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Perspective

FDA Approval of Remdesivir — A Step in the Right Direction

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On January 31, 2020, the U.S. secretary of health and human services declared a public health emergency in response to Covid-19. This disease, caused by the SARS-CoV-2 virus, can have severe manifestations, including pneumonia, respiratory failure, multiorgan failure, and death. Although there is now an extensive global search for therapies, there remains an unmet need for safe and effective treatment options for patients.

On May 1, 2020, on the basis of preliminary results from phase 3 trials, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to allow the use of remdesivir for the treatment of suspected or laboratory-confirmed Covid-19 in adult and pediatric patients hospitalized with severe disease.[1] The scope of the EUA was subsequently expanded on August 28, to allow use in a broader hospitalized population. On October 22, the FDA approved remdesivir for use in adults and pediatric patients (12 years of age or older and weighing at least 40 kg) for the treatment of Covid-19 requiring hospitalization.[2]

This approval was based largely on the results of three phase 3 clinical trials in hospitalized patients with disease of varying severity. These were the Adaptive Covid-19 Treatment Trial (ACTT-1) sponsored by the National Institute of Allergy and Infectious Diseases and the supportive trials GS-US-540-5774 and GS-US-540-5773 sponsored by Gilead Sciences. ACTT-1, which had a rigorous design, provided the most compelling evidence of efficacy.

ACTT-1 was a phase 3, multinational, randomized, double-blind, placebo-controlled trial that evaluated the safety and efficacy of remdesivir in hospitalized patients with mild, moderate, or severe Covid-19.[3] A total of 1062 eligible patients were randomly assigned in a 1:1 ratio to receive remdesivir or placebo for up to 10 days. The primary efficacy end point was time to recovery through day 29. In the overall population, the median time to recovery was 10 days in the remdesivir group as compared with 15 days in the placebo group (recovery rate ratio, 1.29; 95% confidence interval [CI], 1.12 to 1.49; P<0.001). The predefined key secondary end point of odds of clinical improvement at day 15, based on an eight-category ordinal scale, also significantly favored remdesivir over placebo (odds ratio, 1.54; 95% CI, 1.25 to 1.91). The 29-day mortality was 11% in the remdesivir group, as compared with 15% in the placebo group (hazard ratio, 0.73; 95% CI, 0.52 to 1.03) — a result that left uncertainty about whether remdesivir provides a survival benefit in addition to accelerating time to recovery.

GS-US-540-5774 was a phase 3, multinational, 1:1:1 randomized,

open-label trial that evaluated the safety and efficacy of 5 days of remdesivir, 10 days of remdesivir, and standard of care in 584 hospitalized patients with moderate Covid-19.[4] The primary efficacy end point was clinical status on day 11, assessed on a seven-category ordinal scale. The odds of improvement on the ordinal scale were higher in the 5-day remdesivir group at day 11 than in the group receiving the standard of care (odds ratio, 1.65; 95% CI, 1.09 to 2.48; P=0.02). The odds of improvement in clinical status did not differ significantly between the 10-day remdesivir group and the standard-of-care group (odds ratio, 1.31; 95% CI, 0.88 to 1.95).

GS-US-540-5773 was a phase 3, multinational, 1:1 randomized, open-label trial that evaluated the safety and efficacy of 5 days as compared with 10 days of remdesivir in 397 hospitalized patients with severe Covid-19.[5] The primary efficacy end point was clinical status assessed on a seven-point ordinal scale on day 14. After adjustment for baseline differences between groups, clinical status at day 14 did not differ significantly between patients assigned to 5-day and 10-day courses of remdesivir (odds ratio for improvement, 0.75; 95% CI, 0.51 to 1.12), with no differences in recovery or mortality rates. Overall, results in this trial were suggestive of similar treatment effects with 5-day and 10-day regimens in this patient population.

The main limitations of the Gilead-sponsored trials included their open-label design and the lack of a standard-of-care group in GS-US-540-5773. It is possible that the open-label design contributed to the differences in outcomes in these trials, specifically, a numerical difference favoring the 5-day remdesivir group over the 10-day remdesivir group in both trials. In GS-US-540-5773, virtually all patients in the 5-day group received 5 days of therapy or less, whereas nearly half of patients in the 10-day group received the full 10 days of therapy; similarly, in GS-US-540-5774, virtually all patients in the 5-day group received 5 days of therapy or less, whereas more than a third of patients in the 10-day group received the full 10 days of therapy. Hence, discharge decisions may have been influenced by the patients' assigned durations of intravenous therapy, which potentially affected results on the ordinal scale that ranged from 1 (not hospitalized) to 7 (death). The limitations of these trials led to uncertainty with respect to the optimal duration of treatment for hospitalized patients.

The FDA is aware of the recent preprint from the Solidarity trial, a large, open-label, simple, randomized trial that included a comparison of remdesivir with the standard of care in hospitalized patients with Covid-19. That trial's primary objective was to assess in-hospital mortality, and it did not find a statistically significant difference in mortality between the remdesivir and standard-of-care groups. This finding is not inconsistent with ACTT-1, which also did not establish a mortality difference between remdesivir and placebo. However, ACTT-1 did demonstrate robust results on time to recovery and odds of clinical improvement in a placebo-controlled, double-blind trial, whereas Solidarity was not designed to rigorously assess these end points.

The major safety signals identified in the FDA review included hepatotoxicity (manifested as an elevation in aminotransferase levels and associated with duration of administration) and hypersensitivity reactions, both of which are described in the prescribing information for remdesivir. The FDA considered the safety profile for remdesivir acceptable for the indicated patient population (i.e., adults and certain pediatric patients requiring hospitalization for treatment of Covid-19). Postmarketing pharmacovigilance will be important in further defining the safety profile of remdesivir.

The approval of a new drug product under the Food, Drug, and Cosmetic Act requires substantial evidence of effectiveness and a demonstration of safety for the drug's intended use or uses. In considering approval of a drug, the FDA conducts a benefit–risk assessment based on rigorous scientific standards to ensure that the product's benefits outweigh its risks for the intended population. For remdesivir, this assessment included review by a multidisciplinary team that comprehensively assessed safety, efficacy, and product quality, including independent analyses of data from the clinical trials. Confirmation of data integrity was also an integral part of the review and included inspections of selected clinical trial sites as well as the clinical trial sponsors.

Given the unmet medical need for safe and effective therapeutics for Covid-19, the FDA used several mechanisms to facilitate product development and expedite the review of the new drug application (NDA) for remdesivir. These included granting a fast-track designation, which increases opportunities for a sponsor to engage with the FDA, and granting a rolling review as part of the fast-track

process, which allows a sponsor to submit, and the FDA to review, sections of the NDA as they arrive. The NDA also received a priority review designation, which places the review on an expedited timeline. These mechanisms enabled a comprehensive review to be completed less than 3 months after the last component of the NDA was submitted.

There remains uncertainty surrounding the optimal dosing of remdesivir in pediatric patients, pregnant patients, and patients with renal or hepatic impairment. These uncertainties result, in part, from the important public health priority of expediting the development and review of a safe and effective therapeutic agent in the setting of an unmet medical need and will be addressed through postmarketing requirements and postmarketing commitments.

The approval of remdesivir marked an important step toward addressing the needs of patients with Covid-19. Nonetheless, the absence of a demonstrated survival benefit highlights the need for continued therapeutic development.

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