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CLINICAL CORRESPONDENCE

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Cystic fibrosis: Does it matter to avoid crushing Elexacaftor/Tezacaftor/Ivacaftor (ETI) tablets?

Patrick Lebecque MD, PhD[1] | Matthieu Thimmesch MD[1] | Jessica Meurrens BSN[1] | Philippe Jeanmart PharmD[2]

[1]Cystic Fibrosis Reference Center of Liège, CHC MontLegia, Liège, Belgium

[2]Clinical Chemistry Department, CHC MontLegia, Liège, Belgium

Correspondence: Matthieu Thimmesch, MD, CHC MontLegia, Boulevard Patience et Beaujonc 2, 4000 Liège, Belgium.
Email: matthieu.thimmesch@gmail.com

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To the Editor,

A combination of three modulators (Elexacaftor/Tezacaftor/Ivacaftor: ETI) has unprecedented efficacy in most patients with cystic fibrosis (CF). In Europe, this life-changing CFTR modulator is approved for use from the age of 6 years and is available in tablet form only. The official FDA recommendation clearly states that "tablets should be swallowed whole." In Europe, the drug's leaflet is even more explicit, adding that the tablets must not be chewed, crushed or broken before swallowing.

Here, we report on a successful clinical trial of crushed ETI tablets in a patient with a severe form of oral pill aversion.

An 17-year-old young woman with CF (CFTR genotype: F508del/N1303K, presenting feature: meconium ileus) was followed in our CF outpatient clinic. Her clinical course was stable, with no pulmonary exacerbation during the last 2 years. She suffered from a severe form of oral pill aversion. Adherence to treatment was considered high, but the patient and her mother always used to prefer syrups or to crush tablets with a mortar and pestle. In Belgium, ETI reimbursement was very late (September 2022). Behavioral interventions were intensified in June but remained unsuccessful. The patient and her mother were fully informed of the lack of data on the efficacy of crushed ETI. However, given the stakes involved, they confirmed in writing their request for an off-label therapeutic trial and agreed in advance to the subsequent publication of its results. Ethics board review was exempted for this trial. Clinical benefits were impressive: cough disappeared within 1 week, while within 4 months percent predicted forced expiratory volume in 1 second (ppFEV1) increased by 21.9% predicted and weight increased by 3.7 kg (BMI: 21.5–23). In addition, sweat chloride level decreased by 59 mmol/L and normalized (Figure 1).

It is well known that some children and even adolescents are unable to swallow tablets, which has prompted some clinicians to teach them to swallow tablets as part of pediatric quality improvement projects.[1] ETI is not only a milestone in the treatment of CF, it is also an extremely expensive drug. In this context, some pediatric CF Centers have implemented successful swallowing training sessions (« pill swallowing schools »). What is less known is that even in adults, pill aversion—defined as non-physiological-related dysphagia[2]—is not uncommon and can lead to poor adherence, poor treatment outcomes and useless financial strains. Several approaches to pill aversion, including behavioral interventions, often appear to be fruitful solutions.

In fact, no published study has investigated the effect of physical modification of ETI tablets on the clinical efficacy of this drug. Due to this lack of knowledge, the therapeutic trial in this patient looked like a type 2 N-of-1 trial.[3] Here, crushed ETI resulted in evident clinical benefit which clearly exceeded the mean improvements that can be expected from this drug according to the literature. This benefit also meets and exceeds the Burgel's criteria in a recent French compassionate study.[4] What Burgel et al. reported is that, even in currently ineligible CF patients, the efficacy of ETI can often be documented on the basis of clinical improvement within 4–6 weeks. In this French observational study, an increase in ppFEV1 ≥ 10 percentage points and a decrease in sweat chloride concentration ≥ 20 mmol/L were considered robust indicators of responders. The extent to which maximum ETI benefit is achieved in our patient using crushed ETI cannot be determined from these data. Blood monitoring

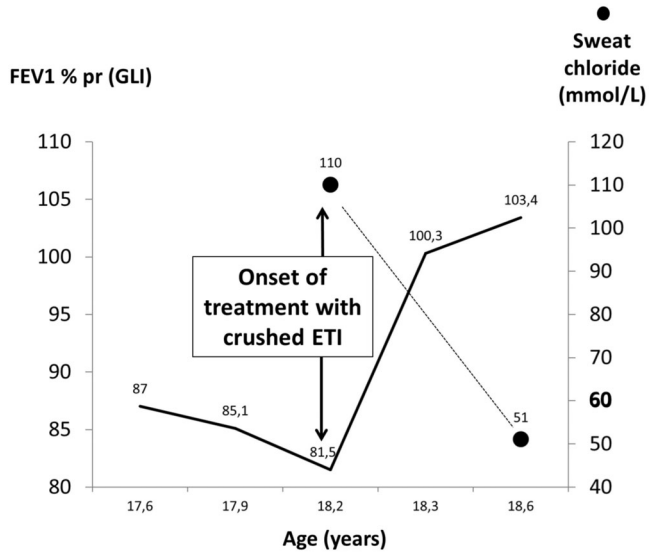

FIGURE 1 ppFEV1 and sweat chloride concentration before and under crushed ETI. ETI, Elexacaftor/Tezacaftor/Ivacaftor; ppFEV1, percent predicted forced expiratory volume in 1 second.

of modulators is not currently available in Belgium and it is costly abroad.

This case actually also illustrates one of the many circumstances where access to therapeutic drug monitoring (TDM) of modulators would be useful.[5] Pharmacokinetics of these drugs can vary widely from patient to patient, depending on absorption, drug or food interactions, pharmacogenetic factors, competition for plasma protein binding sites or hepatic dysfunction. In practice however, this is seldom taken into account and recommended ETI doses no longer vary above a weight of 30 kg. Yet, although rarely leading to permanent discontinuation of treatment, toxicities of ETI are quite common and may require dose adjustment. In France, TDM of caftors together with clinical criteria and blood liver function tests are already used in a multicenter national study to tailor ETI doses in CF children with liver dysfunction. And in Germany, TDM of ETI showed that daily doses could be reduced without decrease in FEV1 in one-third of patients, avoiding unnecessary exposure to high drug seric concentrations with their costs and risks of toxicities. TDM could also help to ensure that a less-than-expected clinical response is not due to suboptimal drug levels or poor compliance. Should this not be the case, a search for complex alleles may be indicated.

In conclusion, this case strongly suggests that crushing ETI does not compromise its clinical efficacy and may be valuable in some rare, difficult situations. Further, in combination with careful monitoring of clinical outcomes and TDM this could allow more appropriate personalized doses to be prescribed, reducing the risk of toxicity and, at times, saving money.

AUTHOR CONTRIBUTIONS

Patrick Lebecque: Conceptualization; writing—original draft; visualization; supervision. **Matthieu Thimmesch**: Writing—review and editing. **Jessica Meurrens**: Conceptualization. **Philippe Jeanmart**: Resources; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Matthieu Thimmesch http://orcid.org/0000-0001-6058-3373

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