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## Remdesivir for coronavirus 2019 (COVID-19): More promising but still unproven

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### ABSTRACT

From December 2019 to May 22, 2020 the emerging and ever-increasing pandemic of coronavirus 19 (COVID-19) had no effective and safe treatment. Not surprisingly, remdesivir attracted worldwide attention. In a trial published online ahead of print, of 1063 patients, 541 were assigned at random to remdesivir and 522 to placebo. The primary prespecified endpoint was mean recovery time and patients assigned to remdesivir had a mean recovery time of 11 days versus 15 days for those assigned a random to placebo. ( $p < 0.001$ ). With respect to mortality, the prespecified secondary endpoint, 34/538 patients in remdesivir and 54/521 in placebo died after 28 days, yielding a possible 31% reduction that approached but did not achieve statistical significance ( $p = 0.059$ ).

The only other published trial of remdesivir randomized 237 patients in China. In that trial, 178 patients were assigned at random to remdesivir compared to 79 assigned to placebo. Those assigned at random to remdesivir experienced a possible but nonsignificant 23% faster time to clinical improvement of 21 days compared with 23 for those assigned to placebo [hazard ratio 1.23 [95% CI, 0.87-1.75]]. With respect to mortality there was no suggestion of any benefit. In fact, the mortality rate in those receiving remdesivir was 15% (22/150) compared with 13% (10/77) for those assigned to placebo.

Ongoing randomized trials should be designed, conducted and analyzed to provide the necessary reliable data on mortality to resolve the remaining clinical uncertainties.

From December 2019 to May 22, 2020, the emerging and ever-increasing pandemic of coronavirus 19 (COVID-19) had no effective and safe treatment. Not surprisingly, remdesivir has attracted worldwide attention.

In this Short Communication, we review the totality of available evidence, especially the reliable data from randomized trials to detect the plausible small to moderate effects. We conclude that the current totality of evidence on remdesivir supports an urgent necessity to obtain reliable data from randomized trials of sufficient size, dose and duration in order to distinguish reliably between the alternative hypothesis of a significant benefit on mortality and the null hypothesis.

Worldwide, from January to June 2020 over 7.1 million cases and over 400 thousand deaths from coronavirus 19 (COVID-19) have been reported. North and South America have reported over 3 million cases, with 2.0 million reported from Europe, over 1.3 million from Asia, over

189 thousand from Africa and over 8 thousand from Oceania [1]. These sobering statistics underscore the urgent need for worldwide collaborative efforts to test benefits and risks and implement treatment and prevention strategies of proven benefit.

On May 22, 2020, in the Adaptive Covid-19 Treatment Trial (ACTT-1) published online ahead of print, of 1063 patients, 541 were assigned at random to remdesivir and 522 to placebo. The primary prespecified endpoint was mean recovery time and patients assigned to remdesivir had a mean recovery time of 11 days versus 15 days for those assigned a random to placebo. ( $p < 0.001$ ). With respect to mortality, the prespecified secondary endpoint, 34/538 patients in remdesivir and 54/521 in placebo died after 28 days, yielding a possible 31% reduction that approached but did not achieve statistical significance ( $p = 0.059$ ).

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remdesivir compared to 79 assigned to placebo. Those assigned at random to remdesivir experienced a possible but nonsignificant 23% faster time to clinical improvement of 21 days compared with 23 for those assigned to placebo [hazard ratio 1.23 [95% CI, 0.87-1.75]]. With respect to mortality there was no suggestion of any benefit. In fact, the mortality rate in those receiving remdesivir was 15% (22/150) compared with 13% (10/77) for those assigned to placebo [3].

When the evidence is incomplete, it is appropriate for healthcare providers to remain uncertain [4]. The current alarming and ever-increasing pandemic of COVID-19, which has more than a 10 fold higher mortality rate than influenza [1], and, for which, dexamethasone is the only drug demonstrating a benefit on mortality [5], has created a situation of dire need. In such circumstances, regulatory and public health authorities appropriately feel the need to take action with only incomplete evidence which ultimately may or may not turn out to justify the early actions [6]. In that regard, it should be noted that, to the best of our knowledge, no other regulatory body throughout the world except for the United States (US) Food and Drug Administration (FDA), has taken such action, possibly due to their perception of the need for greater certainties about the balance of risks and benefits of remdesivir, especially with respect to mortality, which remains uncertain.

The most rational clinical decisions for individual patients and policy decisions for the health of the general public can be made when they are based on a sufficient totality of evidence [4]. At present, the totality of evidence on remdesivir for COVID-19 consists of the limited information from the two trials described above, as well basic research addressing possible mechanisms and animal studies suggesting that remdesivir inhibits animal and human coronaviruses similar to SARS-COV-2 [7–9]. In addition, several case reports and two case series which are descriptive studies of possible utility only to formulate, but not test hypotheses, have been published.

With respect to safety of remdesivir in the ACTT trial, 114 patients (21.1%) in the remdesivir group and 141 (27.0%) in the placebo group experienced serious adverse effects [1]. Specifically, 28 (5.2%) in remdesivir and 42 (8.0%) experienced respiratory failure. In the trial from China there were no significant differences in adverse event rates. In that trial the most commonly reported adverse events were constipation, hypoalbuminemia, hypokalemia, and liver function abnormalities. Further and more importantly, there were also no significant differences between the remdesivir and placebo groups for serious adverse events [2].

Additional potentially relevant information about the safety of remdesivir, may be inferred from the Pomona Tulinde Maisha (PALM) trial (Together Save Lives in the Kiswahili language) of Ebola virus which showed no benefit [10]. In that trial, 673 patients were randomized into 4 treatment arms, including 173 to remdesivir and 29 experienced serious adverse events. After a blinded review by an independent pharmacovigilance committee 4 events were judged to be due to study medications. In remdesivir, one fatality occurred during the infusion. It remains uncertain whether these results would be applicable to patients with COVID-19.

Early in the epidemic of Acquired Immune Deficiency Syndrome (AIDS) despite the existence of any known effective treatments, there was substantial resistance to the conduct of placebo-controlled trial. A single, small, randomized and placebo-controlled trial demonstrated evidence for a survival benefit of azathioprine (AZT). Although this amount of information was less than would typically be needed to support approval of a new drug, an expanded access program was approved by the US FDA and implemented. This action allowed many thousands of affected patients to receive this drug. Further evidence which accrued later, while not contradicting the initial short-term efficacy result, showed that the benefit was time-limited and that the initially studied dose was highly toxic and could be substantially reduced [6].

During the West African Ebola outbreak of 2014–15, there was also substantial resistance to the conduct of properly randomized trials.

Fortunately, concomitant with numerous delays, the epidemic had waned so avoidable premature deaths did not occur [6,11]. During the 2009 H1N1 influenza (“swine-flu”) outbreak, the US FDA issued an Emergency Use Authorization for peramivir, an experimental antiviral drug, for the treatment of hospitalized patients [12,13]. Within 24 h, more than 1100 critically ill patients with H1N1 were administered this agent. Although effectiveness of this agent was never clearly demonstrated, 31% of patients had an adverse event or medication error [13].

Randomized trials provide reliable results about small to moderate treatment effects because of their unique ability in large samples to distribute, on average, both known and unknown confounders equally between the groups [4,14]. Thus, the current randomized evidence renders remdesivir to be more promising for the treatment of hospitalized COVID-19 patients, but still unproven because of remaining uncertainties about whether there is a clear benefit on mortality. Fortunately, ongoing trials may provide the needed evidence. One such ongoing trial, sponsored by the World Health Organization, has a “best supportive care” arm as a control, and with mortality as the primary endpoint [15]. This trial is testing remdesivir as well as several other experimental treatments. In addition, the manufacturer of remdesivir is conducting another randomized trial comparing their drug to optimal standard of care in patients hospitalized for COVID-19. The primary endpoint of this trial is clinical improvement with mortality as a secondary endpoint [16].

We believe that the current evidence, albeit incomplete, justifies compassionate use of remdesivir for severely ill patients with COVID-19. We remain cautiously optimistic that further reliable randomized evidence that should be forthcoming soon will confirm or refute whether there is a mortality benefit of remdesivir for the treatment of COVID-19. At present, however, we must also remain cognizant of the alternative hypothesis. This is, to paraphrase Thomas Huxley, “The great tragedy of science - the slaying of a beautiful hypothesis by an ugly fact.” [17] The randomized data from ACTT-1 and China provide the hypothesis has become more promising based on the randomized data from ACTT-1 and China, but remains unproven due to a lack of sufficient randomized data on mortality. The ACTT and China randomized trials add important and relevant information to the evidence which remains incomplete so it is appropriate for healthcare providers to remain uncertain [4]. The most urgent necessity is to obtain reliable data from ongoing randomized trials of remdesivir of sufficient size, dose and duration in order to distinguish reliably between the alternative hypothesis of a significant benefit on mortality and the null hypothesis.

## CRediT statements

Richard Shih: Conceptualization, Methodology, Investigation, Writing Original Draft, Project Administration, Dennis Maki: Conceptualization, Methodology, Investigation, Writing-Review and Editing.

Charles H. Hennekens: Conceptualization, Methodology, Investigation, Writing-Review and Editing, Visualization, Supervision.

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## Declaration of competing interest

Professors Shih and Maki have no disclosures.

Professor Hennekens reports that he serves as an independent scientist in an advisory role to investigators and sponsors as Chair of data monitoring committees for Amgen, British Heart Foundation, Cadila, Canadian Institutes of Health Research, DalCor, and Regeneron; to the Collaborative Institutional Training Initiative (CITI), legal counsel for Pfizer, the United States Food and Drug Administration, and UpToDate; receives royalties for authorship or editorship of 3 textbooks and as co-inventor on patents for inflammatory markers and cardiovascular

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