Cystic Fibrosis Research News

Title:
THE COMBINATION ELEXACAFTOR/TEZACAFTOR/IVACAFTOR (ETI) MODULATES THE DE NOVO SYNTHETHIC PATHWAY OF CERAMIDES IN A GENOTYPE-INDEPENDENT MANNER

Lay Title:
The combination elexacaftor/tezacaftor/ivacaftor (eti) alters the lipid composition of the lung cells irrespective of cftr mutation

Authors:
Nara Liessi, Valeria Tomati, Valeria Capurro, Nicoletta Loberto, Mar Garcia-Aloy, Pietro Franceschi, Massimo Aureli, Nicoletta Pedemonte and Andrea Armirotti

Affiliations:
- Istituto Italiano di Tecnologia, Genova, Italy;
- IRCCS Istituto Giannina Gaslini, Genova, Italy;
- Università degli Studi di Milano, Milano, Italy
- Fondazione Edmund Mach, Trento, Italy

What was your research question?
We want to understand if the triple drug combination (elaxacaftor/tezacaftor/ivacaftor (ETI), the active molecules of Kaftrio, has any effect on the lung cells that is not directly related to ETI ability to rescue the function of CFTR.

Why is this important?
The importance of our work lies in three main points:
1) by understanding how a (very) effective CF drug works, we will hopefully be able to design new, even more effective drugs;
2) by discovering new cellular mechanisms that are associated with CFTR rescue, we will be able to exploit these mechanisms to discover new CF drugs, perhaps targeting mutations that are currently not treated;
3) considering that Kaftrio is a life-saving drug, it is important to monitor for any potential safety concerns that might arise from its long-term use (that are observed for almost any drug).

What did you do?

Cystic Fibrosis Research News

We treated primary lung cells, obtained from CF and non-CF donors and grown in the laboratory, with ETI for 48 hours. The sample group consisted of 10 F508del-CFTR participants, 4 subjects with minimal function (not rescuable) CFTR and 10 non-CF participants. At the end of the experiment, we measured the levels of an important family of lipids (fats), named sphingolipids, that have very relevant biological functions.

What did you find?

We discovered that the exposure to ETI increases the amount of dihydrosphingolipids (DHS), a class of very important lipids. We theorise that this happens because ETI slows down the action of a human enzyme named DEGS1. Quite surprisingly, this happens for both CF and non-CF people and also for those that have virtually no CFTR protein to rescue. This is thus an side effect of ETI, not related to the rescue of CFTR function.

What does this mean and reasons for caution?

This means that ETI has at least an effect on cell function, never described before, that is not directly correlated to its known function on CFTR. Since increased amounts of DHS have been associated with abnormalities of the central nervous system, we hope that our work will trigger further studies, aiming at better understanding our observation.

What's next?

We believe that dedicated clinical studies will need to understand if the same increase in DSH is observed in people with CF undergoing Kaftrio therapy. We also need to understand which mechanism lays behind this 'off-target' effect of ETI.

Original manuscript citation in PubMed

https://pubmed.ncbi.nlm.nih.gov/37088636/

cfresearchnews@gmail.com