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Evaluation of the Impact of Elexacaftor/Tezacaftor/Ivacaftor on aerobic capacity in children with Cystic Fibrosis aged 6 to 11 years: Actual observations and clinical perspectives.

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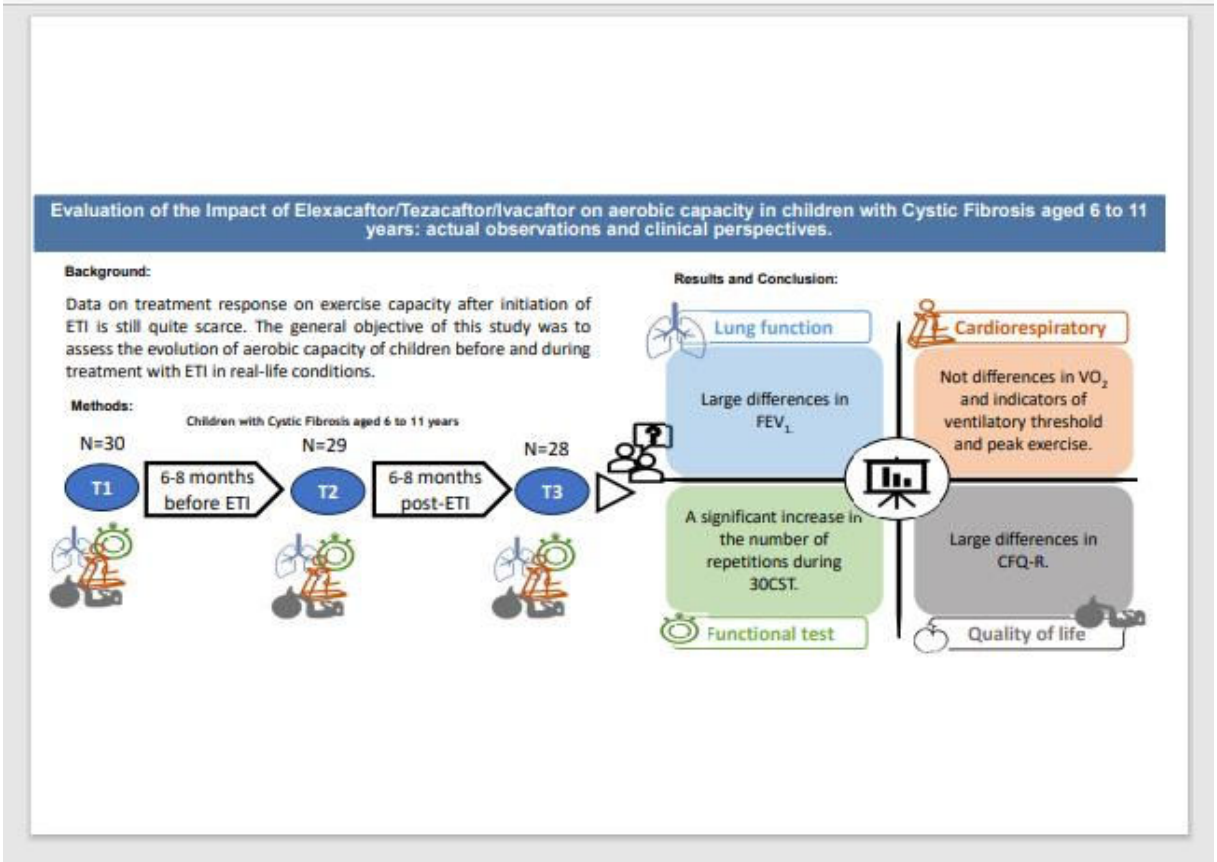
Graphical Abstract



Abstract

Background: Cystic fibrosis causes exercise limitation due to impaired lung function and other complications, which in turn increases the chance of mortality. CFTR modulators, particularly the elexacaftor/tezacaftor/ivacaftor (ETI) combination, improve lung function in children older than 6 years in real-life studies.

Objective: This study aimed to assess the impact of ETI on aerobic capacity in children with CF aged 6 to 11 years under real-life conditions and to evaluate whether prior CFTR modulator treatment affects these outcomes.

Methods: A multicenter, prospective cohort study was conducted with -pediatric CF patients. Participants underwent evaluations 6-8 months before ETI (T1), at the start of ETI (T2), and 6-8 months post-treatment (T3). Primary outcomes included cardiorespiratory fitness assessed via peak oxygen consumption (VO_2peak) during a cardiopulmonary exercise test (CPET), and secondary outcomes encompassed lung function, quality of life, physical activity, and functional mobility.

Results: Of the 28 patients (mean age 9.02 ± 1.59 years), 19 were ETI-naive, and 9 had prior CFTR modulator treatment. Significant improvements were observed in FEV_1 ($p<0.001$), and several functional mobility tests (30CST, Stair Climb Test, 10MWT). However, VO_2peak showed no significant changes between T1 and T3. Quality of life scores improved notably in emotional, eating, and respiratory domains, and a slight improvement was noted in physical activity levels (p=0.037).

Conclusions: ETI treatment significantly enhances lung function and certain aspects of quality of life and physical fitness in pediatric CF patients. However, it does not significantly alter aerobic capacity (VO_2peak) within the observed period.

Keywords: Cystic fibrosis, ETI (Elexacaftor/Tezacaftor/Ivacaftor), Aerobic capacity, Quality of life, Real-life.

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease most found in Caucasian populations (1). The most prevalent mutation is F508del, of which 88% of patients have at least one copy (2). F508del is classified as a class II mutation, which are characterized by a misfolding of the CFTR protein making it unable to reach the cell surface (3). During the last decade, research has been focusing on the underlying dysfunction of the CFTR gene using new drugs, so called CFTR modulators. The highly effective modulator combination elexacaftor/tezacaftor/ivacaftor (ETI) was approved in Spain for people with CF (pwCF) > 12 years in 2020, and the age of use was reduced to over 6 years old from September 2022 (4).

The meta-analysis done by Kapuni *et al* highlights a substantial increase in forced expiratory volume (FEV_1) in both children and adults in multiple studies (3). It was also found to increase quality of life of patients, reduce pulmonary exacerbations and increase weight gain (3). Although FEV_1 has been considered as the best predictor of mortality in both CF children and adults, it should not be forgotten that CF is a multisystemic disease affecting other systems such as the cardiovascular system as well as the peripheral muscles (5,6). Adding a test for aerobic fitness would enable to have a complete picture for the prognosis. Peak oxygen consumption (VO_2 peak), which is measured during a cardiopulmonary exercise test (CPET), is the main parameter in the evaluation of aerobic capacity and has been found to be a good predictor of survival in pwCF (7,8). Patients with lower VO_2 peak rates showed a 4.9-fold increased risk for a fatal outcome (8).

As of today, only a few studies have measured aerobic fitness with CPET in patients under ETI treatment, showing a clinical improvement (9,10) or no effect (11).

Data on treatment response on exercise capacity after initiation of ETI is still quite scarce. Therefore, the general objective of this study was to assess the evolution of aerobic capacity of children before and during treatment with ETI in real-life conditions. A second objective was to assess if those same variables would be affected by a previous CFTR modulator treatment.

Our hypothesis was that ETI would not improve aerobic capacity in patients with CF although an increase could be observed in the pulmonary function. Also, that the difference of the variables over time would be lower in patients which already received a CFTR treatment previously.

Methods

Study design

The present study was a multicenter, prospective cohort study. The study protocol adhered to the "Ethics guidelines of the Declaration of Helsinki", the last modification made in 2019, and was approved by the Ethics Committee of the Niño Jesús University Children's Hospital (CI: R-0086/19). The effects of the administration of ETI on quality of life and physical fitness were measured 6-8 months (T1) before its onset, at the time of onset (T2) and 6 to 8 months after its onset (T3). For the second objective of this study, the cohort was separated into two groups, a "modulator-naive" group in which ETI is their first treatment and another group, in which patients switched treatment.

Participants

The study was carried out in patients diagnosed with CF under follow-up in the 3 CF units of Madrid (Spain). Inclusion criteria included: sweat chloride ≥ 60 mEq/L and/or two variants of the CFTR gene characterized as pathogenic; aged between 6 and 11 years old; eligible to receive treatment with CFTR protein modulating drugs. Some of the secondary measures were lost to follow-up due to de difficulty of ensuring that the children of that age stayed in the hospital accompanied by their parents long enough to obtain all the measures. The tables show the number of children in whom each measure was obtained.

Primary outcomes

Cardiorespiratory fitness

Cardiorespiratory fitness was assessed by a maximum test on a treadmill (Technogym Run Race 1400HC; Gambettola, Italy). The ramp protocol was adapted to the pediatric and CF population. Breath-

by-breath gas exchange data were collected through open-circuit spirometry (Ergostik- Cardiopart GERATHERM- AMEDTEC®), utilizing specialized pediatric face masks, in conjunction with electrocardiogram recording. The test aimed to assess both VO_2peak and ventilatory threshold 1 (VT1) in reaction to maximal effort. The highest recorded VO_2peak was observed during any continuous 20-second interval as previously described (13). The VT1 was determined by the changes in the ventilatory equivalents for VO_2 and VCO_2 and changes in end-tidal oxygen, and carbon dioxide pressures (12). The test was considered as maximum if the following criteria were met: (i) 90% of predicted heart rate; and (ii) respiratory exchange ratio (RER) > 1.05 (13).

Secondary outcomes

Lung function

Spirometry was conducted using a Master Screen spirometer (Jaeger, Germany) in accordance with the guidelines of the American Thoracic Society and European Respiratory Society (ATS/ERS) (14). The data were presented in both absolute values and z-scores, utilizing the Global Lung Initiative (GLI) reference equations (15).

Quality of life and lifestyle

Revised Cystic Fibrosis Quality of Life Questionnaire (CFQ-R) was used to assess the health-related quality of life in pwCF, covering physical, emotional, and social domains. Physical activity level (PA) was measured using the PAQ-C (Physical Activity Questionnaire for Children). In order to avoid bias, all patients are moderately active. The KIDMED questionnaire was used to assess adherence to the Mediterranean diet.

Functional tests

The Timed Up and Go (TUG) test of 10 m and the Timed Up and Down Stairs (TUDS) tests were used to measure children's functional mobility. The TUG test is described as the time needed to stand up from a seated position in a chair, walk 10 m, turn around, return to the chair and sit down (16). The TUDS

test is described as the time to ascend and descend 12 stairs (17). Finally, the 30-Second Chair Stand test (30CST) was also performed to evaluate lower body strength (18).

Anthropometry

Anthropometric data and body composition height and weight were measured using a mechanical balance (ASIMED model BARYS PLUS C®) equipped with a telescopic height measuring meter to calculate body mass index (BMI). The cut-offs used to describe nutritional status were those proposed according to the World Health Organization. The participants' body composition (body fat and lean mass) was assessed using the bifrequency mode (at 5/50 kHz) bioimpedance analysis method (BodyStat 1500MDD®). Body fat mass index and fat-free mass index were calculated and expressed as percent (%) values.

Statistical analysis

All statistical analysis was performed using IBM SPSS Statistics 28.0 for MAC version (28.0.1.1 (14)). The normal distribution of the variables was verified with the Shapiro-Wilk and Levene tests and with P-P and Q-Q graphs. The mean and standard deviation were used to describe parametric variables, the median and interquartile range (IQR) for non-parametric variables. The repeated measures ANOVA test was used for the analysis of the effect of time (T1, T2 and T3). The level of statistical significance was set at $p < 0.05$.

Results

Participants and baseline characteristics

Of the 33 patients aged 6-11 years with CF on ETI treatment, 28 were included in the study (figure 1) and completed all tests at baseline (mean±SD age: 9.02±1.59 years). Baseline characteristics for the study population are presented in **Table 1**. Of the 28 children included in the study, some of the secondary measures were lost to follow-up. The tables (2, 3 and 4) show the number of children in whom each measure was obtained.

Cardiorespiratory fitness and lung function after treatment implementation

The cardiorespiratory fitness of 28 patients was evaluated over several months and the data is presented in **Table 2**. No significant changes were found between T1 and T3 for VO_2peak, VO_2, PVO_2, VE/VO_2. A significant change was found in the FEV_1 (p<0.001), RER_{peak} (p=0.043) and BR (p=0.017) with an increase of 42%. Finally, the heart rate variables showed no significant changes.

Quality of life and lifestyle after treatment implementation

The CFQ-R was used to measure the health-related quality of life (HRQOL) of children with CF. The score of most of the domains improved but only the emotion (p=0.005), eat (p=0.02) and respiratory (p=0.001) domains showed a significant difference between T1 and T3. Regarding the lifestyle questionnaires, KIDMED showed no significant differences, on the other hand, PAQ-C questionnaire improved slightly (p=0.037).

Functional tests after treatment implementation

A significant increase in the number of repetitions during 30CST was observed from T1 to T3 going from 19.64 to 28.77 (p<0.001). The score for the Stair Climb Test also improved significantly, going from 7.66 sec to 7.02 sec (p=0.029). Lastly, the 10MWT improved by a second from T1 to T3 (p=0.003).

Anthropometrics after treatment implementation

Between T1 and T3, a decrease in body fat percentage of 5% and an increase of around 6% of lean body mass were observed but this was not significant. The body fat and fat free mass indexes also showed no significant differences over treatment period.

Participants with previous CFTR treatment

Nine patients switched treatment going from ivacaftor/lumacaftor to ETI. **Table 3** shows the changes from baseline to follow-up including primary and secondary outcomes in patients with previous CFTR treatment. For the cardiopulmonary variables, significant changes were found for the VE/VO_2 (p=0.015)

and BR (p=0.024). No significant changes were observed in the different CFQ-R domains. Regarding functional exercise capacity, a significant improvement was observed for the 30CST score which went from 19.5 to 28 (p=0.026).

Patients with ETI as their first CFTR modulator

Nineteen children were started on ETI as their CFTR modulator. **Table 4** shows the changes in primary and secondary outcomes from baseline to follow-up for modulator-naive patients. Regarding cardiopulmonary variables, FEV1 (p=0.004) showed a significant increase from T1 to T3. For the HRQOL, significant improvements were found in emotional (p=0.003), eating (p=0.048) and respiratory (p=0.004) domains. Those are similar to what was observed for the whole cohort. No significant differences were observed for the lifestyle questionnaires. This group also shows a significant improvement in 30CST score going from 19.96 to 29.06 (p=0.001). The 10-meter walk test improved by half a second (p=0.044) Lastly, with regard to anthropometrics, a significant increase was found for the FFMI (p=0.007).

Discussion

The present study evaluated the effects of an ETI treatment on exercise capacity in children with CF in real life conditions. Few published data exist on the impact of new modulators on cardiorespiratory fitness in pwCF, particularly with ETI and in children of our age range. This study also examined the possible difference in response between patients who had received previous CFTR modulator therapy and those who didn't. The hypotheses were that ETI would not improve cardiorespiratory fitness although an increase could be observed in the pulmonary function. Also, the difference over time would be lower in patients who had already received a CFTR treatment previously.

No improvements were observed in VO_2 peak, the main parameter for evaluating cardiorespiratory fitness. There were also no significant improvements when separated into modulator-naive patients and patients with previous CFTR treatment. Previous research has also investigated the impact of CFTR modulators on VO_2 peak (ml/kg/min) in pwCF and conclusions are quite different. Ahmed *et al*

observed no significant difference in VO_2 peak in a cohort of 19 adolescents, 4 to 8 months after treatment (19). They also found no significant differences when splitting the group into naive and previously treated patients. Similarly, Gur *et al* found no significant improvements in VO_2 peak three months after the initiation of ETI (20). Wilson *et al*, studied the impact of lumacaftor/ivacaftor on exercise tolerance in pwCF compared to patients on placebo and found no significant improvement in VO_2 peak (11). However, some studies observed improvements in VO_2 peak (9,10,21,22). Philipsen *et al*, in a study involving 229 CF patients aged 12 and older, found significant improvements in VO2 peak (+0.6 ml/kg/min, 95% CI (0.1-1.1)) and other cardiopulmonary variables after one year of ETI treatment (21). Causer *et al* also showed an improvement in peak VO_2 with 6 weeks of ETI treatment in three adolescents with CF (9). They explained that those with more severe lung disease and lowest fitness levels had the greatest improvements. Studies using second generation CFTR-modulator treatment such as ETI also found improvements in VO_2 peak after 1 year and 2 years of treatment (10,22). In our study, exercise capacity did not improve despite an improvement in lung function. Our patients have mild lung function impairment, which may influence the results; however, it is possible that patients with severe lung disease experience ventilatory limitations during exercise, reaching a respiratory reserve close to 0, and may see improvements following the use of the modulator (23).

To determine if CPET was done maximally, a VO_2 plateau is mostly looked for, which is difficult to obtain in healthy populations and even harder in pwCF. Therefore, secondary variables such as the respiratory exchange ratio (RER) help to determine a maximal effort. An RER of 1.1 or higher during CPET is a commonly accepted criterion indicating maximal effort. For children with CF it is set at 1.05. In this case, a significant increase in RER was observed from T1 (0.98 (0.08)) to T3 (1.03 (0.08)) in the whole cohort. RER is getting closer to 1.05, meaning that the patients are closer to performing maximally during exercise testing. All test were done at 85% of maximum heart rate at all three timepoints during this study.

A decrease in VE/VO_2 is generally a positive indicator of respiratory efficiency and overall fitness, meaning that the body is becoming more efficient at extracting and utilizing oxygen (24). Unexpectedly, in this case, an increase in the VE/VO2 was observed in the group that had previous treatment, which is the opposite of what was found by Philipsen *et al* and Gur *et al* for example (20,21). This unexpected result could simply be explained by the small sample number, but an explanation could also be found at peripheral muscle level and more precisely at the endothelial cells where CFTR also plays a role (9). Adequate physical activity may play a more significant role in overall improvements than enhancements in lung function and the better functioning of the CFTR, highlighting the importance of a correct dose of physical exercise rather than focusing solely on pulmonary function improvements.

Improvements were also observed in BR in the whole cohort and in the patient group that received previous treatment. Ahmed *et al* also found improvements in BR after 4 to 8 months on ETI treatment, particularly un modulator-naive patients (19). A low BR and low VO_2 peak are suggested to be related to respiratory pathologies (13). As CF progresses, it limits ventilation and therefore, also limits exercise capacity (23). BR could be used as marker to follow the progression of CF.

As expected, lung function improved with ETI. Significant improvement in FEV_1 was found in the whole cohort and in the group with no previous treatment. There are few studies that have investigated this parameter in real life conditions and in this age group, but under different settings, similar results were found in previous research (19,20,21, 25,26).

In summary, cardiorespiratory fitness depends on central factors (heart and lungs) and peripheral factors (muscular bioenergetics). Although our patients show improved pulmonary function following the initiation of ETI, their baseline impairment is mild. Therefore, their exercise intolerance is primarily due to muscular bioenergetic deficiencies (27) . Addressing muscular alterations requires more time and potentially the integration of a stimulus, such as appropriately tailored high-intensity physical exercise (28).

To assess the impact of ETI treatment on quality-of-life, the CFQ-R questionnaire was used. In this study a significant improvement was found in three domains for the whole cohort; emotion, eat and respiratory. Same improvements were also found in the modulator-naive group. McNally *et al* for example, assessed quality of life over 1-year ETI treatment in 117 pwCF (12 years and older) in real-world conditions, showed a 14.2 points (95% CI, 11.3, 17.2) improvement for the respiratory domain (29). The responses can vary depending on the severity of the disease, where pwCF that are more severely affected have a bigger room for improvement. It needs to be mentioned this study was done in children and that age can play a major role in the perception of certain aspects, which could explain why the emotional domain improved in this case. Generally, it seems that the respiratory domain benefits the most of the ETI therapy.

Functional capacity was assessed using the 30CST, stair climb test and 10MWT. The whole cohort improved in all of them. Gur *et al* found a significant improvement in the 6MWT but mentions that firm conclusions cannot be drawn to small sample size (20). Aubriot *et al* found improvements in the 1STST but no improvements in the 6MWT (30).

Several studies have shown improvements in BMI which could be explained by an improved nutritional status (9,20). A better functioning of the CFTR protein would lead to better pancreatic function and improved digestion and absorption of nutrients (9,20). In this study, despite good adherence to the Mediterranean diet, no significant improvements were observed regarding BMI - for -age - z- score, body fat and lean mass percentages. These results may be related to the measurement and comparison of these parameters in absolute value, instead of using BMI - for -age - z- score.

There are some limitations to be considered in this study. The main limitation is the small sample size. Especially when separated into two subgroup “modulator-naive” and “previous CFTR treatment”, where the “previous CFTR treatment” group consisted of only nine patients. Additionally, the lack of randomization may have introduced selection bias, potentially affecting the comparability of groups and the generalizability of the findings.

The strength of this study is that is the first study to measure exercise capacity in children 6 to 11 years old under ETI treatment in real life conditions.

Conclusion

This study confirms that there is a beneficial effect of ETI on lung function in children 6 to 11 years old with pwCF. However, those improvements were not translated to cardiorespiratory fitness parameters even though patients increased physical activity. More research is needed to understand the other factors that can play a role in exercise capacity such as muscle oxidative capacity.

Authors' contributions

M.P.R: Methodology, Writing - Original Draft, Formal análisis

M.B: Formal Analysis, Investigation, Data Curation, Writing - Original Draft

P. F. G: Clinical trial sample recruitment, Resources, Writing - Review & Editing, Funding acquisition

C. M. G: Methodology, Writing - Review & Editing

A. M. T: Clinical trial sample recruitment

A. L. N: Methodology, Writing - Review & Editing

M. R. V. Clinical trial sample recruitment

M.R: Investigation, Formal analysis, Data Curation, Writing - Review & Editing

V.S.S: Conceptualization, Methodology, Supervision, Funding acquisition, Writing - Review & Editing, Project administration,

Conflicts of interests

Margarita Pérez-Ruiz, Alejandro López-Neyra and Verónica Sanz-Santiago have received speaking fees from Vertex Pharmaceuticals®.

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Ethical Disclosures

Protection of humans and animals. The authors declare that no experiments on humans or animals have been carried out for this research.

Confidentiality of data. The authors declare that no patient data appear in this article. In addition, the authors have acknowledged and followed the recommendations according to the SAGER guidelines depending on the type and nature of the study.

Privacy rights and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence to generate texts. The authors declare that they have not used any type of generative artificial intelligence in the writing of this manuscript or for the creation of figures, graphs, tables, or their corresponding captions or legends.

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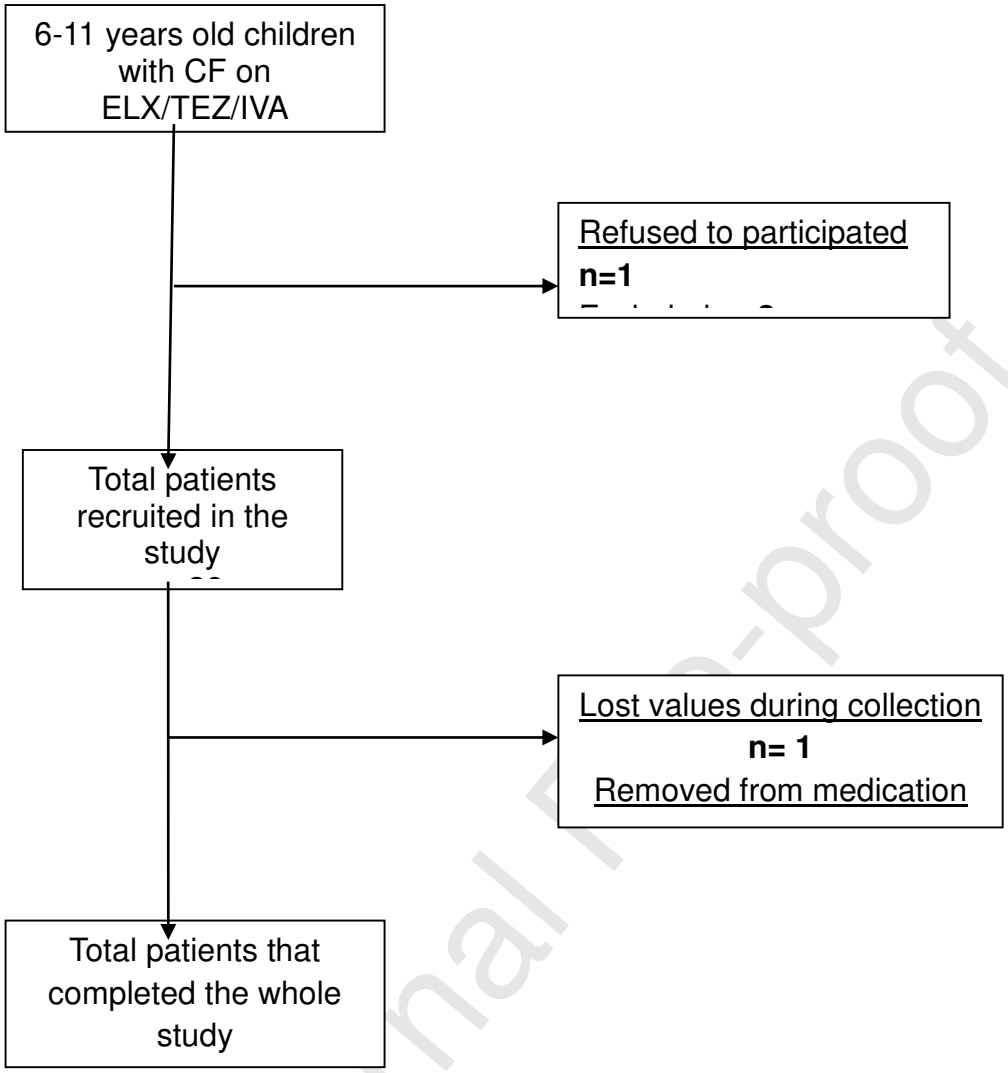

Fig 1. Participant flow chart.

Table 1. Baseline characteristics (T1) of the study participants

	n=28
Demographics	
Sex, Men, n (%)	18 (64.3)
Age (years), mean (SD)	9.07 (1.59)
Anthropometrics**, mean (SD)**	
Height (cm)	131.93 (8.54)
Height (z-score)	-0.08 (0.87)
Weight (kg)	27.73 (5.3)
Weight (z-score)	-0.69 (0.58)
BMI	15.82 (1.81)
BMI (z-score)	-0.30 (0.74)
Body Fat %	25.18 (10.44)
Lean body mass %	74.47 (10.54)
BFMI	3.98 (1.71)
FFMI	11.44 (2.07)
Pulmonary function**, mean (SD)**	
FEV_1 (l)	1.64 (0.36)
FEV_1 (z-score)	-0.34 (0.94)
FVC (l)	1.97 (0.41)
FVC (z-score)	0.02 (0.70)
Cardiorespiratory capacity, **mean (SD)**	
VO_{2peak} (ml/kg/min)	39.04 (5.67)
VO_{2peak} (% predicted)	87.39 (11.39)
VE/ VCO_2 VT1	26.94 (2.66)
RER_{peak}	0.98 (0.078)
Heart $rate_{peak}$ (bpm)	177.82 (13.76)
Genotype**, n (%)**	
F508del homozygous	9 (32.1)
F508del heterozygous	19 (67.9)
Previous modulator therapy, **n (%)**	
No	19 (67.9)
Yes	9 (32.1)
Clinical diagnoses**, n (%)**	
Exocrine pancreatic insufficiency	25 (89.3)
CF-related diabetes mellitus	1 (3.6)
Microbiology**, n (%)**	
Chronic *Pseudomonas aeruginosa*	1 (3.6)
Chronic *methicillin-resistant Staphylococcus aureus*	0
Chronic *Burkholderia cepacia*	0
Functional exercise capacity**, mean (SD)**	
30CST (n)	19.64 (5.92)
Stair climb test (s)	7.62 (1.14)
10MWT (s)	9.93 (1.08)
Quality of life questionnaires**, mean (SD)**	

CFQ_RPHYSICAL	91.03 (8.18)
CFQ_REMOTION	78.04 (12.61)
CFQ_REAT	66.66 (28.98)
CFQ_RTREAT	73.51 (18.88)
CFQ_RSOCIAL	72.89 (15.69)
CFQ_RBODY	73.08 (31.46)
CFQ_RRESPIRAT	83.34 (12.25)
CFQ_RDIGEST	71.80 (27.80)
***Lifestyle questionnaires*, mean (SD)**	
KIDMED score	7.8 (2.12)
PAQ-C score	3.32 (0.58)

BMI: body mass index; BFMI: body fat mass index; FFMI: fat-free mass index; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; VO_2peak: peak oxygen uptake; VE: ventilation; VCO_2: carbon dioxide volume; VT1: Ventilatory threshold 1; RER: respiratory exchange ratio; 30CST: 30 Second Chair Stand Test; 10MWT: 10 meter walk test; PAQ-C: Physical Activity Questionnaire for Children;; kg: kilograms; m: meters; cm: centimeters; g: grams; ml: milliliters l: liters; SD: standard deviation; Data are presented as mean (SD) or n (%).

Table 2. Changes from baseline to follow-up including primary and secondary outcomes

	n	T1	T2	T3	*p-value*	η^2_p
Cardiopulmonary variables mean (SD)						
VO_{2peak} (ml/kg/min)	28	39.04 (5.67)	36.71 (5.92)	39.08 (8.13)	0.218	0.110
VO_2 VT1	28	21.78 (4.19)	19.73 (3.17)	21.94 (6.24)	0.109	0.156
PVO_2 VT1	28	56.32 (9.06)	54.5 (9.15)	53.57 (9.04)	0.552	0.045
VE VO_2 VT1	28	22.52 (2.78)	24.10 (4.02)	24.37 (6.82)	0.095	0.166
FEV_1 (l) z-score	27	-0.32 (0.95)	-0.60 (1.07)	0.57 (1.21)	**<0.001**	0.468
RER_{peak}	28	0.98 (0.08)	1.00 (0.07)	1.03 (0.08)	**0.043**	0.215
RR	28	21.5 (16.52)	26.87 (12.95)	30.72 (13.19)	**0.017**	0.277
Heart $rate_{peak}$ (bpm)	28	178.89 (12.79)	181.52 (13.29)	182.15 (11,56)	0.274	0.098
Heart rate 2 min REC	27	133.33 (17.47)	136.67 (15.2)	136.48 (16.63)	0.314	0.089
Anthropometrics, mean (SD)						
Weight (z-score)	28	-0.69 (0.58)	-0.68 (0.61)	-0.62 (0.60)	0.319	0.084
Height (z-score)	28	-0.08 (0.87)	-0.001 (0.89)	-0.13 (0.92)	**0.034**	0.229
BMI (z-score)	28	-0.30 (0.74)	-0.40 (0.76)	-0.2 (0.66)	0.158	0.132
Body Fat %	23	25.18 (10.44)	23.90 (6.34)	20.03 (7.75)	0.070	0.224
Lean body mass %	22	74.47 (10.54)	76.47 (5.89)	80.12 (7.91)	0.075	0.228
BFMI	19	3.98 (1.71)	4.11 (2.74)	3.22 (1.63)	0.234	0.157
FFMI	18	11.44 (2.07)	11.91 (1.82)	12.25 (2.80)	0.467	0.091
Quality of life questionnaires, mean (SD)						
CFQ_R physical	26	91.03 (8.18)	83.12 (18,76)	90.17 (12.50)	0.103	0.173
CFQ_REMOTION	26	78.04 (12.61)	78.20 (12.09)	83.97 (10.59)	**0.005**	0.359
CFQ_REAT	26	66.66 (28.98)	68.80 (28.98)	79.92 (19.88)	**0.020**	0.278
CFQ_RTREAT	26	73.51 (18.88)	76.07 (19.04)	79.06 (18.41)	0.398	0.074
CFQ_RSOCIAL	26	72.89 (15.69)	69.22 (14.21)	73.99 (14.64)	0.355	0.083
CFQ_RBODY	26	73.08 (31.46)	79.49 (21.70)	83.76 (18.12)	0.300	0.096
CFQ_RRESPIRAT	26	83.34 (12.25)	72.76 (20.21)	90.06 (10.01)	**0.001**	0.427
CFQ_RDIGEST	26	71.80 (27.80)	67.94 (30.52)	80.77 (23.42)	0.074	0.195
Functional exercise capacity, mean (SD)						
30CST (n)	22	19.64 (5.92)	27.73 (6.64)	28.77(4.87)	**<0.001**	0.630
Stair climb test (s)	24	7.66 (1.18)	7.23 (0.87)	7.02 (1.12)	**0.029**	0.275
10MWT (s)	26	10 (1.03)	9.62 (1.26)	9.06 (1.17)	**0.003**	0.389
Lifestyle questionnaires, mean (SD)						
KIDMED score	24	7.92 (2.16)	8.25 (2.03)	7.71 (2.18)	0.209	0.133
PAQ-C score	24	3.30 (0.59)	3.01 (0.70)	3.32 (0.64)	**0.037**	0.259

VO_2peak: peak oxygen uptake; VO_2 UV1: ; PVO_2 UV1: maximum oxygen uptake; VE: ventilation; FEV_1: forced expiratory volume in 1 second; RER_{peak}: respiratory exchange ratio; RR: respiratory reserve ; BFMI: body fat mass index; FFMI: fat-free mass index; 30CST: 30 Second Chair Stand Test; 10MWT: 10 meter walk test; ml: milliliters; SD: standard deviation. Differences were assessed through one-way repeated measures ANOVA. η^2_p **:** partial eta-squared effect size. Significance was set at $p<0.05$.

Table 3. Changes from baseline to follow-up including primary and secondary outcomes in patients with previous CFTR treatment.

	n	T1	T2	T3	*p-value*	η^2_p
Cardiopulmonary variables mean (SD)						
VO_{2peak} (ml/kg/min)	9	39.22 (4.61)	37.53 (5.15)	40.10 (7.92)	0.437	0.093
VO_2 VT1	9	21.40 (4.18)	20.66 (2.93)	22.83 (7.07)	0.507	0.077
PVO_2 VT1	9	54.58 (8.10)	55.74 (9.71)	51.89 (8.26)	0.310	0.129
VE VO_2 VT1	9	22.70 (3.08)	22.97 (3.09)	22.98 (3.09)	0.940	0.007
FEV_1 (l) z-score	8	-0.44 (0.95)	-0.76 (1.20)	0.44 (1.09)	**0.004**	0.475
RER_{peak}	9	0.98 (0.08)	0.10 (0.08)	1.00 (0.070)	0.426	0.096
RR	8	23.41 (15.76)	26.20 (10.57)	29.58 (8.89)	0.275	0.141
Heart $rate_{peak}$ (bpm)	8	176.32 (13.80)	180.21 (14.56)	182.68 (11.63)	0.057	0.286
Heart rate 2 min REC	9	130.28 (18.96)	134.44 (16.42)	135.56 (18.32)	0.280	0.147
Anthropometrics. mean (SD)						
Weight (z-score)	9	-0.53 (0.52)	-0.62 (0.55)	-0.55 (0.63)	0.205	0.364
Height (z-score)	9	0.11 (0.83)	0.17 (0.71)	0.05 (0.81)	0.545	0.159
BMI (z-score)	9	-0.27 (0.71)	-0.38 (0.77)	-0.28 (0.66)	0.232	0.158
Body Fat %	8	22.81 (6.63)	23.10 (5.85)	20.61 (7.83)	0.431	0.122
Lean body mass %	7	77.13 (6.56)	77.67 (5.10)	79.39 (7.82)	0.509	0.099
BFMI	4	3.63 (1.19)	4.19 (3.03)	3.49 (1.64)	0.659	0.062
FFMI	4	11.10 (1.46)	12.32 (1.92)	13.06 (1.77)	**0.007**	0.596
Quality of life questionnaires. mean (SD)						
CFQ_R physical	9	90.85 (8.08)	84.97 (13.57)	90.85 (12.10)	0.188	0.200
CFQ_REMOTION	9	80.14 (13.05)	77.94 (11.94)	86.52 (8.27)	**0.003**	0.535
CFQ_REAT	9	71.89 (26.39)	71.90 (28.09)	85.62 (15.59)	**0.048**	0.333
CFQ_RTREAT	9	71.90 (17.62)	75.82 (18.10)	79.09 (17.95)	0.450	0.101
CFQ_RSOCIAL	9	73.67 (15.89)	71.42 (15.16)	76.47 (12.31)	0.390	0.118
CFQ_RBODY	9	64.71 (34.97)	75.17 (20.23)	85.62 (17.90)	0.071	0.297
CFQ_RRESPIRAT	9	83.82 (11.21)	71.08 (20.86)	90.69 (9.72)	**0.004**	0.514
CFQ_RDIGEST	9	76.47 (22.87)	72.54 (26.97)	84.32 (20.81)	0.275	0.158
Functional exercise capacity. mean (SD)						
30CST (n)	6	19.69 (6.59)	28.94 (5.96)	29.06 (5.20)	**0.001**	0.624
Stair clim test (s)	8	7.48 (1.08)	7 (0.62)	7.08 (1.22)	0.084	0.298
10MWT (s)	9	10.07 (0.80)	9.53 (1.03)	9.35 (1.07)	**0.044**	0.340
Lifestyle questionnaires. mean (SD)						
KIDMED score	8	7.56 (1.55)	7.69 (1.54)	7.50 (1.71)	0.854	0.022
PAQ-C score	8	3.34 (0.66)	2.95 (0.6)	3.32 (0.58)	0.061	0.329

VO_{2peak}: peak oxygen uptake; VO2 UV1: ; PVO2: maximum oxygen uptake; VE: ventilation FEV_1: forced expiratory volume in 1 second; RER_{peak}: respiratory exchange ratio; RR: respiratory reserve; BFMI: body fat mass index; FFMI: fat-free mass index; 30CST: 30 Second Chair Stand Test; ml: milliliters; SD: standard deviation. Differences were assessed through one-way repeated measures ANOVA. η^2_p: partial eta-squared effect size. Significance was set at $p<0.05$.

Table 4. Changes from baseline to follow-up including primary and secondary outcomes in patients with no previous CFTR treatment.

	n	T1	T2	T3	*p-value*	η^2_p
Cardiopulmonary variables mean (SD)						
VO_{2peak} (ml/kg/min)	19	38.64 (7.78)	34.97 (7.33)	36.94 (8.62)	0.37	0.248
VO_2 VT1	19	22.56 (4.35)	17.78 (2.87)	20.07 (3.60)	0.058	0.557
PVO_2 VT1	19	60 (10.34)	51.89 (7.70)	57.11 (10.08)	0.140	0.429
VE VO_2 VT1	19	22.12 (2.14)	26.49 (4.85)	27.31 (11.01)	**0.015**	0.700
FEV_1 (l) z-score	19	-0.049 (0.96)	-0.224 (0.58)	0.86 (1.50)	0.135	0.487
RER_{peak}	19	0.978 (0.08)	1.00 (0.039)	1.07 (0.09)	0.078	0.517
RR	19	17.47 (18.61)	28.47 (18.20)	33.42 (20.77)	**0.024**	0.710
Heart $rate_{peak}$ (bpm)	19	185 (7.54)	184.63 (9.78)	180.88 (12.09)	0.392	0.268
Heart rate 2 min REC	18	139.44 (12.85)	141.11 (12.01)	138.33 (13.41)	0.602	0.135
Anthropometrics. mean (SD)						
Weight (z-score)	19	-0.77 (0.60)	-0.71 (0.64)	-0.65 (0.60)	0.186	0.180
Height (z-score)	19	-0.16 (0.89)	-0.08 (0.97)	-0.21 (0.98)	0.057	0.286
BMI (z-score)	19	-0.35 (0.85)	-0.42 (0.79)	-0.28 (0.72)	0.716	0.091
Body Fat %	15	29.64 (14.82)	25.40 (7.35)	18.94 (8.01)	0.198	0.417
Lean body mass %	15	68.77 (15.25)	73.89 (7.04)	81.69 (8.50)	0.136	0.549
BFMI	15	5.28 (2.86)	3.80 (1.42)	2.22 (1.32)	0.255	0.745
FFMI	13	9.98 (2.84)	10.84 (1.03)	10.14 (4.02)	0.835	0.113
Quality of life questionnaires. mean (SD)						
CFQ_R physical	19	91.36 (8.83)	79.63 (26.64)	88.89 (13.89)	0.463	0.198
CFQ_REMOTION	19	74.08 (11.37)	78.70 (13.08)	79.17 (13.18)	0.472	0.193
CFQ_REAT	19	56.79 (32.61)	62.96 (31.43)	69.14 (23.43)	0.133	0.438
CFQ_RTREAT	19	76.54 (21.84)	76.54 (21.84)	79.02 (20.36)	0.899	0.030
CFQ_RSOCIAL	19	71.43 (16.15)	65.08 (11.90)	69.31 (18.15)	0.298	0.292
CFQ_RBODY	19	88.89 (14.69)	87.66 (23.20)	80.25 (19.07)	0.597	0.137
CFQ_RRESPIRAT	19	82.41 (14.70)	75.93 (19.74)	88.89 (11.02)	0.258	0.321
CFQ_RDIGEST	19	62.96 (35.14)	59.26 (36.43)	74.08 (27.78)	0.183	0.385
Functional exercise capacity. mean (SD)						
30CST (n)	19	19.50 (4.13)	24.50 (7.82)	28.00 (4.19)	**0.026**	0.839
Stair climb test (s)	16	8.02 (1.35)	7.69 (1.148)	6.88 (0.94)	0.251	0.369
10MWT (s)	17	9.88 (1.42)	9.78 (1.68)	8.50 (1.19)	0.062	0.548
Lifestyle questionnaires. mean (SD)						
KIDMED score	16	8.63 (3.07)	9.38 (2.50)	8.13 (3)	0.099	0.538
PAQ-C score	16	3.22 (0.43)	3.12 (0.90)	3.32 (0.79)	0.649	0.134

VO_{2peak}: peak oxygen uptake; VO2 UV1: ; PVO2: maximum oxygen uptake; VE: ventilation FEV_1: forced expiratory volume in 1 second; RER_{peak}: respiratory exchange ratio; RR: respiratory reserve; BFMI: body fat mass index; FFMI: fat-free mass index; 30CST: 30 Second Chair Stand Test; 10MWT: 10 meter walk test; ml: milliliters; SD: standard deviation. Differences were assessed through one-way repeated measures ANOVA. η^2_p: partial eta-squared effect size. Significance was set at $p<0.05$.