Drug combination remains safe and effective in patients with cystic fibrosis after four years

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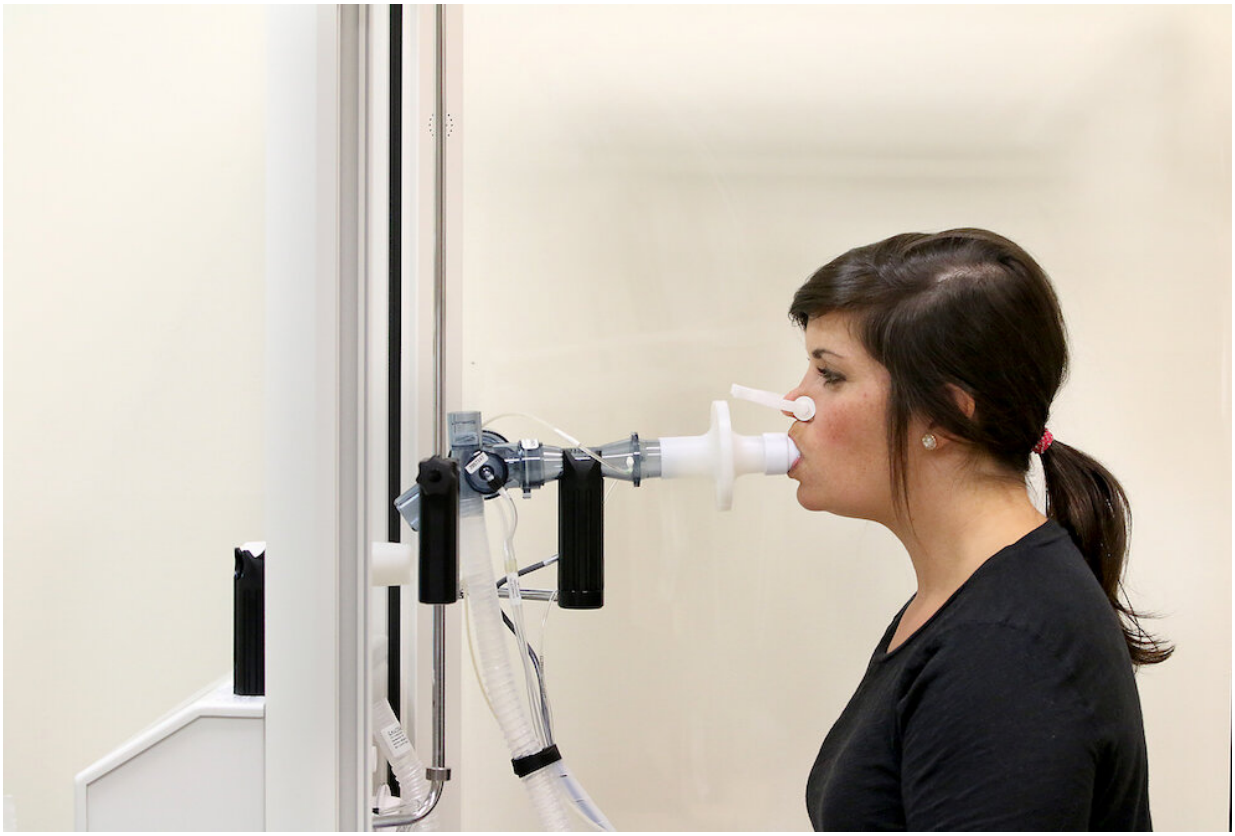

A coordinator at the South Carolina Clinical and Translational Research (SCTR) Institute's Nexus Research Center demonstrating pulmonary function testing, one of the endpoints used in the TEZ/IVA trial. Credit: Medical University of South Carolina

Patients with cystic fibrosis (CF) face difficulty breathing and a decline in lung function and are at risk of early death. CF is an inherited condition that results in thick mucus build-up, persistent infection and inflammation in the lungs.

Medical University of South Carolina (MUSC) researcher Patrick Flume, M.D., was lead author of a recent *Journal of Cystic Fibrosis* article reporting the findings of a trial of a two-drug combination for treating CF. The study demonstrated long-term safety and clinical benefit of the combination therapy. Flume is director of the MUSC Adult Cystic Fibrosis Center and co-director of the South Carolina Clinical & Translational Research (SCTR) Institute.

Patients 12 years and older who received the combination regimen of tezacaftor (TEZ) and ivacaftor (IVA) for four years did not experience any serious safety concerns and tolerated it well, suggesting its appropriateness for long-term use. These patients had previously participated in a 120-day trial of the same combination. The extension trial was conducted in SCTR's Nexus Research Center.

Not only did patients tolerate the combination regimen over the course of the 96-week extension study, but they also maintained the improvements they had achieved in the earlier trial. The long-term safety and tolerability of this combination regimen is good news for patients with CF, many of whom will need to be on CF drug treatments for the rest of their lives.

Breakthrough therapies for cystic fibrosis

Although drugs to treat the symptoms of CF have been around for some time, the approval of IVA in 2012 marked a breakthrough in the treatment of the disease. It spawned a new class of CF drugs called modulators that addressed the underlying problem in CF rather than

merely treating the sequelae of CF. When patients were treated with a combination of CF modulators targeting the structure and function of the protein, the effects were even more profound.

The trial reported here assessed the long-term efficacy and safety of treating patients with a combination of two CF modulators, TEZ and IVA (TEZ/IVA). While this trial was still being conducted, a three-part regimen composed of TEZ/IVA plus elexacaftor (Trikafta) was approved in 2019 and has since become standard of care.

"With TEZ/IVA, you see about a 2% to 3% increase in lung function in patients with CF, whereas with the triple, we see more like a 15% improvement in the lung function," said Flume. "Patients are also less likely to require hospitalization. For example, before 2019, I would have anywhere from four to six people in the hospital on any given day. Now I have zero to one."

These breakthrough therapies have dramatically improved the quality and length of patients' lives.

"When I started in this business, the median survival was in the mid-20s, but now it's in the mid-50s," said Flume. "I would tell you that if you had a child born with CF today, you should raise that child with the expectation of a long life. It shows how remarkable these modulators are and what their potential could be."

How IVA and TEZ work

The protein, known as the cystic fibrosis transmembrane regulator, or CFTR, controls the movement of water in the lung tissues, allowing for thin, free-flowing mucus production. More than 90% of patients with CF have at least one F508del mutation in the CFTR gene. Those who carry two copies of this mutation, acquired from both parents, have a more

severe form of CF. While some patients who inherit the mutation from only one parent may have less severe disease, others may still develop a severe form of CF.

IVA was the first small molecule that targeted the CFTR protein directly. It binds to the CFTR protein at the cell surface, holds the gate of the channel open and keeps the protein channel open longer to allow for the movement of water and decrease the thickness of mucus. However, this drug is appropriate only for those persons who have a mutation that produces protein at the cell surface, which does not occur in patients with F508del.

TEZ, referred to as a corrector, binds to the CFTR protein and helps the protein to maintain shape so that it can function better. This is important for those with F508del, as it can increase the quantity of protein at the cell surface, where it can now be acted upon by IVA.

What this study adds

Although clinicians recommend taking the three-drug combination regimen because of its increased effectiveness in improving lung function compared to TEZ/IVA, some patients cannot tolerate it and so must remain on the dual therapy. For example, one adverse effect of the triple combination is weight gain. In some cases, patients taking the triple combination have gained upward of 50 pounds. This study shows that patients who do not tolerate the triple combination can continue to benefit safely from the two-part regimen long term.

This study's findings that TEZ/IVA is safe and well-tolerated over the long term also builds confidence that two of the three drugs in the standard-of-care therapy can be used safely over time. Again, this is important reassurance for patients who will likely take the drugs for the rest of their lives. Should safety issues arise, these data will be useful in

pinpointing the problematic agent in the combination regimen.

The way forward

Clinician-researchers will continue to optimize combination therapy with CF modulators. Although refinements of these combination therapies continue to improve patient outcomes, Flume knows that can't continue forever.

"Eventually, we're going to hit the ceiling—right? We can't just keep going up and up and up, but we just don't know where that ceiling is," he explained. "We had imagined we were there, and then ivacaftor blew that out of the water."

Although modulators have improved the quality of life and increased the lifespan for many patients with CF, not all patients can tolerate them and not all have the F508del mutations that the CF modulators target. To help these subsets of patients, clinicians and scientists will continue to develop new CF therapies.

More information: Patrick A. Flume et al, Long-term tezacaftor/ivacaftor safety and efficacy in people with cystic fibrosis and an F508del-CFTR mutation: 96-week, open-label extension of the EXTEND trial, *Journal of Cystic Fibrosis* (2022). DOI: 10.1016/j.jcf.2022.12.006

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