Cystic Fibrosis Research News

Title:

Treatment effects of elexacaftor/tezacaftor/ivacaftor on people with cystic fibrosis heterozygous for 3849+10kbC->T and a class I mutation

Lay Title:

Elexacaftor/tezacaftor/ivacaftor can be effective for people with cystic fibrosis with the 3849 gene variant

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What was your research question?

People with cystic fibrosis (pwCF) whose CFTR genes include the 3849+10kbC->T variant (3849 variant) are eligible for either ivacaftor or tezacaftor/ivacaftor, but not elexacaftor/tezacaftor/ivacaftor (ETI), based on responses to these CFTR medications in laboratory testing. If pwCF with the 3849 variant receive ETI, would they enjoy an additional clinical benefit?

Why is this important?

PwCF have enjoyed significant health benefits since the introduction of CFTR modulators. These medications are available to most, but not all, pwCF. The CFTR modulators were tested on the various genetic variants responsible for CF, and the FDA only approved the medications for pwCF with variants that demonstrated a positive laboratory response. The laboratory responses, while informative, do not necessarily capture all of the potential effects of the CFTR medications. PwCF with variants non-responsive in a laboratory setting have

nonetheless, in certain variants, experienced clinical benefits of CFTR modulators in real life settings.

What did you do?

We analysed retrospectively 10 pwCF with either one or two of the 3849 variant genes who received ETI. These pwCF were initially treated with either ivacaftor or tezacaftor/ivacaftor based on the FDA approval for these medications. We reviewed various health parameters, including pulmonary function tests, before these 10 pwCF commenced ETI and then followed these parameters while these pwCF were taking ETI, to determine if they enjoyed any incremental clinical benefit from ETI.

What did you find?

We found that the 10 pwCF with the 3849 variant experienced improved clinical benefits upon transitioning to ETI. The benefits were observed in pulmonary function tests and sweat chloride tests, which can be a proxy for the body's response to the medication. These pwCF also enjoyed an increase in weight and a decrease in pulmonary exacerbations. While the improvement in each parameter alone was not universal, for example some of the 10 pwCF had less meaningful improvements in their pulmonary function tests, the overall trend in clinical benefit was positive for these pwCF on ETI.

What does this mean and reasons for caution?

Our results demonstrate that pwCF with the 3849 variant may benefit from treatment with ETI, and the clinical benefit may exceed the benefits of ivacaftor or tezacaftor/ivacaftor. The additional benefit of ETI may be attributable to elexacaftor, which in addition to correcting the misfolding of the CFTR protein, may potentiate the cell membrane channel to allow for greater availability of the CFTR protein. Nevertheless, this study only included 10 pwCF with the 3849 variant and the results may not be generalizable to other pwCF with the 3849 variant.

What's next?

As our study only analysed 10 pwCF with the 3849 variant, additional data for pwCF with the 3849 variant successfully treated with ETI is needed in order to further substantiate these results.

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