Letters

Concerns about subgroup analyses and reason for stopping remdesivir trial

I read with interest the results of the remdesivir arm of the Canadian Treatments for COVID-19 (CATCO) trial, published in *CMAJ*.[1] I would like to congratulate the entire team on this massive undertaking, in extremely challenging circumstances.

I do have a few concerns regarding the trial results and presentation, as follows:

1. How was the decision made to stop the trial in April? The authors described CATCO as a subtrial of the World Health Organization–led Solidarity trial.[2] In Solidarity, although no upfront sample size calculations were performed, there was an independent data safety and monitoring board (DSMB) that evaluated the trial results, and presumably decisions to stop were taken in consultation with the DSMB? The authors of the *CMAJ* article note that CATCO continued beyond the cessation of the Solidarity trial and an additional 300 patients were enrolled. Therefore, what triggered the decision to stop in April 2021? Did CATCO have an independent, Canadian DSMB? Did stopping occur after discussions with them? Or did the trial run out of funding?

2. If indeed there was no clear rationale for stopping in April 2021, are the results seen in CATCO a "random high" and a false positive? I feel this should be stated explicitly in the limitations section. In addition, note that for the primary outcome effect estimate and for the 60-day mortality effect estimate, the 95% confidence intervals cross 1.

3. In many ways, CATCO is a country-level subgroup of Solidarity, and most people would agree that subgroup results are only hypothesis generating and should be treated as such. I feel the conclusion overstates the findings and is potentially misleading.

4. Although it is biologically plausible that, when given early to patients on low-flow oxygen, remdesivir may be effective (supported by a recent trial of remdesivir for patients not in hospital[3]), the subgroups in CATCO do not show this signal for early versus late use of remdesivir (again noting the enormous limitations of subgroups). My point is that the conclusions should be toned down to reflect the uncertainty and limitations of the trial.

Once again, congratulations on this important undertaking.

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References

1. Ali K, Azher T, Baqi M, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. *CMAJ* 2022;194:E242-51.
2. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19—interim Solidarity trial results. *N Engl J Med* 2021;384:497-511.
3. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med* 2022;386:305-15.

Competing interests: Bharath Kumar Tirupakuzhi Vijayaraghavan was a site investigator at Apollo Hospitals for the World Health Organization Solidarity trial in India.