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Novel drug combo improves function of protein underlying cystic fibrosis

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A novel two-drug combination has the potential to target and restore a defective protein underlying cystic fibrosis (CF), according to two phase III clinical trials conducted at 187 medical centers around the world, including Johns Hopkins.

The drug ivacaftor, in combination with an experimental medication called lumacaftor, led to modest improvements in lung function, but significant reductions in hospitalizations and antibiotics needed for lung infections. These results were published May 17 in the *New England Journal of Medicine*. The drug combination is intended for people 12 and up who have two copies of the most common CF mutation, called F508del.

"This is something the CF community has wanted to do for years, ever since the discovery of the gene causing CF in 1989," says senior study author Michael P. Boyle, M.D., associate professor of medicine at Johns Hopkins and vice president of therapeutics development at the Cystic Fibrosis Foundation. "It is not a cure, but it is the first treatment to target the underlying cause of the most common form of CF. Ongoing trials already are underway, testing even stronger versions of these medications."

Normally, a protein called CFTR controls the salt and water balance in cells lining the lungs. In patients with CF, CFTR is defective, resulting in mucous buildup in the lungs and lung infections. Ivacaftor has been found to restore CFTR function, but only in a small subgroup of 4

percent of patients with CF in whom the protein sits on the cell surface. Lumacaftor helps bring the protein to the cell surface in the most common type of CF, where ivacaftor can help restore it.

In clinical trials called TRAFFIC and TRANSPORT, 1,108 patients with CF were randomly assigned to receive lumacaftor at either 600 milligrams a day or 400 milligrams twice a day, with ivacaftor 250 milligrams twice a day, or placebo, for six months. "After six months, there was a clear benefit" in those taking the active drug, Boyle says.

Across both studies, FEV1, a measure of lung function, improved by an average of 2.6 to 4 percentage points among participants taking the active drug. Considered a modest improvement, this was observed as early as day 15 and continued throughout the study. Patients receiving the active drug also had a 30 to 39 percent reduction in the rate of lung exacerbations, which is considered statistically significant, as well as a statistically significant 61 percent decrease in the number of exacerbations requiring hospitalizations and 56 percent decrease in exacerbations requiring intravenous antibiotics. Some patients were also able to gain weight and had a significantly improved body mass index.

Serious adverse events were reported in up to 23 percent of participants taking the active drug, most often infective pulmonary exacerbation, but were less frequent than those taking placebo. The majority of adverse events reported were mild to moderate and included shortness of breath and chest tightness.

The drugs' manufacturer, Vertex Pharmaceuticals, submitted a New Drug Application for approval of the combination therapy to the Food and Drug Administration last November. A decision is expected this summer, Boyle says.

More information: "Lumacaftor–Ivacaftor in Patients with Cystic

Fibrosis Homozygous for Phe508del CFTR" DOI: 10.1056/NEJMoa1409547

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