EDITOR'S PAGE

The National Institute of Allergy and Infectious Diseases Decision to Stop the Adaptive COVID-19 Trial

On Solid Ethical and Scientific Grounds

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On April 29, the National Institute of Health disclosed the preliminary findings of the ACTT-1 (Adaptive COVID-19 Treatment Trial) (NCT04280705), the first clinical trial in the United States to evaluate an experimental treatment for coronavirus disease-2019 (COVID-19). ACTT was designed as an adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of remdesivir (and eventually other drugs) in hospitalized adults diagnosed with COVID-19. Remdesivir is a nucleoside analog that interferes with the action of viral ribonucleic acid-dependent ribonucleic acid polymerase (1). Patients with COVID-19 were randomized to receive remdesivir or placebo as an inpatient and assessed for up to 29 days as an outpatient. The primary outcome variable was time to recovery by day 29. An independent data and safety monitoring board (DSMB) met on April 27 to review data and shared their interim analysis with the ACTT-1 study team. The DSMB noted that when compared with placebo, remdesivir-treated patients had a shorter time to recovery, which is an endpoint that is used frequently in influenza

trials. Preliminary results from ACTT show that patients treated with remdesivir had a 31% faster time to recovery than those who received placebo ($p < 0.001$). For the remdesivir treatment arm, the median time to recovery was 11 days for patients treated when compared with 15 days for those who received placebo. There was a trend toward improved survival in the remdesivir treatment arm ($p = 0.059$). Based on these findings, the DSMB recommended that there was no need for a placebo-only group in the next phase of the ACCT study, which planned to test baricitinib, a Janus kinase inhibitor, against remdesivir. Following the DSMB meeting, the National Institute of Allergy and Infectious Diseases (NIAID) chose to offer patients in the placebo arm of ACCT-1 the opportunity to receive open label remdesivir, rather than allowing these patients to remain in the placebo arm, so that additional mortality data could be collected.

Although the results of the ACCT-1 clinical trial fell short of being a home run because of the short-term endpoint that was chosen, these results constitute the first randomized scientific evidence that antiviral agents can be used to treat patients with COVID-19, and thus represent an important win for the health care community in the war against COVID-19. However, the ACCT-1 trial has been sharply criticized by many experienced clinical trialists because they felt that the NIAID should have allowed the investigators to collect additional data to learn whether remdesivir saved lives. Dr. Steven Joffe, who is a pediatric oncologist and bioethicist and the Interim Chair, Department of Medical Ethics and Health Policy at the University of Pennsylvania, stated that he believed

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that the NIAID likely took the right steps in making its decision to give remdesivir to the placebo patients, but raised concerns about using time to improvement, not death, as the measure of success, in the first place. He stated, “I don’t find this endpoint very compelling, and to me the real issue is the decision to design the trial around the endpoint of time to recovery defined in the way they defined recovery. . . . To me, the decisions that are this weighty ought to be based on clinically important endpoints. (2)” Dr. Steven Nissen, a well-known experienced clinical trialist and cardiologist at the Cleveland Clinic, did not believe that allowing placebo patients to take remdesivir was the correct decision. He stated, “I believe it is in society’s best interest to determine whether remdesivir can reduce mortality, and with the release of this information doing a placebo-controlled trial to determine if there is a mortality benefit will be very difficult.” He went on to say that he viewed the NIAID’s decision as “a lost opportunity”(2).

We believe that the controversies surrounding the NIAID’s decision to terminate the ACCT-1 trial in the midst of the COVID-19 epidemic raise important questions about the goals and conduct of clinical trials during a public health crisis. In particular, the ACCT-1 trial controversy illustrates the tension between the competing goals of clinical research: the production of ideal scientific knowledge that benefits society—in this case mortality outcome data—with the protection of individual participants in the face of a deadly pandemic; and the need to make treatments quickly available to very sick patients (3).

Based on the data that was available to the NIAID and the ACCT-1 investigators, we believe there are valid scientific reasons for designing and conducting a single arm versus placebo trial with remdesivir, without mortality as a primary outcome. First, among the lessons learned from treating patients with the human immunodeficiency virus is that effective current antiretroviral therapy has evolved from monotherapy with azidothymidine to a combination of 2 antiretroviral reverse transcriptase inhibitors to a highly active triple antiretroviral therapy. There is no biological precedence for first-generation antiviral therapies reducing mortality when given as a single agent. Second, remdesivir was among the treatment arms that were dropped in the NIAID-sponsored PALM (Pamoja Tulinde Maisha [“Together Save Lives” in the Kiswahili language]) trial (4), because the remdesivir treatment arm had the highest mortality of the 4 different anti-Ebola treatment arms that were being tested.

From an ethical standpoint, the ACCT-1 trial design and decision to stop the placebo arm early are justifiable, especially when considering prior research conducted during pandemics. While examining the clinical trials conducted during the 2014/15 Ebola outbreak, the National Academies of Science, Engineering, and Medicine observed that the very idea of randomized clinical trials (RCTs) was highly controversial: “RCTs are the preferred research design because they allow researchers to directly compare the outcomes of similar groups of people who differ only in the presence or absence of the investigational agent. However, many stakeholders argued that RCTs would be unethical in the context of the Ebola epidemic. The arguments against RCTs were varied, but most were primarily based on one central assumption: that it was unethical and unacceptable to deprive patients of an agent that could potentially prevent or treat Ebola, given the high mortality rate and lack of known and available treatment options” (5). The National Academies of Science, Engineering, and Medicine committee supported RCTs at the outset of the Ebola outbreak because it was unknown whether any agents would be safe and effective; true equipoise existed between the experimental treatment and placebo. Thus, the use of placebo in the ACCT-1 trial was warranted based on established scientific and ethical grounds. However, at the point when NIAID stopped the ACCT-1 trial, it would be difficult to say that there was no effective agent to justify the continued use of placebo in ACCT-1 or in the adaptive clinical trials designs that will follow ACCT-1. The most recent version of the World Health Organization Declaration of Helsinki (2013) states when a known effective treatment exists, new treatments must be tested against it except when “it is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention” (6). Could one really say that withholding remdesivir after it was found to shorten time to recovery—the primary trial outcome participants were told about in the consent form—would not place patients who were hospitalized with COVID-19 at an additional risk of “serious or irreversible harm as a result of not receiving the best proven intervention?” It is also worth noting that ACCT-1 was not designed nor powered for a mortality outcome. Moreover, during a period of pandemic, it is fair to assume that most hospitalized patients want to try something that is effective rather than continuing on placebo.

Clinical research necessarily involves balancing competing priorities and values such as producing generalizable knowledge that benefits society while minimizing harms and maximizing benefits to trial participants (3). The principles articulated in the Declaration of Helsinki describe a common approach to balancing the goals of gaining new medical knowledge and protecting patients who enroll in clinical trials: Even in ordinary times, we cannot withhold a proven intervention when doing so risks harming patients. This alone could justify stopping a trial early. During times of pandemic, the urgent need for an initial proven intervention just strengthens the case for prioritizing patients' needs over ideal scientific endpoints.

Nevertheless, broadly recognized principles of public health ethics require that we infringe as little as possible against competing values or priorities such as knowledge regarding survival in clinical trials as we pursue a goal such as providing acutely ill patients with a proven intervention (7). That is to say, even if we prioritize the protection of study participants and society's need for an initial proven intervention, we should support efforts to determine whether remdesivir reduces mortality to whatever extent is possible after dropping placebo controls. Conceivably this can be done with remdesivir in the context of nonrandomized clinical trials that use propensity matching of treated patients and untreated case control subjects. Admittedly, the results will not be as definitive as an RCT and may represent

a lost opportunity; however, this may be the type of scientific compromise that is both reasonable and required in the context of the public health crisis that we are currently facing and will likely have to face again in the future. Many aspects of evidence-based medicine are based on less than perfect evidence, and we must never forget that the participants enrolling in a clinical trial during a deadly pandemic are first and foremost patients who trust their physicians to do what is best for them. As always, we welcome your thoughts on the ACCT-1 trial, either through social media (#JACC:BTS) or by e-mail (jaccbts@acc.org).

ADDENDUM

The partial results of the ACCT-1 trial were published online (8) after this editorial was completed. In ACCT-1, the Kaplan Meier estimates of mortality by 14 days were, respectively, 7.1% and 11.9%, in the remdesivir and placebo groups (hazard ratio 0.70; 95% CI 0.47-1.04). The Kaplan Meier estimates of mortality for 28 days had not been analyzed at the time this preliminary report was published because patients had not yet completed their 29th visit.

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