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Cystic Fibrosis Research News

Title:

CFTR modulator therapy for cystic fibrosis caused by the rare c.3700A>G mutation

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What was your research question?

Cystic fibrosis (CF) is caused by loss-of-function mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Modulators (drugs that target the underlying defect in CFTR protein) are currently approved for ~90% of people with CF. In this study, the possible use of modulators was investigated for the c.3700A>G CFTR mutation, a relatively common CF-causing mutation in Qatar.

Why is this important?

Clinical manifestations of the c.3700A>G mutation include lung disease and infections, low bone density, and late-onset pancreatic insufficiency, though disease severity is variable. Modulators have been transformative for people living with CF. The potentiator Kalydeco was first approved for G551D-CFTR, and, currently, for any mutation that is responsive by clinical and/or cell-based assessment. Trikafta contains Kalydeco plus two correctors and is approved for people with CF with at least one F508del CFTR mutation. People with CF for which modulators are approved are mainly found in the US and Europe. It is important to identify modulators for other CFTR mutations.

What did you do?

The c.3700A>G mutation generates two protein products: one protein with a missense mutation (the wrong amino acid) (termed I1234V-CFTR), and one protein with a deletion of amino acids from the nucleotide binding domain 2 (termed I1234del-CFTR). To study these

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CFTR products, Fischer rat thyroid (FRT) cell models with I1234V-CFTR or I1234del-CFTR were generated and CFTR activity in response to modulators was assessed. A I1234del-CFTR-expressing gene-edited cell model generated from human bronchial epithelial cells was also studied, as well as epithelial cells isolated from the nasal cavity of an individual with c.3700A>G homozygous CF. Finally, two limited N-of-1 clinical studies (where one individual is the entire trial) were performed to test the efficacy of Trikafta in people with homozygous c.3700A>G.

What did you find?

In FRT cells, I1234V-CFTR was active whereas I1234del-CFTR required potentiators (including Kalydeco) and correctors (including those in Trikafta) for activation. In FRT cells, I1234del-CFTR activity was remarkably increased when additional potentiators identified by our group – called "co-potentiators" – were used with Kalydeco. Modulators also enhanced I1234del-CFTR activity in the gene-edited human bronchial epithelial cells. In contrast, no CFTR activity was seen in the nasal epithelial cells. To reconcile the different response to modulators in cell models versus nasal epithelial cells, Trikafta was used in two c.3700A>G individuals: the first showed decreased sweat chloride and symptomatic improvement, and the second showed a small improvement in lung function.

What does this mean and reasons for caution?

These results support the potential benefit of approved CFTR modulators for CF caused by the c.3700A>G mutation. The study also suggests further benefit of investigational co-potentiators and mutation-specific correctors.

What's next?

Further evaluation of Trikafta in people with c.3700A>G is warranted. Further development of next generation modulators, including co-potentiators and unique correctors, may offer benefit to people with CF with rare CFTR mutations that do not respond to current drugs.

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