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Title:

Ivacaftor in Cystic Fibrosis With Residual Function: Lung Function Results From an N-of-1 Study

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What was your research question?

Do people with cystic fibrosis (CF), who also have a reduced amount of chloride transport (chloride movement across cellular membranes) due to residual function mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, respond to treatment with a drug called ivacaftor?

Why is this important?

Some people with CF have mutations that are very rare or that have not been fully characterized. This makes it difficult to enroll enough people in traditional clinical studies to test the effects of medications. Instead of a traditional comparison between two or more groups of people with and without ivacaftor treatment, this study was designed to allow comparison of each person to themselves with and without ivacaftor treatment (a series of N-of-1 trials). The results of this study provide new information about the impact of ivacaftor in people with CF with residual *CFTR* function and may help researchers design future studies in people with rare mutations.

What did you do?

We enrolled and randomized 24 children and adults (aged 12 years or over), and 21 completed the study. We assigned each person alternating cycles of ivacaftor and no ivacaftor (placebo) treatment, with each person given 1 of 4 different sequences of taking the treatment. These were a series of double-blind trials where neither the participant nor the experimenter knew when each participant was receiving a particular treatment. All participants received a total of 4 rounds of alternating treatment (2 rounds of ivacaftor and 2

rounds of placebo) that was given for 2 weeks each, and this ended with 8 weeks of ivacaftor only in an open-label treatment period where all participants knew they were getting ivacaftor. To evaluate the impact of ivacaftor, we compared data from each person at baseline (before starting treatment) and after receiving ivacaftor to data from the same person after they had received placebo at different time points throughout the study.

What did you find?

People (aged 12 years or over) with CF with residual function mutations had better lung function after 2 weeks of ivacaftor treatment than they did after 2 weeks with placebo. Participants also had improvements in lung function over the longer 8-week period of ivacaftor treatment. In this study, safety was generally similar to previous larger studies.

What does this mean and reasons for caution?

Our findings suggest that ivacaftor treatment improves lung function in people with CF with residual function mutations. Alternating participants between ivacaftor and placebo treatment is unusual and should be considered carefully. Also, the 2-week treatment periods used for part of our study may not have been long enough to understand fully how well the ivacaftor treatment worked. However, our results were consistent with those from previous studies that evaluated ivacaftor treatment in people with CF with residual function mutations.

What's next?

This study highlights the need for more studies to be conducted to understand better the effects of ivacaftor treatment in people with CF with rare mutations. This study also shows that the N-of-1 study design may play a role in future clinical studies of CF and other rare diseases.

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