Drug combination fails to improve outcomes in influenza

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A new combination of antiviral drugs did not improve clinical outcomes

in hospitalized patients with severe influenza, according results from a recent clinical trial published in *The Lancet Infectious Diseases*.

The findings warrant further investigation into new therapeutic strategies that can effectively improve clinical outcomes for these patients, said Michael Ison, MD, MS, professor of Medicine in the Division of Infectious Diseases, of Surgery in the Division of Organ Transplantation and a co-author of the study.

Between 2018 and 2019, an estimated 29 million people contracted influenza in the United States, and of them, 380,000 were hospitalized, resulting in 20,000 deaths, according to recent data from the Centers for Disease Control and Prevention.

For the last two decades, the standard of care for treating outpatients and hospitalized patients with severe influenza has been neuraminidase inhibitors (NAIs), such as oseltamivir, zanamivir and peramivir. These inhibitors block viruses' ability to travel from an infected cell to infect other healthy cells.

Another treatment more recently approved by the FDA called baloxavir marboxil—a cap-dependent endonuclease inhibitor—functions differently. Once the influenza virus infects a healthy cell by binding to its sialic acid sugars, baloxavir blocks a key mechanism that allows new viral particles to be produced, ultimately stunting the spread of the virus.

In a previous phase 3 clinical trial, adolescent and adult patients with influenza who were given baloxavir demonstrated improved symptoms compared to those receiving placebo and a greater reduction in viral load compared to receiving placebo or neuraminidase inhibitors.

For the current clinical trial, a total of 366 adolescent and adult patients hospitalized with influenza—87 percent diagnosed with influenza A

infection, the most common strain of influenza—were randomly assigned to receive either a combination of baloxavir and NAIs, or a placebo and NAIs.

"We know patients that are in the hospital have more virus than patients that don't require hospitalization, and the virus is there for a longer period of time. By adding baloxavir to neuraminidase inhibitors, you have two drugs with two different mechanisms that could decrease viral load much more quickly, and in theory, we thought it would make people get better much more quickly," said Ison, who is also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University and also director of the Northwestern University Clinical and Translational Sciences (NUCATS) Institute's Center for Clinical Research.

Unfortunately, the investigators found in the current trial that this wasn't the case. In the baloxavir group, the average time for patients to demonstrate signs of clinical improvement was 97.5 hours, whereas in the control group, the average time for clinical improvement was 100.2 hours.

Ison said these results are similar to previous studies evaluating the efficacy of baloxavir in outpatients with influenza, where although there was greater amount of viral reduction seen in patients who received baloxavir with another drug, there was ultimately no significant difference in clinical outcomes.

Another key takeaway is that although baloxavir wasn't associated with any significant clinical benefit, patients who received the combination demonstrated less resistance at the end of receiving treatment compared to those who just received the NAI.

According to Ison, this may benefit patients at high risk of developing

resistance, such as transplant patients and other immunocompromised patients who can have higher viral loads than other patients.

"We typically have not recommended the use of baloxavir because of the high risk of resistance emerging in this patient population. But there is need for studies to use the combination in that population to see if there are better outcomes and, more importantly, if we see less resistance by using the two drugs together. There may also need to be other markers that we're looking at beyond viral load," Ison said.

More information: Deepali Kumar et al, Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial, *The Lancet Infectious Diseases* (2022). DOI: 10.1016/S1473-3099(21)00469-2

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