European Cystic Fibrosis Society

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Cystic Fibrosis Research News

Title:

CFTR modulation with elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis assessed by the β-adrenergic sweat rate assay

Lay title:

The effect of CFTR modulation with elexacaftor-tezacaftor-ivacaftor on the anxiety sweat rate in people with cystic fibrosis

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What was your research question?

We aimed to find out whether therapy with the new CFTR modulator elexacaftor-tezacaftor-ivacaftor (ELX-TEZ-IVA) improves the production of so-called 'anxiety sweat', a sweat response mediated by CFTR. This anxiety sweat can be used to quantify CFTR function. Unlike the commonly queried sweat test for CF diagnostics, the anxiety sweat is directly dependent on functional CFTR. It is therefore only barely detectable, if at all, in pancreatic insufficient people with CF.

Why is this important?

We need to assess and quantify a persons' responses to ELX-TEZ-IVA. For this, measuring lung function improvement is not enough since it does not correlate enough with CFTR function. Anxiety sweat testing is a potential test to measure the improvement of CFTR function, as it is very accurate and sensitive, though not established in clinical routine yet.

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What did you do?

We developed a new, very easy and time-saving variation of the previously described method using low-cost hardware and an automated software to analyze sweat bubble formation and calculate sweat rates. We measured the common 'heat sweat' (cholinergic sweat rate) and the 'anxiety sweat' (b-adrenergic sweat rate) in people with CF before (13 people) and after 12±4 weeks of therapy with ELX-TEZ-IVA (23 people) and compared the results to the chloride content measured in the sweat test. Additionally, we performed the test in 24 individuals without CF and 18 parents of people with CF as controls.

What did you find?

First, we found that our new method is very sensitive in discriminating people with CF that are pancreatic insufficient from healthy controls. Our assay also demonstrated as described previously that parents of people with CF show approximately 50% of the rate of the b-adrenergic sweat of healthy controls which corresponds to them carrying one mutation in the CFTR gene.

Under therapy with ELX-TEZ-IVA, the majority of people showed significant improvements in the sweat test with sweat chloride levels decreasing from the CF range to the intermediate or healthy range. However, surprisingly, the b-adrenergic sweat rate remained nearly unaffected by CFTR modulation with ELX-TEZ-IVA, as only three individuals normalized. 12 individuals showed very little activation of their b-adrenergic sweat rate, while in eight people it remained undetectable.

What does this mean and reasons for caution?

Our findings show that the b-adrenergic sweat production was only little affected by the CFTR modulation with ELX-TEZ-IVA, though the users benefitted well regarding their sweat chloride concentration (the commonly used test). We conclude that the b-adrenergic sweat production requires better correction of CFTR function than the pharmacological rescue by ELX/TEZ/IVA provides.

What`s next?

The high sensitivity, the low-costs, the automated-analysis and the easy and well-tolerated procedure enables us to use the test in clinical routine diagnostics, especially when common diagnostics were inconclusive as it is often the case for people with CFTR-related diseases. Additionally, the limited response of the b-adrenergic sweat to CFTR modulation with ELX-TEZ-IVA makes the test an interesting tool to evaluate future, more effective CFTR modulators to assess their ability to improve CFTR function.

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