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Title:

Therapeutic benefit observed with the CFTR potentiator, ivacaftor, in a CF patient homozygous for the W1282X CFTR nonsense mutation

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What was your research question?

We assessed whether a cystic fibrosis (CF) drug, called ivacaftor (Kalydeco), is effective in treating people with CF with a specific type of mutation (termed W1282X) in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. W1282X is known as a nonsense mutation, meaning that the CFTR protein created from the CFTR gene does not fully form and is shorter in length than normal.

Why is this important?

Currently there are no effective long-term treatment options for ~11% of people with CF whose disease is caused by CFTR nonsense mutations. Illness in these people is typically severe because the CFTR protein is usually non-functional. However, W1282X is a unique nonsense mutation because the CFTR protein has some function despite the fact that it is shorter than normal. Understanding whether ivacaftor, which is FDA-approved to treat people with CFTR gating mutations (a different type of mutation that results in a full-length CFTR protein that has abnormal function), has clinical benefit for people with the W1282X mutation is important because it could provide new therapeutic options for some people with nonsense mutations.

What did you do?

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In the laboratory, we first tested the effects of ivacaftor on indicators of CFTR function in different types of cells including (i) human airway cells with the W1282X mutations (ii) rat CF cells with the W1282X mutation (iii) nasal cells collected from a W1282X-homozygous person with CF (i.e. both CFTR genes had a W1282X mutation). Based in part on results observed from this testing, twice daily ivacaftor treatment was initiated for the patient—a 31 year-old female who was approaching end-stage disease. Clinical outcomes including lung function, sweat chloride, exacerbations, body mass index (BMI), and daily insulin requirements were assessed for a 3-year period.

What did you find?

We found that ivacaftor treatment increased CFTR function in human airway and rat CF cells with the W1282X mutation. This effect was further enhanced when ivacaftor was combined with another drug (called G418) that was previously observed to be effective in treating CFTR nonsense mutations. In the study patient, nasal cells also showed improved CFTR function in the presence of ivacaftor and the patient demonstrated improvement in pulmonary exacerbation frequency, BMI, and insulin requirement to manage diabetes over 3 years following clinical treatment; however, lung function remained stable and sweat chloride did not improve.

What does this mean and reasons for caution?

Our findings suggest that ivacaftor had a modest clinical benefit for a person with two copies of the W1282X-CFTR mutation. These observations are consistent with laboratory studies indicating increased CFTR function with ivacaftor treatment in nasal cells from the same person and in W1282X-CFTR human and rat cells. Results highlight how testing drugs in cells in the laboratory can potentially help predict patient-specific clinical benefit and accelerate the delivery of efficacious drugs to people with CF (particularly those not benefitting from available therapies). Results should be interpreted with knowledge that testing techniques using human nasal cells are in development and continue to advance.

What's next?

While combination therapy of ivacaftor and lumacaftor (CFTR corrector, Orkambi), was recently approved for people with the most common CFTR homozygous mutation (F508del), ongoing studies have predicted that this therapy may also be effective in those with nonsense mutations. Further studies are required to explore this combination therapy in more people with CF.

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