Cystic Fibrosis Research News

Title:

Real-world pharmacokinetics of elexacaftor-tezacaftor-ivacaftor in children with cystic fibrosis: a prospective observational study

Lay Title:

Tracking the journey of elexacaftor-tezacaftor-ivacaftor in the bodies of children with cystic fibrosis

Authors:

Steffie E.M. Vonk, PharmD[1], Suzanne W. J. Terheggen-Lagro, MD, PhD[2], Eric G. Haarman, MD, PhD[2], S. Hashimoto, MD, PhD[3], Anke H. Maitland – van der Zee, PharmD, PhD[3], Ron A.A. Mathôt, PharmD, PhD[1], E. Marleen Kemper, PharmD, PhD[1,4] on behalf of the Amsterdam Mucociliary Clearance Disease (AMCD) research group

Affiliations:

[1]Amsterdam UMC location University of Amsterdam, Department of Hospital Pharmacy & Clinical Pharmacology, Meibergdreef 9, Amsterdam, The Netherlands
[2]Amsterdam UMC location University of Amsterdam, Emma Children's Hospital, Department of Pediatric Pulmonology and Allergy, Meibergdreef 9, Amsterdam, The Netherlands
[3]Amsterdam UMC location University of Amsterdam, Department of Pulmonary Medicine, Meibergdreef 9, Amsterdam, The Netherlands
[4]Amsterdam UMC location University of Amsterdam, Department of Vascular Medicine, Amsterdam, The Netherlands

What was your research question?

We aimed to explore how elexacaftor-tezacaftor-ivacaftor (ETI) travels trough the bodies of children with cystic fibrosis. This process is called pharmacokinetics. Better knowledge of ETI's pharmacokinetics and factors that are associated with differences between children, may contribute the development of more individualized dosing schemes.

Why is this important?

ETI has shown positive effects in most children with cystic fibrosis, but the effect is variable. Some children respond, while others do not or have side effects. Understanding of the pharmacokinetics (how the drug travels through the body) in children, especially in real-world settings, could help optimize dosing. This could influence treatment outcomes, side effects and costs.

Cystic Fibrosis Research News

What did you do?

We conducted a study involving 30 children aged 6-17 years old with cystic fibrosis, who were using ETI as part of their regular treatment. Over a year, we collected blood samples at different time points to analyse how ETI travelled trough their bodies, and built a computer model to describe this process. With the computer model we calculated various pharmacokinetic parameters, like the drugs' exposure during the day (AUC). We compared these parameters with reported values in the literature and looked for any links between drug exposure and clinical outcomes or side effects.

What did you find?

We found a large variability in the ETI exposure between and within age and dosing groups. Most children had drug concentrations high enough for a clinical response. Especially those aged 6-11 years weighing more than 30 kg (receiving the adult dose), seemed to have higher ETI exposure compared to the other age groups, which could cause side effects and result in unnecessary high treatment costs. So ETI dose may be reduced in some children. No direct relationship between drug exposure and clinical response or side effects was found.

What does this mean and reasons for caution?

Our findings suggest that while most children respond well to ETI, high drug exposure and concentrations above the ranges needed for clinical response, could lead to unnecessary side effects and increased costs. The lack of a clear link between drug exposure and clinical effect highlights the need for further research. Lower doses may be effective for certain children, but careful monitoring is crucial to avoid under-treatment or loss of efficacy.

What's next?

Future studies should explore the relation between exposure and efficacy and/or side effects in larger groups of patients. With this information the computer models developed in this study could be further optimized, and serve as a basis for more personalized dosing.

Original manuscript citation in PubMed

https://pubmed.ncbi.nlm.nih.gov/40089408/