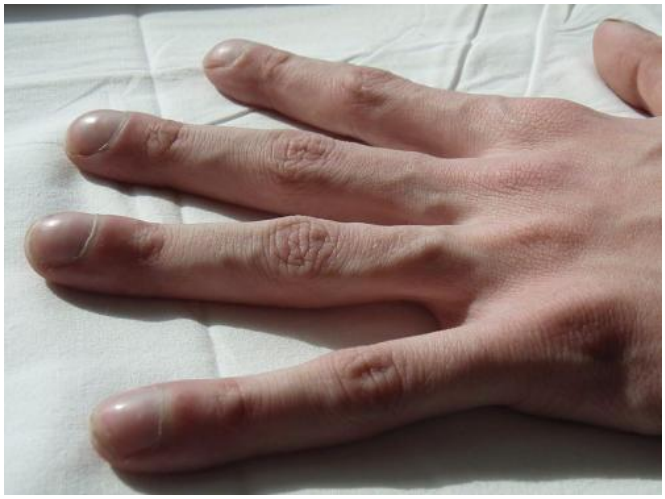
Three-drug combo improves lung function in most common genetic form of cystic fibrosis

1 November 2019



"Clubbing" of the fingers is a classic features of Cystic Fibrosis, although not present in many patients. Credit: Jerry Nick, M.D./ Wikipedia

A phase three clinical trial that UT Southwestern participated in determined that a three-drug combination improved lung function and reduced symptoms in cystic fibrosis (CF) patients who have a single copy of the most common genetic mutation for the disease.

Earlier this month, the Food and Drug Administration approved the therapy based on the results of this international study, published today in the *New England Journal of Medicine*. A companion investigation appearing simultaneously in The Lancet reported on people with one or two copies of the mutation.

Dr. Raksha Jain, Associate Professor of Internal Medicine at UT Southwestern Medical Center, is corresponding author of the *NEJM* article and an investigator on The Lancet study. Dr. Jain is presenting both studies at the North American Cystic Fibrosis Conference in Nashville this week.

CF is a chronic, progressive, and frequently fatal genetic disease that affects the respiratory and digestive systems in children and young adults. The sweat glands and the reproductive system are also usually involved. Individuals with CF have a shortened lifespan.

"Although there are over a thousand different disease-causing mutations, nearly 90 percent of people with cystic fibrosis have at least one copy of the most common mutation, the Phe508del CFTR allele," Dr. Jain said.

An estimated 80,000 people worldwide are affected by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, she said. People inherit a gene from each parent that encodes the CFTR protein.

"This three-drug combination was highly effective in people with cystic fibrosis who inherited the Phe508del CFTR mutation, improving health outcomes and symptoms," said Dr. Jain, referring to the *NEJM* study on those with one mutated copy of the gene.

In the clinical trial conducted at 115 sites in 13 countries from June 2018 to April 2019, 403 patients of ages 12 and older were randomized to receive either elexacaftor-tezacaftor-ivacaftor combined therapy or a placebo. The trial was co-sponsored by Vertex Pharmaceuticals.

Lung function was measured at four and 24 weeks. Compared with patients receiving a placebo, lung function in the treatment group was significantly improved at four weeks and sustained through week 24. In addition, lung flare-ups, or increases in

symptoms, were 63 percent lower in the treatment group. Study participants also answered questionnaires regarding their quality of life and respiratory symptoms—with those in the treatment group reporting higher scores in these areas.

Excessive amounts of salt via sweating is a hallmark of cystic fibrosis. The treatment group had a lower concentration of salt in their sweat than the placebo group, which demonstrates how this therapy in targeting the underlying cause of the disease, she added.

Adverse events leading to discontinuation occurred in 1 percent of those getting the drug combination. Although the therapy was generally safe and well-tolerated, long-term studies are needed to further understand potential side effects, Dr. Jain said.

"The CF community is working hard to find highly effective therapies for people who are not eligible for this treatment because they don't have the appropriate gene mutation," said Dr. Jain, a Dedman Family Scholar in Clinical Care and Director of the UTSW Adult Cystic Fibrosis Center.

More information: Peter G. Middleton et al, Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele, *New England Journal of Medicine* (2019). DOI: 10.1056/NEJMoa1908639

Provided by UT Southwestern Medical Center