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AUTHOR REPLY

Reply to Yan and Muller, "Remdesivir for COVID-19: Why Not Dose Higher?"

Kavita Juneja,[a] Rita Humeniuk,[a] Danielle Porter,[a] Huyen Cao,[a] Joy Feng[a]

[a]Gilead Sciences, Inc., Foster City, California, USA

In their Letter to the Editor "Remdesivir for COVID-19: Why Not Dose Higher?" Yan and Muller assert that the clinical efficacy of remdesivir at its currently approved dose (200 mg intravenously [i.v.] on day 1 followed by 100 mg/day i.v. for up to 9 days) is questionable and advocate for higher dosing. However, the totality of the available data demonstrates that remdesivir, at its current dose, is a safe and efficacious treatment for patients hospitalized with coronavirus disease 2019 (COVID-19).

In early 2020, Gilead and collaborators rapidly initiated multiple studies in parallel to address the urgent need for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) therapeutics. Selection of the RDV dosing regimen for the treatment of COVID-19 was based on the pharmacokinetics (PK) bridge from animal data to human doses and efficacy using (i) the results of *in vivo* efficacy studies conducted in SARS-CoV-2- and Middle East respiratory syndrome (MERS-CoV)-infected rhesus monkeys, (ii) available PK data in healthy rhesus monkeys, and (iii) PK and safety data from phase 1 single- and multiple-dose first-in-human studies (1–5). The dosing regimen selected (200 mg i.v. loading dose, followed by 100 mg/day i.v. maintenance dose for up to 10 days) proved to be safe and efficacious in three pivotal phase 3 studies, including ACTT-1, a randomized, double-blind, placebo-controlled study—the gold standard for evaluating the safety and effectiveness of investigational drugs.

ACTT-1 evaluated the safety and efficacy of a 10-day remdesivir regimen compared with placebo in hospitalized adults with COVID-19 ($n = 1{,}062$). Remdesivir was superior to placebo in shortening time to recovery ($P < 0.001$) and significantly improved odds of clinical improvement by day 15 compared with placebo ($P < 0.001$). The study also demonstrated safety, with a similar rate of adverse events in the remdesivir and placebo groups (6). Gilead-sponsored trials added to the evidence supporting remdesivir's positive benefit-risk profile in hospitalized patients. SIMPLE-Severe, a phase 3 randomized, open-label, multicenter study in hospitalized patients with severe COVID-19, showed that a shorter 5-day course of remdesivir produced a similar outcome to the longer 10-day course ($P = 0.1563$) (7). SIMPLE-Moderate, a phase 3 randomized, open-label, multicenter study, demonstrated that a 5-day remdesivir regimen produced greater odds of clinical improvement at day 11 compared with standard of care ($P = 0.0174$) (8). Both groups in SIMPLE-Moderate experienced similar rates of adverse events. Based on these data, the U.S. Food and Drug Administration issued an Emergency Use Authorization on 1 May 2020. Since then, remdesivir has received full or conditional approval in numerous countries, and >1 million patients have been treated with remdesivir at the current dose and duration. Collectively the data show that the approved dose of remdesivir achieves a favorable benefit-safety profile for patients.

Virologic outcomes were not assessed in these studies in real time because of the need for rapid study execution and limited testing capacity during the early stages of the pandemic, but analyses from the ACTT-1 study are ongoing. A recent case report in an immunocompromised patient with prolonged SARS-CoV-2 shedding demonstrated

Citation Juneja K, Humeniuk R, Porter D, Cao H, Feng J. 2021. Reply to Yan and Muller, "Remdesivir for COVID-19: why not dose higher?" Antimicrob Agents Chemother 65:e00085-21. https://doi.org/10.1128/AAC.00085-21.

This is a response to a letter by Yan and Muller https://doi.org/10.1128/AAC.02713-20.

Accepted manuscript posted online 18 March 2021

Published 18 March 2021

that remdesivir treatment resulted in a direct antiviral effect with suppression of viral replication in lung secretions (9). Notably, recent evidence from monoclonal antibody studies shows that viral load in the upper respiratory tract detected by nasopharyngeal swabs may have limited ability to predict COVID-19 outcomes (10).

The results of the WHO Solidarity study do not diminish the positive findings of these three pivotal phase 3 studies, nor do results from the Wang et al. study in China (11, 12). The Solidarity study, large and ambitious in scope, was designed and powered to evaluate a broad clinical endpoint of mortality. However, it was not designed to evaluate subgroups or more nuanced endpoints, such as time to recovery and odds of clinical improvement, which are important outcomes for both patients and overburdened health care systems (13, 14). The double-blind, placebo-controlled study conducted by Wang et al., although laudable in its design, lacked adequate power (underpowered at 58%) to draw meaningful conclusions, although the observed efficacy signal was consistent with the ACTT-1 findings among individuals with a symptom duration of >10 days (15).

Although the favorable benefit-risk profile for the currently approved dose and duration of remdesivir treatment has been clearly established, we also recognize the acute need to further enhance patient outcomes. Additional clinical trials are ongoing and planned to evaluate remdesivir in combination with anti-inflammatory agents in subpopulations and in outpatient settings. We will continue to share emerging data with regulatory authorities and the scientific and medical communities as we work together to help address the needs of patients with this devastating disease around the world.

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