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CARDIOPULSE

# Avoiding the termination of ACTT

## Innovative decision-making that could have avoided terminating the Adaptive COVID-19 Treatment Trial (ACTT) while facilitating widespread availability of remdesivir.

## Introduction

As of 25 June 2020, the COVID-19 pandemic has exerted an unprecedented impact across the globe. More than 9.30 million cases have been reported worldwide, including >479 000 deaths.[1] The recommendations of the World Health Organization (WHO) have led to a 'lockdown' of more than a third of the world's population, and many countries have closed their borders, affecting both the industry supply chain and global travel. Pressure has also increased on healthcare systems by raising the demand for rapidly developed diverse treatments and encouraging the 'cutting of corners' to accelerate progress. As a consequence, the combined medical and societal pressures for approval of an effective antiviral drug have been overwhelming. Society was thus challenged with one of the toughest quandaries in medicine: how to successfully balance the requirement to rigorously test a new medicine for safety and effectiveness on the one hand with the moral imperative to make available a treatment that is effective, as quickly as possible.

With this background, on 29 April 2020, the National Institute of Allergy and Infectious Diseases (NIAID) announced that the remdesivir trial (known as the Adaptive COVID-19 Treatment Trial, or ACTT), the first clinical trial launched in the USA to evaluate an experimental treatment for COVID-19, was 'positive'.[2]

Preliminary results announced on 29 April indicated that patients who received remdesivir had a 31% faster time to recovery than those who received placebo ($P < 0.001$). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. The results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir vs. 11.6% for the placebo group ($P = 0.059$).

Underlying that ray of hope, though, was one of the most difficult challenges in medicine: how to equitably balance the requirement to rigorously test a new medicine for safety and effectiveness with the moral imperative to make a treatment that is efficacious available to patients as quickly as possible. At the core of this quandary was the difficult decision by the Data Safety Monitoring Committee (DSMC) when to end the trial. The details of this fateful decision are incomplete at the time of this writing. As reported in a preliminary report (*New England Journal of Medicine*), on 27 April 2020, the DSMC reviewed the results.[3] Although this review was originally planned as an interim analysis, at that time, the DSMC recommended that the preliminary primary analysis report and mortality data from the closed safety report be provided to trial team members from the NIAID. These results were subsequently made public (*New England Journal of Medicine*).[3]

What we do know with certitude is that the NIAID decided to start giving remdesivir to patients who had been assigned to receive a placebo in the study. As a consequence, this decision effectively limited the ability of the investigators to collect additional data about the ability of remdesivir to save lives. In the trial, 8% of the participants given remdesivir died, compared with 11.6% of the placebo group, a difference that was not statistically significant, thereby suggesting, but not proving, remdesivir's benefits.

F. H. Clifford Lane, NIAID's clinical director, said 'from the standpoint of the agency, the study had answered the question it was designed to answer: The median time that hospitalized Covid-19 patients on remdesivir took to stop needing oxygen or exit the hospital was, at 11 days, four days shorter than those who were on placebo'. 'How many patients would we want to put at risk of dying', Lane asked, for that last little bit of proof? Remdesivir, Lane noted, was not a home run, but is probably better than nothing'.[4]

Steven Nissen, a well-regarded veteran clinical trialist and cardiologist at the Cleveland Clinic, disagreed that giving placebo patients remdesivir was the right call. Nissen wrote: 'I was appalled by the PROCESS and the decision used to close out the ACTT Trial. Stopping a trial at an interim analysis for a "soft endpoint" when there was an opportunity to continue to achieve a mortality benefit makes absolutely no sense' (personal communication, 8 June 2020).

On 1 May 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of remdesivir for the treatment of hospitalized 2019 coronavirus disease (COVID-19) patients.[5]

As all readers of this journal know well, the primary responsibility of the independent DSMC is to protect the safety and welfare of patients who participate in clinical trials. During the study, the DSMC is responsible for evaluating significant adverse events in real time and conducting interim reviews of outcome and safety data to make recommendations on continuing, terminating, or modifying the trial. According to the DSMC charter, major study design modifications and/or protocol amendments should be reviewed and approved by the DSMC prior to implementation.

A well-designed clinical trial includes a clearly specified primary outcome. Consequently, many people perceive a clinical trial as being 'successful' if it demonstrates at its pre-specified *P*-value that the treatment that is being studied shows benefit on that primary outcome. The act

of specifying a primary outcome enables statistical machinery to test that outcome both at the end of the study and during its course.

Also, interim analyses should preferably be pre-specified in the trial protocol to minimize bias from unplanned analyses. DSMC recommendations typically include either: continuing the trial as planned; stopping early for hazard; stopping because efficacy is unequivocally established; or stopping because continuing the trial is futile.

Getting back to a consideration of the ACTT remdesivir trial, my opinion is that the DSMC of this NIH trial provided the wrong recommendation. Data on mortality cannot be considered sufficiently solid to recommend study discontinuation. A consequence of this recommendation was that patients in the placebo arm were crossed over to the active treatment arm. Consequently, a definite answer on the true efficacy of remdesivir on patients' outcomes will not be possible, at least on the basis of this study. The primary endpoint, in my opinion, is not sufficient to be considered as the basis for recommending remdesivir to all patients.

In the context of competing exigencies, I pose the following question: was there a pathway forward for both avoiding termination of the ACTT clinical trial and simultaneously responding to compelling societal demand and humanitarian considerations for making remdesivir available widely for treatment of afflicted COVID patients? I suggest that the European Medicines Agency (EMA) processing of ataluren and its action to grant conditional approval for treatment of patients with Duchenne muscular dystrophy may constitute a teaching moment. For background, Duchenne muscular dystrophy causes muscles to increasingly weaken and waste. Most of those diagnosed with this disease, usually before the age of 5, will use a powered wheelchair before they are 12, will not have the muscle strength to pick up a glass of water by the age of 20, and will in all probability never live to 30 years.

On 23 May 2014, the EMA announced that it would recommend that ataluren receive 'conditional approval'.[6] The next step was for the European Commission to review this decision. Ataluren has been developed by PTC Therapeutics to overcome a specific change in the DNA called a nonsense mutation which causes 10–15% of cases of Duchenne muscular dystrophy. Ataluren was the first ever drug to treat an underlying genetic cause of Duchenne muscular dystrophy in children and young people affected, outside of a clinical trial.

Being granted conditional approval in the EU meant that ataluren is placed on the market for 1 year, with provision for yearly renewal. PTC agreed to monitor the safety and effectiveness of the treatment whilst undertaking further trials to provide additional data—for example, the Phase III trial PTC had already started—to confirm the results of the previous trials.

This decision by the EMA was received with jubilation by the families of the patients and their many supporters. Following the decision by the EMA, each of the patients was finally able to have independent access to the drug without needing to be part of a clinical trial.

There are many obvious analogies between the 2014 regulatory challenge with ataluren and that with remdesivir today. As with COVID-19 today, in 2014, there was compelling pressure from the families of young children afflicted with Duchenne muscular dystrophy, coupled with intense societal pressure to make ataluren available, without awaiting the demonstration of efficacy with a Phase III clinical trial.

In France, there are two exceptional procedures termed ATU and RTU,[7] which are designed to ensure broad and equitable access and the greatest possible security for the use of medicines outside the existing regulatory fields. The Temporary Authorization for Use (ATU) which allows patients to benefit from pharmaceutical specialties where they do not have any marketing authorization, provided that they are intended for the treatment of serious or orphan diseases and in the absence of appropriate treatment. The Recommendation for Temporary Use (RTU)[7] which allows monitoring of off-label prescribed medicines, provided that there is none covered therapeutic need, and that the benefit/risk ratio of the medicinal product is presumed favourable, in particular from published scientific data or effectiveness and safety data.

I propose that these several cited examples of exceptional procedures inform an important lesson; the lesson to be learned is that there were and there are, novel regulatory pathways available to render remdesivir available to patients with an over-riding clinical need on the one hand, without compromising the integrity of an ongoing clinical trial by recommending study discontinuation. We can only speculate as to whether a recommendation for continuation would ultimately have established efficacy.

Adhering to the axiom that the 'Perfect is the enemy of the good', I suggest that the solution established for making ataluren available by the EMA in the absence of formal clinical trial data demonstrating efficacy, could have served as a model for effectively dealing with the challenge of facilitating widespread access to remdesivir without the necessity of terminating an extremely important clinical trial that potentially could have provided rigorous data establishing the efficacy of remdesivir.

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## References

References are available as supplementary material at *European Heart Journal* online

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