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Cystic Fibrosis Research News

Title:

LUMACAFTOR/IVACAFTOR IN PEOPLE WITH CYSTIC FIBROSIS WITH AN *A455E-CFTR* MUTATION

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What was your research question?

We wanted to find out if lumacaftor/ivacaftor (ORKAMBI) worked for people with cystic fibrosis (pwCF) with an *A455E*-CF mutation. We also tested cultured cells from pwCF, called organoids, to see if a response to lumacaftor/ivacaftor in organoids would indicate that the individual would also respond.

Why is this important?

If this study worked, lumacaftor/ivacaftor could potentially be used for treating pwCF with an *A455E* mutation. Lumacaftor/ivacaftor is a CFTR modulator, which is a type of treatment that can fix changes to the CFTR protein caused by a *CFTR* genetic mutation. Only recently other CFTR modulators have become available in Europe for pwCF with an *A455E* mutation. Additionally, it is important to learn more about how organoids from pwCF can predict a response in real life to lumacaftor/ivacaftor treatment, since this could help identify more treatment options for pwCF.

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What did you do?

We identified 20 pwCF with an *A455E* mutation in the Netherlands, and compared the effects of treatment with lumacaftor/ivacaftor to treatment with a placebo (no active substance) control. The clinical treatment outcomes we looked at were changes in lung function, a questionnaire filled in by the participants, and sweat chloride levels, which can be used to measure how well the CFTR protein is working. The changes in response to lumacaftor/ivacaftor in the participants' organoids were compared to the clinical treatment outcomes to see if they matched.

What did you find?

This study showed a positive response to lumacaftor/ivacaftor in the participants' organoids and sweat chloride levels and the questionnaire, but the participants did not show improvements in lung function. The changes in the participants' organoids did not match the changes in lung function or sweat chloride levels.

What does this mean and reasons for caution?

Only a small number of pwCF have an *A455E* mutation, making it a rare mutation. Demonstrating a clinical effect in pwCF with rare mutations is difficult since there are so few pwCF to evaluate in studies. Because of that, the results of this small study might be due to some participants having a weaker or stronger result. This study did not show an effect of lumacaftor/ivacaftor on lung function. The participants' cultured cells responded to lumacaftor/ivacaftor in the laboratory, but this did not match the changes in lung function or sweat chloride levels in each individual.

What's next?

More research is needed to find treatments for pwCF with rare mutations and to understand how organoids can be used to identify individuals who will respond to treatment with a CFTR modulator.

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