

Cystic Fibrosis Research News

Title:

RESPONSE TO ELEXACAFTOR/TEZACAFTOR/IVACAFTOR IN INTESTINAL ORGANIDS DERIVED FROM PEOPLE WITH CYSTIC FIBROSIS

Lay Title:

IS ELEXACAFTOR/TEZACAFTOR/IVACAFTOR ALWAYS BETTER THAN EZACAFTOR/IVACAFTOR?

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What was your research question?

Does the combination of therapeutic compounds ELX/TEZ/IVA (Kaftrio® or Trikafta®) show greater efficacy than TEZ/IVA (Symkevi® or Symdeko®) when it is tested on the model of minigut (= intestinal organoids)? Are any differences in response to the ELX/TEZ/IVA observed between miniguts from various individuals with cystic fibrosis?

Why is this important?

It is well known that the treatment response to the CFTR modulators may differ between people with CF of the same CFTR mutations. As this is very likely true also for the latest drug Kaftrio, prescribed to patients with F508del/F508del genotype, the minigut testing could be very helpful to tailor the CFTR modulator therapy and to identify persons with lower than expected response to ELX/TEZ/IVA.



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What did you do?

We cultured intestinal organoids from 17 people with CF with identical CFTR mutations (F508del/F508del, the most common combination). The organoids were incubated in the presence of ELX/TEZ/IVA or TEZ/IVA. Then, we compared the treatment responses to these two combinations. Also, we performed genetic analysis to search for any CFTR gene variants that might explain potential differences in treatment responses.

What did you find?

We found out that ELX/TEZ/IVA is in general much more effective than TEZ/IVA. However, we saw some differences between individuals. We reported one case where we did not see any difference between TEZ/IVA and ELX/TEZ/IVA. The genetic analysis of this person showed a unique CFTR gene variant, never described before.

What does this mean and reasons for caution?

The superiority of ELX/TEZ/IVA was previously observed in clinical trials. We were first to confirm that this superiority can be also replicated in the laboratory conditions with intestinal organoids. The unexpected finding of essentially no improvement in response with ELX/TEZ/IVA when compared to TEZ/IVA in one patient underlines the importance of laboratory testing that should help to choose the best CFTR medication in future.

What's next?

We are currently testing the organoids from more people with F508del/F508del genotype to check the response variability on a larger scale and to gather more detailed information about their CFTR background.

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