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Cystic Fibrosis Research News

Title:

Changes of CFTR functional measurements and clinical improvements in Cystic Fibrosis patients with non p.Gly551Asp gating mutations treated with ivacaftor

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What was your research question?

Cystic fibrosis is caused by mutations in the CFTR gene, and there are many different types of mutations. The new drug ivacaftor helps to treat CF patients with a specific type of CFTR mutation referred to as a 'gating mutation'. The most common gating mutation is called p.Gly551Asp, but there are many other mutations in this category that can also respond to ivacaftor to varying degrees. Our goals was to find out whether there was a correlation between the clinical response to ivacaftor in patients with gating mutations other than p.Gly551Asp, and the changes in CFTR function that could be observed in response to the drugs in cells derived from the patients.

Why is this important?

There is an increasing need for clinically relevant and reliable tests to predict the response to new CF drugs that are entering clinical trials. Our study, which looked at CFTR function in several different types of cells derived from CF patients, is a step along the path to developing such tests.

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What did you do?

We tested CFTR activity in two different types of cells from 6 CF patients with gating mutations in CFTR before, and three weeks to six months after ivacaftor initiation. We assessed CFTR activity in the sweat gland using the sweat chloride concentration test, and, a second method, we used sweat rate test in two of the patients. The nasal potential difference (NPD) test was used to explore CFTR function in the cells of the respiratory system.

What did you find?

Five of the six patients demonstrated rapid clinical improvement in response to ivacaftor treatment, with significant decrease in sweat chloride measurements, reaching normal values in 3 patients as early as 3 weeks after the start of ivacaftor treatment. Two of these patients, siblings carrying the p.Asp1152His mutation, displayed a typical CF response at sweat secretion test, which was significantly modified to normal following treatment.

NPD was also significantly modified in the patients who responded well to ivacaftor, but none of the patents achieved a totally normal result on this test. Furthermore, there was a significant correlation between the change in FEV1 (a measure of lung function) and both the change in NPD score or the change in sweat test.

One of the six patients studied did not show significant clinical improvement, or changes in the tests of CFTR function. This may be because the patient could not absorb ivacaftor efficiently.

What does this mean and reasons for caution?

Changes in CFTR functional measurements, as assessed by the sweat chloride concentration test and the NPD test, the most extensively validated CFTR function test, correlate with the clinical response in these patients. However, we observed differences in the degree of improvement in each of the various measures, which illustrates how different cells in the body can respond differently to drugs like ivacaftor. When interpreting these kind of findings, it is important to keep in mind other factors that might influence the results, such as the ability of a patient's body to absorb the drugs.

What's next?

Whether all patients with residual CFTR function will respond well to Ivacaftor remains unknown. The use of the tests described here could be helpful in predicting the clinical response in patients with gating mutations other than p.Gly551Asp.

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