Virus behavior may impact results in COVID-19 drug tri-als

Differences in how COVID-19 behaves from person to person may contribute to the inconsistent findings reported in clinical trials for antiviral drugs, an analysis published Tuesday by PLOS Medicine found.

This inconsistence can be made worse because many coronavirus drug studies focus on enrolling seriously ill patients to provide them with a potentially effective treatment, the researchers said.

As a result, many of these trials may compare drug efficacy in people with severe illness against non-treatment, or placebo, in those with milder symptoms, they said. To address this issue, recruiting study participants shortly after symptom onset or after testing positive for the virus could make patient groups more similar, according to the researchers.

"At the early phase of the pandemic, physicians decided who needed to be treated and non-treated based on compassionate use programs, which is non-random," study co-author Keisuke Ejima told UPI in an email.

"If so, we may not see the difference between treated and untreated individuals because those treated get better due to treatment and those untreated were not seriously sick from the beginning," said Ejima, an assistant research scientist in biostatistics at Indiana University in Bloomington.

Drugs are typically evaluated in randomized controlled clinical trials in which at least two groups of similar participants are treated differently to determine which approach works best, researchers said. However, treating all seriously ill patients with one treatment, and those with less severe symptoms with another, may produce varying results, according to the researchers. Since the beginning of the pandemic, several treatments for COVID-19 have emerged from rapidly conducted clinical trials, including the antiviral drug remdesivir and monoclonal antibodies, which are essentially manmade immune cells.

Still, while these treatments have shown some benefit in those hospitalized with severe illness, none has proved to be a "cure" for the virus, Ejima and his colleagues said.

For this study, the researchers used a model that replicated the dynamics, or behavior, of the coronavirus after someone is infected.

They combined the model with clinical data to examine how viral load, or the amount of virus in a person's throat, changes over time.

Significant differences appeared in the rate of viral load decline between patients, with some people experiencing more rapid drops than others, according to the researchers.

This could explain why some study participants have responded better to antiviral drugs in some trials than others, the researchers said.

To examine this, they simulated potential findings of randomized clinical trials for COVID-19 drugs that successfully interrupt virus replication, or spread, within the human body.

Even if a drug reduced viral replication by 95 percent, the associated randomized clinical trial would need to enroll more than 13,000 people to receive it plus the same number of people given a placebo for comparison, to detect statistically significant differences, the researchers said.

Trials of this size would be difficult to manage and expensive, according to the researchers.

However, when they altered the simulated randomized clinical trials so that participants were treated within one day of onset of their symptoms, only up to about 600 participants were needed for each group. This suggests that randomized clinical trials for COVID-19 drugs could be improved by enrolling participants as soon as possible after symptoms appear, or by setting enrollment criteria based on the time that has passed since symptom onset, the researchers said.

"Studies employing randomization have gradually increased" over the course of the pandemic, Ejima said.

"However, most studies employing randomization recruit patients regardless of the time since symptom onset and, from our quick survey, the average time from symptom onset to randomization was 7.2 days, which is too late," he said.