

Results

Patients

Of the 1114 patients who were assessed for eligibility, 1062 underwent randomization; 541 were assigned to the remdesivir group and 521 to the placebo group (intention-to-treat population) (Figure 1); 159 (15.0%) were categorized as having mild-to-moderate disease, and 903 (85.0%) were in the severe disease stratum. Of those assigned to receive remdesivir, 531 patients (98.2%) received the treatment as assigned. Fifty-two patients had remdesivir treatment discontinued before day 10 because of an adverse event or a serious adverse event other than death and 10 withdrew consent. Of those assigned to receive placebo, 517 patients (99.2%) received placebo as assigned. Seventy patients discontinued placebo before day 10 because of an adverse event or a serious adverse event other than death and 14 withdrew consent.

A total of 517 patients in the remdesivir group and 508 in the placebo group completed the trial through day 29, recovered, or died. Fourteen patients who received remdesivir and 9 who received placebo terminated their participation in the trial before day 29.

The mean age of the patients was 58.9 years, and 64.4% were male (Table 1).

Most patients had either one (25.9%) or two or more (54.5%) of the prespecified coexisting conditions at enrollment, most commonly hypertension (50.2%), obesity (44.8%), and type 2 diabetes mellitus (30.3%).

Primary Outcome

Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 10 days, as compared with 15 days; rate ratio for recovery, 1.29; 95% confidence interval [CI], 1.12 to 1.49; $P < 0.001$) (Figure 2 and Table 2). In the severe disease stratum (957

patients) the median time to recovery was 11 days, as compared with 18 days (rate ratio for recovery, 1.31; 95% CI, 1.12 to 1.52) (Table S4).

The benefit of remdesivir was larger when given earlier in the illness, though the benefit persisted in most analyses of duration of symptoms (Table S6). Sensitivity analyses in which data were censored at earliest reported use of glucocorticoids or hydroxychloroquine still showed efficacy of remdesivir (9.0 days to recovery with remdesivir vs. 14.0 days to recovery with placebo; rate ratio, 1.28; 95% CI, 1.09 to 1.50, and 10.0 vs. 16.0 days to recovery; rate ratio, 1.32; 95% CI, 1.11 to 1.58, respectively) (Table S8).

Safety Outcomes

In the as-treated population, serious adverse events occurred in 131 of 532 patients (24.6%) in the remdesivir group and in 163 of 516 patients (31.6%) in the placebo group (Table S17). There were 47 serious respiratory failure adverse events in the remdesivir group (8.8% of patients), including acute respiratory failure and the need for endotracheal intubation, and 80 in the placebo group (15.5% of patients) (Table S19). No deaths were considered by the investigators to be related to treatment assignment.

Grade 3 or 4 adverse events occurred on or before day 29 in 273 patients (51.3%) in the remdesivir group and in 295 (57.2%) in the placebo group (Table S18); 41 events were judged by the investigators to be related to remdesivir and 47 events to placebo (Table S17). The most common nonserious adverse events occurring in at least 5% of all patients included decreased glomerular filtration rate, decreased hemoglobin level, decreased lymphocyte count, respiratory failure, anemia, pyrexia, hyperglycemia, increased blood creatinine level, and increased blood glucose level (Table S20). The incidence of these adverse events was generally similar in the remdesivir and placebo groups.

Discussion

The findings in our trial should be compared with those observed in other randomized trials of remdesivir. Wang et al. enrolled 237 patients (158 assigned to remdesivir and 79 to placebo) in China early in the pandemic and showed a shorter time to improvement (a two-point improvement) with remdesivir: 21.0 days (95% CI, 13.0 to 28.0) in the remdesivir group and 23.0 days (95% CI, 15.0 to 28.0) in the placebo group (hazard ratio for clinical improvement, 1.23; 95% CI, 0.87 to 1.75).¹⁴ That trial did not complete full enrollment owing to local control of the outbreak, had lower power than ACTT-1 owing to the smaller sample size and a 2:1 randomization, and was unable to demonstrate any statistically significant clinical benefits of remdesivir. In the recently published, open-label, randomized study of remdesivir in hospitalized patients with moderate-severity Covid-19 (83% were not receiving oxygen at baseline), patients who received remdesivir for 5 days had higher odds of clinical improvement than those receiving standard care (odds ratio, 1.65; 95% CI, 1.09 to 2.48; $P=0.02$). This benefit was not seen with the 10-day course ($P=0.18$).¹⁵ We believe that these other studies support our findings regarding the efficacy of remdesivir; however, our study was larger, blinded, and fully enrolled.

The primary outcome of the current trial was changed early in the trial, from a comparison of the eight-category ordinal scale scores on day 15 to a comparison of time to recovery up to day 29. Little was known about the natural clinical course of Covid-19 when the trial was designed in February 2020. Emerging data suggested that Covid-19 had a more protracted course than was previously known, which aroused concern that a difference in outcome after day 15 would have been missed by a single assessment at day 15. The amendment was proposed on March 22, 2020, by trial statisticians who were unaware of treatment assignment and had no knowledge of outcome data; when this change was proposed 72 patients had been enrolled. Although changes in the primary outcome are not common in trials for diseases that are well understood, it is recognized that in some trials, such as those involving poorly understood diseases, circumstances may require a change in the way an outcome is assessed or may necessitate a different outcome.¹⁶ The original primary outcome became the key secondary end

point. In the end, findings for both primary and key secondary end points were significantly different between the remdesivir and placebo groups.

Numerous challenges were encountered during this trial. The trial was implemented during a time of restricted travel, and hospitals restricted the entrance of nonessential personnel. Training, site initiation visits, and monitoring visits often were performed remotely. Research staff were often assigned other clinical duties, and staff illnesses strained research resources. Many sites did not have adequate supplies of personal protective equipment and trial-related supplies, such as swabs. However, research teams were motivated to find creative solutions to overcome these challenges. Throughout the trial, we were able to enroll a diverse population, similar to the population that was being infected with SARS-CoV-2 during that period.

Given the preliminary results about remdesivir, the Food and Drug Administration issued an Emergency Use Authorization on May 1, 2020 (modified on August 28, 2020), to permit the use of remdesivir for treatment in adults and children hospitalized with suspected or laboratory-confirmed Covid-19. Remdesivir has also received full or conditional approval in several other countries since that time. However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient for all patients. Current strategies are evaluating remdesivir in combination with modifiers of the immune response (e.g., the Janus kinase [JAK] inhibitor baricitinib in ACTT-2, and interferon beta-1a in ACTT-3). A variety of therapeutic approaches including novel antivirals, modifiers of the immune response or other intrinsic pathways, and combination approaches are needed to continue to improve outcomes in patients with Covid-19.

To access the figures and tables referenced in this study, as well as a complete list of members of the ACTT-1 Study Group, visit the [original article](#).

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