trial in which study procedures and data collection were minimized and patients were managed according to local standards. This form of design is meant to facilitate enrollment and generalize to real world settings.

Baseline factors were well balanced between treatment groups. Approximately 35%, 45%, and 19% of patients were respectively <50, 50-69, and ≥70 years of age. Over 70% of patients had been hospitalized for under 2 days at the baseline visit, but it is unclear to how long patients had been symptomatic before treatment initiation. Over 60% of enrollment occurred in Asia or Africa with remaining enrollment roughly evenly split between Latin America and Europe. The study population was 62% male, 25% of patients had a history of diabetes, and 21% of patients had a history of heart disease. In terms of baseline respiratory support, approximately 28%, 63%, and 8% of subjects were respectively not receiving supplemental oxygen, receiving non-ventilatory oxygen support, and already ventilated.

The primary endpoint was in-hospital mortality. The understanding of this reviewer is that follow-up was not attempted for post-discharge deaths but that such events would be counted in the primary analysis if they were recorded.

One potential issue with an in-hospital mortality endpoint is that in theory it could be misleading if discharge times systematically differ between groups and there is appreciable post-discharge death. Representatives from the study team claimed at an October 10, 2020 teleconference with the Agency that post-discharge deaths were likely rare because discharge was prompted by improved patient status.

Results for in-hospital mortality were as follows.[3]

- Remdesivir: 301/2743 (11.0%)
- Local standard of care control group: 303/2708 (11.2%)
- (Remdesivir – control) risk difference: -0.2% (95% CI: -1.9% to 1.5%)

Hence, this trial did not detect a mortality benefit for remdesivir. Furthermore, the lower limit of the confidence interval for the risk difference ruled out any mortality advantage of more than 2% on the absolute difference scale.

The previous statistical review had stated that "There is remaining uncertainty regarding whether remdesivir reduces all-cause mortality." While numerical results in ACTT-1 were suggestive of a mortality benefit (particularly for the subgroup with non-ventilatory oxygen requirements) this larger trial was unable to confirm this hypothesis.

The ACTT-1 primary endpoint of time to recovery was largely driven by hospital discharges. In contrast to ACTT-1 the SOLIDARITY trial did not detect a remdesivir

[3] The confidence interval for the risk difference was computed by this reviewer as the authors had presented results in terms of a stratified relative risk. This analysis considers in-hospital mortality as a binary endpoint and does not attempt to account for censoring.

benefit on time to discharge. It also did not detect a benefit for an endpoint defined as the composite of mortality or progression to ventilation (for those not already ventilated at baseline).

The main question under consideration in this addendum is whether the SOLIDARITY results should alter the statement in the previous statistical review that "Overall, this application provides statistically reliable evidence that remdesivir is effective for the treatment of COVID-19 in hospitalized patients."

Collective results from the two trials are consistent with remdesivir having a neutral or small impact on all-cause mortality. While ACTT-1 results were suggestive of improved mortality there remained residual statistical uncertainty, and the most straightforward interpretation of the two trials is that they have now ruled out a large mortality benefit. In terms of treatment effects on non-mortality endpoints, it is considered unlikely that differences between ACTT-1 and SOLIDARITY represented only random variation. The SOLIDARITY authors have noted that chance baseline imbalances in the two trials led to remdesivir groups having disproportionately fewer ventilated patients than the control group in ACTT-1 and more ventilated patients than the control group in SOLIDARITY. However, is unlikely that this chance variation alone was responsible for the ACTT-1 finding of strong statistical evidence for a treatment effect on the primary endpoint of time of recovery, which was driven by results in patients who were not ventilated at baseline. Likewise, ACTT-1 provided strong evidence for an effect on the key secondary endpoint of the Day 15 ordinal scale using a proportional odds analysis, which represented a general shift to improved oxygen support levels at this timepoint. Rather than chance variation, the most straightforward interpretation of the two large trials is that there were heterogeneous treatment effects on non-mortality endpoints. This heterogeneity may have been influenced by the fact that ACTT-1 was double blind while SOLIDARITY was open label as well as other differences in the designs and background conditions. Consequently, the thinking of this reviewer is that SOLIDARITY results do not refute the treatment effects on the primary and key secondary endpoint in ACTT-1.

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