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ORIGINAL ARTICLE

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Effectiveness and safety of elexacaftor/tezacaftor/ivacaftor treatment in children aged 6-11 years with cystic fibrosis in a real-world setting

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Abstract

Background: Elexacaftor-tezacaftor-ivacaftor (ETI) is a highly effective cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulating therapy for people with CF and at least one F508del variant. However, there is limited data about the safety and efficacy of this therapy in pediatric populations and in real-world settings. This study aimed at evaluating the effectiveness, tolerability, and safety of ETI in children with CF.

Methods: This was a prospective observational study including all children aged 6–11 years who initiated ETI therapy between October 2022 and March 2023 at the Pediatric CF Center of Milan (Italy). Study outcomes included changes in sweat chloride concentration, FEV_1, $LCI_{2.5}$, body mass index (BMI), tolerance, and safety. Mean changes in study outcomes from baseline through 24 weeks were estimated using mixed-effects regression models.

Results: The study included 34 children with CF (median age: 8.3 years). At Week 12, we observed an average decrease in $LCI_{2.5}$ of 2.3 units (95% confidence interval [CI]: −3.1; −1.5). At Week 24, sweat chloride concentration decreased by 63 mEq/L (95% CI: −69; −58), FEV_1 increased by 8.8 percentage point (95% CI: 3.7; 13.9) and BMI increased by 0.15 standard deviation scores (95% CI: 0.04; 0.25). Skin rashes appeared in 6 patients which spontaneously resolved within a few days. One month after treatment initiation, one patient experienced an elevation in liver function test results, which subsequently decreased during follow-up visits without necessitating discontinuation of therapy.

Conclusions: Our data indicate that ETI therapy is well tolerated by children with CF and is effective in improving signs of lung function abnormalities from early childhood.

KEYWORDS
CFTR modulators, children, cystic fibrosis, Elexacaftor, Ivacaftor, Tezacaftor

1 | INTRODUCTION

In recent years, the development of modulators of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) targeting the underlying defect in the CFTR protein, has represented a significant breakthrough in the treatment of CF. These therapies and in particularly the triple combination of Elexacator/Tezacaftor/Ivacaftor (ETI), enhance the availability and activity of the CFTR ion channel on epithelial surfaces, opening up new horizons for managing this challenging disease.[1]

Individuals with CF undergoing ETI treatment experience substantial improvements in lung function, a decrease in the frequency of exacerbations and respiratory symptoms, improved nutritional status, and an overall enhancement in their quality of life.[2–4]

Real-world data on the effectiveness and safety of ETI therapy in the pediatric population receiving ETI are scanty.[5] However, this population is of particular interest given the potential opportunities of preventing the progression of lung disease, typically occurring in early childhood.

Additionally, with the availability of these life-changing therapies, there is a growing need to identify noninvasive monitoring indices capable of tracking treatment response and disease progression, particularly in children, where assessing ETI efficacy can be challenging.

In this study, we evaluated the effectiveness and safety of ETI therapy in children with CF aged 6–11 years, using data collected in a real-world setting, beyond the controlled setting of clinical trials.

2 | METHODS

2.1 | Study design

This prospective observational single-center study was carried out at the CF Centre of Milan, Italy, with approval from the local ethics committee (protocol number 594_2016). Before their enrollment, all parents provided written informed consent. Between October 2022 and March 2023, we recruited 34 children aged 6–11 with CF who initiated ETI treatment.

The inclusion criteria comprised a confirmed diagnosis of CF in accordance with the diagnostic guidelines, an age between 6 and 11 years and eligibility for the combination treatment regimen of ETI, which, at the time of the study, required carrying at least one F508del pathogenetic variant.[6]

Children underwent comprehensive assessments, including sweat tests, clinical evaluations, anthropometric measurements, spirometry, and multiple breath washout nitrogen ($MBWN_2$) tests. Follow-up assessments occurred at 4, 12, and 24 weeks post-treatment initiation, except for sweat chloride measurement which was performed at treatment initiation and at the 24-week follow-up visit, and the $MBWN_2$ test which was performed at treatment initiation and after 12 weeks.

The study's effectiveness outcomes included sweat chloride concentration, body mass index (BMI), $ppFEV_1$, $LCI_{2.5}$, and the number of pulmonary exacerbations. We also considered any adverse reactions or adverse events as safety outcomes.

The dosing regimen for ETI was customized based on the patient's weight in accordance with the recommendations. For children weighing less than 30 kg, the regimen was: Elexacaftor 100 mg once daily, Tezacaftor 50 mg once daily, Ivacaftor 75 mg every 12 h. For children weighing 30 kg or more, the dosage mirrored that of adults: Elexacaftor 200 mg once daily, Tezacaftor 100 mg once daily, Ivacaftor 150 mg every 12 h.[7]

2.2 | Sweat test

Sweat tests were conducted by an experienced biologist who performs more than 100 tests annually. Sweat secretion was induced through iontophoresis for 5 min, with a total applied current of 1.5 mA (50 $\mu A/cm^2$), using 0.5% pilocarpine gel discs.[8] The preferred stimulation site for sweat was the lower portion of the forearm flexor. Sweat samples were collected over a 30-min period.

After cleaning the stimulated area with distilled water, sweat was collected in a macroduct coiled plastic tubing collector cup for up to 30 min.[9] The sweat chloride concentrations of the samples were determined using a chloride analyzer (MKII Chloride Analyzer 926S; Sherwood Scientific Ltd.). Sweat collections were deemed insufficient if less than 20 µL.[10]

Each sweat test was performed on both arms, and the highest values were recorded. In case of a difference greater than 10 mEq/L between the two determinations, the test was repeated. Sweat chloride concentrations <40 mmol/L were considered normal, values between 40 and 59 mmol/L were considered in the intermediate range, and values ≥60 mmol/L were indicative of CF.[10]

2.3 | BMI

BMI was calculated as weight divided by height squared and expressed as standard deviation scores (SDS), specific for sex and age. SDS was computed using national growth reference charts.[11]

2.4 | Pulmonary measurements

Spirometry was performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines[12] and always after the $MBWN_2$ test. FEV_1 was converted in the percentage of predicted values ($ppFEV_1$). Patients' lung function was considered in the normal range when $LCI_{2.5}$ was below 7.1.[13] $MBWN_2$ was performed, when the child was in stable condition, using the ExhalyzerD and Spiroware software (version 3.3.1; Eco Medics AG) in compliance with the Standard Operating Procedures.[14] Only results from three reproducible runs, defined as a variation of

functional residual capacity and $LCI_{2.5}$ values within 10% were considered. An adequate environment with distractions for younger children was assured during each test.[15]

2.5 | Pulmonary exacerbations

The number of pulmonary exacerbations requiring oral or intravenous antibiotic therapy was collected through 24 weeks from ETI initiation and during the same weeks of the year preceding ETI initiation. Pulmonary exacerbation was defined according to the presence of at least two of the following symptoms or signs: fever (oral temperature >38°C), more frequent coughing (increase of 50%), increased sputum volume (increase of 50%), loss of appetite, absence from school due to illness (at least 3 or preceding 7 days), or symptoms of upper respiratory tract infection. These symptoms had to have been associated with at least one of the following three additional criteria: decrease in forced vital capacity ≥10%, increase in respiratory rate ≥10 breaths per minute, or peripheral blood neutrophil count ≥15,000 μL.[16]

2.6 | Safety outcomes

Safety and tolerability were assessed by collecting adverse events, clinical laboratory values, electrocardiograms, vital signs, pulse oximetry from the day the patient received the first dose of ETI through 24 weeks of treatment. An adverse event was classified as severe if it resulted in death, a life-threatening condition, hospitalisation or prolonged existing hospitalisation, disability, permanent damage, or required medical/surgical intervention to prevent permanent impairment or damage.[17] As recommended in all patients treated with CFTR modulators, children underwent ophthalmologic examination before starting ETI therapy to exclude the presence of cataract signs. In case of detection of vitreous abnormalities, follow-up examinations were planned every 6 months, otherwise they were scheduled annually.

2.7 | Statistical analysis

Treatment effect in terms of changes in sweat chloride concentration, BMI, $ppFEV_1$, and $LCI_{2.5}$ throughout the study period was estimated using linear mixed-effects regression models with subject-specific random intercept and time since therapy initiation as fixed effect. These models were employed to accommodate repeated measurements within the same subject and handle missing values during follow-up visits. To investigate the impact of ETI therapy on the frequency of respiratory infections, the infection rates during the 24 weeks of ETI treatment were compared to those that occurred during the same weeks in the year before treatment initiation. This approach allowed for the consideration of the expected influence of seasonality on the risk of respiratory infections. Poisson regression was used to estimate the rate ratio of respiratory infections, with the 24 weeks before treatment serving as the reference period. All estimates were provided with 95% confidence intervals (CI).

TABLE 1 Patient characteristics.

Characteristic	*N* = 34[a]
Sex	
Females	12 (35.3%)
Males	22 (64.7%)
Age (years)	8.3 (7.3, 9.9)
Parents' Italian citizenship	
Both parents	27 (79.4%)
One parent	4 (11.8%)
Neither parent	3 (8.8%)
CFTR genotype	
F508del/F508del	11 (32.4%)
F508del/MF variant	23 (67.6%)
Pancreatic insufficiency	34 (100.0%)
Other CFTR modulators before ETI	6 (17.6%)
Diabetes	1 (2.9%)
Pseudomonas aeruginosa colonization	6 (17.6%)
MRSA colonization	6 (17.6%)
Achromobacter xylosoxidans colonization	2 (5.9%)
SCC (mEq/L)	113.5 (103.3, 117.0)
BMI (SDS)	−0.89 (−1.25, −0.19)
BMI category	
Underweight	5 (14.7%)
Normal weight	29 (85.3%)
Overweight	0
Obesity	0
$ppFEV_1$	99.5 (91.3, 110.0)
$ppFEV_1$ category	
<40	0
40–79	2 (6.7%)
≥80	28 (93.3%)
Unknown	4
$LCI_{2.5}$	8.6 (7.5, 9.7)

Abbreviations: BMI, body mass index; CFTR, Cystic Fibrosis Transmembrane Conductance Regulator; $LCI_{2.5}$, lung clearance index; MF, minimal function; MRSA, methicillin-resistant *Staphylococcus aureus*; $ppFEV_1$, percent predicted forced expiratory volume in one second; SCC, sweat chloride concentration; SDS, Standard Deviation Score.

[a]*n* (%); Median (25–75th percentile).

3 | RESULTS

3.1 | Study population

The study included 34 children with CF, of which 22 (64.7%) were males, with a median age of 8.3 years. Baseline characteristics of the participants are outlined in Table 1. The majority (67.6%) carried a F508del variant in combination with a minimal function variant. All children were pancreatic insufficient and most exhibited normal spirometry as indicated by the $ppFEV_1$ values. Most patients ($N = 29$, 85.3%) had abnormal $LCI_{2.5}$ values before ETI initiation. Five patients were underweight, and six were receiving Lumacaftor/Ivacaftor before ETI initiation. The presence of cataract signs was excluded in all children before starting ETI therapy.

3.2 | Effectiveness

Figure 1 shows changes in study outcomes during ETI therapy, while Table 2 shows the estimates of the treatment effect in terms of BMI, $ppFEV_1$, and $LCI_{2.5}$ changes. Four children were unable to perform a reliable spirometry test at the baseline visit and 8 at the 24-week follow-up visit, while reliable measures of $LCI_{2.5}$ were obtained from all children both at baseline and at the 12-week follow-up visit. At Week 24, sweat chloride concentration reduced on average by 63 mEq/L (95% CI: −69; −58). In 24 patients (70.6%) sweat chloride concentration decreased below the threshold indicative of CF (≥60 mEq/L). $ppFEV_1$ increased on average by 8.8 points (95% CI: 3.7; 13.9). At 12-week follow-up $LCI_{2.5}$ decreased by 2.3 points (95% CI: −3.1; −1.5). Only a modest increase in BMI was observed at the 24-week follow-up visit (+0.15 SDS, 95% CI: 0.04; 0.025).

Over the 24-week on ETI treatment, we recorded 57 pulmonary exacerbations (rate: 0.28 per patient-month) compared to the 97 (rate: 0.48 per patient-month) registered during the same period of the year preceding ETI initiation. The rate ratio was 0.59 (95% CI: 0.42; 0.82, $p = 0.002$).

3.3 | Safety and tolerability

The most common adverse events were: pulmonary exacerbations (57 episodes among 26 children, 76.5%) self-limiting skin rash

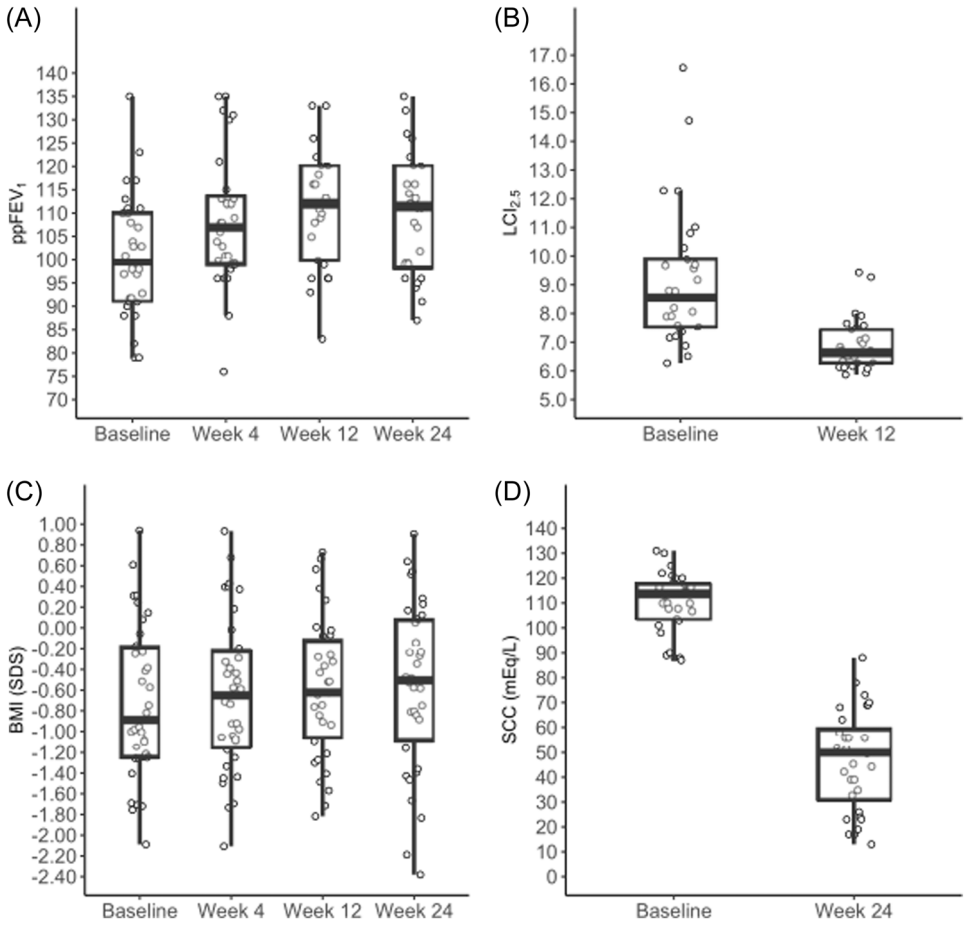

FIGURE 1 Changes from baseline in $ppFEV_1$ (A), $LCI_{2.5}$ (B), BMI (C), and sweat chloride concentration (SCC) (D) during treatment with Elexacaftor/Tezacaftor/Ivacaftor in children with cystic fibrosis aged 6–11 years. BMI, body mass index. $LCI_{2.5}$, lung clearance index; $ppFEV_1$, percent predicted forced expiratory volume in one second; SCC, sweat chloride concentration; SDS, Standard Deviation Score.

TABLE 2 Changes from baseline in sweat chloride concentration, body mass index, forced expiratory volume in one second, and lung clearance index in children with cystic fibrosis aged 6–11 years after therapy with Elexacaftor/Ezacaftor/Ivacaftor.

Study outcome	Time from ETI initation	Estimated marginal means (95% CI)[a]	Difference compared to baseline (95% CI)[a]	*p* Value[b]
SCC (mEq/L)	Baseline	109.9 (104.3; 115.5)	-	<0.001
	Week 24	46.7 (41.0; 52.4)	−63.3 (−68.9; 57.6)	
BMI (SDS)	Baseline	−0.71 (−0.97; −0.45)	-	0.030
	Week 4	−0.63 (−0.89; −0.37)	0.08 (−0.02; 0.19)	
	Week 12	−0.58 (−0.84; −0.32)	0.13 (0.03; 0.24)	
	Week 24	−0.57 (−0.83; −0.31)	0.15 (0.04; 0.25)	
$ppFEV_1$	Baseline	100.9 (96.1; 105.8)	-	<0.001
	Week 4	108.2 (103.2; 113.2)	7.3 (2.5; 12.1)	
	Week 12	111.2 (106.0-116.3)	10.2 (5.2; 15.3)	
	Week 24	109.8 (104.5-115.0)	8.8 (3.7; 13.9)	
$LCI_{2.5}$	Baseline	9.2 (8.5; 9.9)	-	<0.001
	Week 12	6.9 (6.3; 7.6)	−2.3 (−3.1; −1.5)	

Abbreviations: BMI, body mass index; $LCI_{2.5}$, lung clearance index; $ppFEV_1$, percent predicted forced expiratory volume in one second; SCC, sweat chloride concentration; SDS, Standard Deviation Score.

[a]Model-based estimates obtained by mixed-effects linear regression models. Estimates are mean values (95% CI).

[b]Likelihood ratio test.

(6 children, 17.6%) acute otitis media (3 children, 8.8%), liver function test (LFT) elevation (≥3 × Upper Limit of Normality, ULN) (1 child, 2.9%), gastroenteritis with elevated inflammatory markers (1 child, 2.9%), cough (1 child, 2.9%), headache (1 child, 2.9%) and itching (1 child, 2.9%). Two adverse events were deemed severe as they required hospitalization for intravenous antibiotic therapy: one for a respiratory exacerbation episode and the other for gastroenteritis. The remaining episodes of pulmonary exacerbation were treated with oral antibiotics.

At 4-week follow-up visit, one child had elevated alanine aminotransferase (ALT) levels, reaching more than three times the ULN, which is 30 U/L according to our laboratory reference values. The child then took half of the initial dose of ivacaftor for 1 month, while other modulators dosages remained unchanged. Additional blood tests performed 1 week later showed a decrease ALT levels, which remained stable at a subsequent blood tests conducted 1 week later, and at the 12- and 24-week follow-up visits. No other medical intervention or discontinuation of ETI therapy was required.

4 | DISCUSSION

Our prospective study provides evidence regarding the effectiveness of ETI treatment in improving early signs of lung damage in children with CF. We found a significant improvement in lung function, as assessed by increased $ppFEV_1$ (+8.8 percentage points through week 24), reduced $LCI_{2.5}$ (−2.3 units through week 12), and an approximately 40% reduced rate of pulmonary exacerbations, while we did not findan important variation in BMI. ETI was generally safe and well tolerated. Most adverse events were consistent with common manifestations of CF and did not require treatment discontinuation.

The clinical benefit observed in our patients was comparable to what has been reported in recently published clinical trials on pediatric patients. In a Phase 3b randomized, placebo-controlled study enrolling 60 patients receiving ETI and 61 receiving placebo, Mall et al reported a between-group difference in changes from baseline to Week 24 of 11 percentage points for $ppFEV_1$ and of −2.3 units in $LCI_{2.5}$.[18] Similarly, in an open-label study on 66 children with CF aged 6–11 years, Zemanick et al. observed an improvement in ppFEV1 of 10.2 percentage point and a decrease in $LCI_{2.5}$ of 1.7 units.[19] A reduction in $LCI_{2.5}$ of 0.83 units was also reported in younger children aged 2–5 receiving ETI in an open-label 24-week study.[20]

The improvements documented in the studies on pediatric populations with CF hold significant clinical relevance, since an annual increase in $LCI_{2.5}$ of 0.21 units has been estimated in untreated children aged 6-11 years.[21]

While CF impacts many organs and systems, the progression of lung disease, in most cases, plays a central role in determining both the length and quality of life. One of the primary objectives of respiratory management in people with CF is to slow the advancement of lung damage commonly observed in untreated cases. Notably, CF lung disease starts within the first weeks of life, often without noticeable clinical signs and symptoms,[22–24] with a substantial number of children showing detectable structural changes on computed tomography (CT) scan by the age of six.[25]

In adults and adolescents with CF, lung function changes are typically assessed using spirometry.[24] However, this tool has limitations, particularly in the early stages of CF, when subtle structural abnormalities are present. Its low sensitivity during this phase is attributed to the pathological processes mainly affecting the small airways, which go undetected by spirometry. Even when spirometry results indicate normal lung function, CT scans frequently reveal underlying structural damage, such as bronchiectasis.[26,27] However, due to the health risks associated with frequent exposure to ionizing radiation from CT scans, CT scan cannot be repeated frequently, especially in children.

In children with CF proper execution of spirometry is technically challenging and demands excellent patient cooperation. Achieving

this level of co-operation, especially among pediatric patients, is often difficult and sometimes impossible. For this reason, only 26 out of 34 children in our study were able to provide reliable spirometry tests at all follow-up visits. In these children, like in adults, a rapid increase in ppFEV$_1$ values was observed after just 4 weeks of treatment with ETI. This increase became even more significant after 12 weeks of treatment and remained stable through Week 24.

The MBWN$_2$ test is particularly useful for evaluating lung function in preschool children because it requires only passive cooperation and tidal breathing. Consequently, a higher percentage of children are able to successfully perform this test compared to spirometry. Unlike FEV$_1$ or other spirometric measures, LCI evaluate lung function in the peripheral airways. Peripheral airways constitute a larger portion of the lung compared to the central airways and it is also the first portion of the lungs involved in the CF-related lung disease. This distinction is vital because spirometry's accuracy is hampered by its dependence on airway resistance, which significantly decreases in airways beyond the eighth to tenth generation of the bronchial tree.

Others studies conducted in different populations and age groups had also demonstrated that LCI improves shortly after ETI therapy initiation.[20,28] This improvement is primarily attributable to the mobilization of secretions in the lung periphery, a feature that LCI can detect more effectively than other more expensive techniques such as MRI.[28,29] However, we should also consider the limitations of LCI. First, it is more expensive than spirometry and requires specific equipment and trained personnel that are not available in all healthcare facilities. Additionally, the duration of the exam is longer compared to spirometry, especially in young children, and its reliability diminishes in patients with severe airways obstruction.[30]

Therefore, in an era where modulators are being prescribed at increasingly younger age (for children older than 2 years in the United States), alternative tools beyond spirometry are essential for accurate monitoring of treatment effect.

In our pediatric population, pulmonary exacerbation rate decreased by approximately 40%. This result is in line with what has been observed in older population with CF receiving ETI.[31] In a double-blind, placebo-controlled trial involving 403 patients aged 12 years and older with a single Phe508del, Middleton et al. reported a reduction in the exacerbation rate of 63%. However, in interpreting this result, it is important to acknowledge that recurrent respiratory tract infections affect up to 25% of children in their early years of life,[32] irrespective of CF. These infections, typically caused by viruses, are predominantly self-limiting.

In this context an objective parameter such as LCI$_{2.5}$ obtained through instrumental investigation can be valuable for measuring treatment response at different ages, including childhood.

Our data did not show important variations in BMI in children after 24 weeks of treatment with ETI. This result contrast with other studies conducted both in children >12 years and adults,[31,33] showing that ETI promotes weight gain and BMI increase. It also contrasts with an open-label study involving 66 children aged 6–11 years, which reported a mean increase in BMI SDS of 0.37 after 24 weeks of ETI treatment.[19] However, it is important to note that this study was carried out in the pandemic period, a time when children likely remained at home and experienced reduced exposure to respiratory infections, both due to the imposed restrictions on mobility and social contacts, as well as the use of masks. In contrast, our study was conducted during a period, when children had resumed their normal activities and contracted a high number of respiratory infections. Thus, this factor could have had a negative impact on weight gain, preventing us from detecting a possible improvement in BMI.

Treatment with ETI in children 6 through 11 years of age was safe and well tolerated, as shown by a previous open label study,[19] as well as studies in adolescents and adults.[31,33] Among children who presented rash, all events were mild and did not require any treatment. The incidence of transaminase elevation associated with ETI treatment was lower in our study compared to what has been previously reported.[7,18,19] In clinical trials, the occurrence of LFT elevation ranged from 10 to 17.9%. Treated children experienced elevated levels of aspartate aminotransferase and/or alanine aminotransferase exceeding three times the age-specific normal range. Notably, none of the children in our study required discontinuation of ETI. This finding may be, at least in part, attributed to the practice at our center of discontinuing azithromycin treatment in patients who started ETI. While no specific recommendations have been provided for discontinuation of azithromycin in patients receiving ETI therapy, it was discontinued as a precautionary measure to mitigate the potential elevation of LFTs, as the drug primarily undergoes hepatic metabolism. None of our children presented creatine phosphokinase elevation or increased intracranial pressure as reported in a case report of three children.[34]

Our study has some limitations. It was conducted in a single center and included a relatively small sample size, which may limit the generalizability of our results and the precision of our estimates of treatment effect. Additionally, the short-term follow-up period prevents us from inferring the duration of treatment effect. On the other hand, the study is based on real-world data generated during routine clinical practice, confirming in children with CF the results observed in randomized clinical trials.

In conclusion, ETI therapy was well-tolerated and effective in improving pulmonary outcomes in our cohort of children with CF.

AUTHOR CONTRIBUTIONS

Valeria Daccò: Conceptualization; investigation; writing—original draft; project administration; supervision. **Chiara Rosazza**: Data curation; writing—review and editing; investigation. **Alessandra Mariani**: Writing—review and editing; investigation. **Carmela Rizza**: Investigation. **Nicolò Ingianni**: Investigation. **Erica Nazzari**: Investigation. **Vito Terlizzi**: Writing—review and editing. **Francesco Arturo Blasi**: Writing—review and editing. **Gianfranco Alicandro**: Conceptualization; writing—review and editing; supervision; formal analysis; visualization; methodology.

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CONFLICTS OF INTEREST STATEMENT

Valeria Daccò, Chiara Rosaza, Erica Nazzari and Francesco Arturo Blasi report honoraria for lectures and consultancy fees from Vertex Pharmaceuticals.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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