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Bench to Bedside

New Flu Antiviral Candidate May Thwart Drug Resistance

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An influenza antiviral that's currently in development could address a growing clinical problem: drug resistance. Researchers at the Institute for Biomedical Sciences at Georgia State University in Atlanta and colleagues recently described the new compound's promising effects in a study involving influenza-exposed ferrets and human airway epithelia cultures.

Experts say there's an urgent need for flu antivirals with a high barrier to drug resistance. An estimated 290,000 to 650,000 respiratory deaths occur every year around the world due to influenza infections, along with an estimated 3 to 5 million cases of severe illness. People who develop severe or progressive influenza-associated clinical illness should be treated with antivirals, but those on the market are increasingly compromised.

"Growing resistance to antivirals has made some influenza drugs less effective over time, and some studies suggest that resistant viruses can emerge rapidly," said Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, who was not involved with the new study.

One class of drugs has already succumbed to viral resistance: the adamantanes (amantadine and rimantadine) are no longer recommended in the United States for influenza treatment or prophylaxis, except in selected circumstances.

The 4 options the US Centers for Disease Control and Prevention is recommending this flu season are also under threat. Preexisting resistance in circulating viruses is encroaching on oseltamivir, zanamivir, and peramivir, moderately effective neuraminidase inhibitors. And although baloxavir marboxil, a cap-dependent endonuclease inhibitor that blocks viral replication, was effective in clinical trials, resistant viruses emerged in 9.7% of phase 3 trial participants within 5 days.

"We think that the next generation of influenza antiviral drugs must not only be efficacious and safe, but also address the resistance problem," said Mart Toots, PhD, the recent study's lead author.

The new candidate lowered influenza viral loads and reduced symptoms in animal and cell culture experiments, as described in Science Translational Medicine. "Most important, it established a high barrier against viral escape from inhibition," said senior author Richard Plemper, PhD. It was also effective in a model of the human airway lining without damaging the tissue.

The compound, EIDD-2801, is a so-called prodrug that's metabolized into N^4-hydroxycytidine (NHC), a ribonucleoside analog. Plemper and his colleagues previously found that NHC had broad antiviral activity in mouse lung tissue and cultured human airway cells, and did not induce robust resistance.

That study showed that NHC is incorporated into viral RNAs in place of the nucleoside cytidine, increasing the rate of mutations. With enough mutations, the influenza virus can't replicate. This situation—termed viral error catastrophe—could be a new way to kill the flu.

However, macaques administered oral NHC as part of the new study had low blood concentrations of the compound. To improve its clinical potential, the team synthesized EIDD-2801, which showed better oral absorption in the primates.

The researchers next compared EIDD-2801 with oseltamivir or no drug in ferrets, which display hallmarks of human influenza infection. They exposed the animals to various seasonal and pandemic strains, including the swine-origin virus responsible for the 2009 global flu outbreak. Among the animals that received EIDD-2801, the oral treatment efficiently inhibited replication of all strains, rapidly dropping the viral burden when given at first signs of disease, whereas prophylactic oseltamivir had only a minor effect on viral load. The EIDD-2801-treated animals also experienced significantly shorter duration of fever.

To demonstrate the ability of EIDD-2801 to block viral resistance, the researchers repeatedly exposed influenza virus populations to the drug. Genetic sequence analyses showed the viruses developed mutations during the process, but none of the changes mediated resistance.

Viral error catastrophe invoked by the compound likely blocked resistance, as was seen with favipiravir, a similar drug approved in Japan for pandemic influenza. Researchers recently identified a mechanism of viral resistance to favipiravir, but this wasn't observed with EIDD-2801 in the current study.

Time will tell if the influenza virus discovers an escape hatch from the new drug. But for now, EIDD-2801 is "a promising clinical candidate for monotherapy of seasonal and pandemic influenza," the authors wrote.

Additional studies are planned. The human airway epithelium model experiments identified a viable influenza treatment window and effective dose concentrations that were validated in the ferret model. This information will help guide investigators as they determine doses to test in additional preclinical studies and, ultimately, in human clinical trials.

"Although this research is in its early stages," Fauci said, "additional treatment options are urgently needed to effectively fight influenza on a global scale."