Remdesivir and COVID-19

In the first published placebo-controlled trial of remdesivir for treating severe COVID-19, Yeming Wang and colleagues[1] were unable to attain their primary endpoint of time to clinical improvement. Although admittedly underpowered due to early trial termination, remdesivir did not appear to affect rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA load decline and mortality when compared with placebo. Given these disappointing findings, we are left to wonder if a lack of clinically significant outcomes in placebo-controlled trials could have been predicted. By inhibiting early coronavirus life cycle in vitro[2] and in animal models,[3,4] remdesivir might require initiation before the peak viral replication, which is not feasible in the clinical human presentation of COVID-19.

In cell cultures exposed to murine coronavirus, early remdesivir initiation substantially decreased viral titres compared with control.[2] However, this treatment effect was completely lost when initiation occurred just 8 h after infection. In another study, mice administered early remdesivir relative to inoculation with SARS-CoV had substantially reduced lung damage compared with untreated cohorts, an effect that was lost when initiation was delayed by 2 days after inoculation.[3] The need for early treatment has been identified in additional animal models,[4] as Wang and colleagues[1] confirm, with remdesivir initiation following peak viral replication being unable to affect disease severity or mortality.

With in vitro and animal evidence suggesting remdesivir is optimally suited for viral prophylaxis or immediately following viral inoculation, why would there have been any reason to expect a different outcome in humans, where SARS-CoV-2 has a median incubation period of 4 days?[5]

We declare no competing interests.

*Matthew J Glaus, Serena Von Ruden
matthewglaus@chifranciscan.org

St. Francis Hospital, Federal Way, WA 98003, USA

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I commend Yeming Wang and colleagues[1] on their study in the difficult time of the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.

Wang and colleagues[1] calculated a sample size of 453 patients (302 to remdesivir and 151 to placebo). However, only 237 patients were enrolled and randomly assigned (158 to remdesivir and 79 to placebo). The authors' justification for not attaining the predetermined sample size was because at the time of the study, the COVID-19 outbreak was brought under control in China.

This justification is not supported by the facts. Between Feb 4 and Feb 5, 2020, 1 day before study recruitment commenced, 70 people in Hubei province (China) died of COVID-19 and 3694 new cases of the disease occurred in mainland China. By Feb 6, 2020, there were 28 035 cases of COVID-19 in mainland China.[2] On March 11, 2020, 1 day before the final day of the study recruitment, and the day a global pandemic was announced by WHO, there were 80 932 cases of COVID-19 in mainland China, with 4630 deaths.[3] During the study period, the SARS-CoV-2 virus was not under control in China even though lockdowns had occurred.[4,5] Ongoing study recruitment would probably have been possible given the proportion of COVID-19 patients who become critically unwell. This recruitment would have enabled the sample size of 453 to be achieved and definitive results to be obtained. Instead, as highlighted by the authors, the study has "insufficient power to detect assumed differences in clinical outcomes".[1]

It is important at this time of rapid data emergence and publication that key points regarding control, containment, infectivity, and treatments are scrutinised to the fullest degree to ensure that potentially effective treatments can be scientifically validated, and that immediate history is not incorrectly reported.

I receive funding from the Australian and New Zealand College of Anaesthetists and received funding from National Health and Medical Research Council Australia from 2016–20. I am a Fellow of the Australian and New Zealand College of Anaesthetists, a member of the Australian Society of Anaesthetists, Australian Medical Association, and Australian Institute of Company Directors. I am the Australasian Representative on the Scientific Affairs Committee of the World Federation of Societies of Anaesthesiologists.

Alicia Dennis
alicia.dennis@thewomens.org.au

Department of Anaesthesia, Royal Women's Hospital, University of Melbourne, VIC 3052, Melbourne, Australia

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