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Cystic Fibrosis Research News

Title:

Whole-Blood Transcriptomic Responses to Lumacaftor/Ivacaftor Therapy in Cystic Fibrosis

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What was your research question?

It is difficult for healthcare providers to predict who will respond well to medicines (called CFTR modulators) that make the defective CFTR channel work better in people with cystic fibrosis (CF). We sought to determine how blood markers change after treatment with the CFTR modulator lumacaftor/ivacaftor (Orkambi), to indicate who best responds to this medicine.

Why is this important?

CFTR modulators are becoming increasingly available to more people with CF, and many are starting treatment with CFTR modulators at younger ages. However, CFTR modulators are very expensive and not every person responds to these medicines in the same positive fashion. It is important to determine differences between those with a good response to a CFTR modulator (e.g. as indicated by improved lung function, improved nutrition, decreased hospitalizations) and those who do not respond as this will help to improve drug development for all people with CF. Additionally, changes in blood markers may also help identify other pathways in the body that could be targeted for new drug development to relieve persisting symptoms.

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What did you do?

We looked at blood profiles in people with CF before starting treatment with lumacaftor/ivacaftor and six months after start of treatment and compared to people without CF. Blood profiles were examined comprehensively for changes in the body's genetic blueprints. DNA is the body's long-term storage of genetic material, which is made into RNA (a copy of the DNA), and then later converted to proteins that carry out structural and functional roles in our cells. In this study we focused on examining RNA. RNA analysis is similar to looking at a copy (RNA) of a master cookbook (DNA) that contains thousands of recipes for fantastic meals (proteins).

What did you find?

We found that lumacaftor/ivacaftor had a minimal impact upon the overall blood RNA profiles (copies of our genetic blueprints). However, people with CF who had good clinical responses to lumacaftor/ivacaftor (improved lung function and nutrition) had some unique changes in their RNA profiles compared to those who did not respond. Also, we found evidence for changes in several calcium-controlled genes after initiating lumacaftor/ivacaftor. Regardless of pre- or post- use of Orkambi, CF blood profiles had many alterations in inflammation-related genes compared to people without CF.

What does this mean and reasons for caution?

Our findings have implications for the ongoing development and evaluation of CFTR modulators. For young children with CF or people with CF and mild disease, it may be important to use blood markers to assess the response to CFTR modulators when clinical markers such as lung function are not helpful. Further, studying RNA can provide an insight into additional pathways that can be used for therapy development. One example would include calcium signalling, as medications that affect how our cells use calcium could be important for future treatment.

These results should be taken with caution as we were limited to a small group (20) of people aged over 12 years old at the time of study. Findings should be verified in larger groups, as well in persons taking other CFTR modulators besides lumacaftor/ivacaftor.

What's next?

We will validate our blood markers in people with CF taking other CFTR modulators, including the triple combination CFTR modulator (tezacaftor/ivacaftor/elexacaftor). We are also interested in comparing how infants respond compared to older children and adults. Finally, we hope to look at new therapies targeting pathways discovered with this research.

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