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Original Research

Perceived burden of respiratory physiotherapy in people with cystic fibrosis taking elexacaftor–tezacaftor–ivacaftor combination: a 1-year observational study

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Abstract

Background: To limit the progression of disease, people with cystic fibrosis (pwCF) perform daily respiratory physiotherapy, which is perceived as the most burdensome routine in managing their condition. The elexacaftor–tezacaftor–ivacaftor (ETI) combination has changed respiratory management.

Objective: To investigate how the perceived treatment burden changed in 1 year of treatment with ETI.

Design: Prospective observational study.

Methods: *Ad hoc* questionnaires for the pwCF and for the caregivers of pwCF < 18 years were administered before the initiation of ETI therapy and then at 6–12 months. The Cystic Fibrosis Questionnaire-Revised (CFQ-R) and the Sinonasal Outcome Test (SNOT-22) were administered to explore disease-related symptoms and social limitations. The International Physical Activity Questionnaire was used to determine levels of physical activity. Mixed-effect models were fitted to explore whether the time engaged in respiratory physiotherapy changed during 1 year.

Results: The study included 47/184 pwCF aged 21.4 (5.7) years, who completed 1 year of ETI therapy. At 6 months, time on aerosol therapy was decreased by 2.5 (95% CI −32.9 to 27.8) min/day, time on airway clearance therapies (ACTs) was decreased by 8.8 (95% CI −25.9 to 8.3) min/day, and time for cleaning and disinfecting respiratory equipment was decreased by 10.6 (95% CI −26.5 to 5.3) min/day. At 1 year, gains in time saved were nearly 15 min/day on average. At 1 year, 5/47 (10.6%) pwCF reported that they had discontinued positive expiratory pressure mask.

Conclusion: PwCF on ETI may note less time engaged in their daily respiratory physiotherapy routine. Nonetheless, aerosol therapy, ACTs and maintaining respiratory equipment were still perceived as time-consuming daily activities.

Plain language summary

Understanding the challenges of respiratory physiotherapy in individuals with cystic fibrosis using triple therapy: a one-year study.

In order to slow down the progression of their disease, people with cystic fibrosis typically do daily respiratory physiotherapy, which they find to be the most challenging part of managing their condition. The elexacaftor-tezacaftor-ivacaftor combination has changed how they manage their respiratory health. We wanted to see how the perceived difficulty

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of the treatment changed over one year of using elexacaftor-tezacaftor-ivacaftor. We gave questionnaires to people with cystic fibrosis and to their caregivers before they started the triple therapy and again at 6-12 months. We also used two international questionnaires to learn about symptoms and social limitations related to the disease. The International Physical Activity Questionnaire helped us understand their physical activity levels. We used statistical models to see if the time spent on respiratory physiotherapy changed over the year. Our study involved 47 individuals with cystic fibrosis, with an average age of 21 years, who completed one year of elexacaftor-tezacaftor-ivacaftor therapy. After 6 months, time spent on aerosol therapy decreased by 2.5 minutes per day, time on airway clearance therapies decreased by 8.8 minutes per day, and time for cleaning respiratory equipment decreased by 10.6 minutes per day. By the end of the year, they were saving almost 15 minutes per day on average. At one year, 5 out of 47 said they had stopped using the positive expiratory pressure mask. People with cystic fibrosis using elexacaftor-tezacaftor-ivacaftor may find that they spend less time on their daily respiratory physiotherapy routine. However, activities like aerosol therapy, airway clearance therapies, and maintaining respiratory equipment were still seen as time-consuming.

Keywords: airway clearance, CFTR modulators, cystic fibrosis, lung clearance index, respiratory physiotherapy, treatment burden

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Background

Cystic fibrosis (CF) is an inherited and multisystemic disease. The complex systemic clinical manifestations derive from the dysfunction of CF transmembrane conductance regulator (CFTR) protein, which controls ion and water secretion and absorption across epithelial cells. This may lead to an imbalance in the transport of ions and water, resulting in the production of thick, sticky mucus to build up in organs. To limit disease progression, patients perform daily routines (pharmacological therapy, respiratory physiotherapy) and follow dietary recommendations and care for their overall well-being starting at diagnosis. CF-related lung disease is the major cause of morbidity and mortality[1]; the build-up of mucus in the airways causes chronic and recurrent inflammation, leading to epithelial damage, tissue remodelling, and progressive deterioration of lung function, ultimately resulting in respiratory failure.[2] Respiratory mucus is loosened and removed by daily respiratory physiotherapy (RP), which is perceived as the most burdensome routine in disease management (2 h on average every day),[3] consisting of airway clearance therapy (ACT), exercise prescription and education, and inhalation therapy.[4]

A highly effective CFTR modulator therapy, the elexacaftor–tezacaftor–ivacaftor (ETI) compound, was approved in Europe in 2020 for the treatment of patients with at least one copy of p.Phe508del mutation and later extended to other genotype covering up to 90% of individuals with the disease.[5] ETI therapy has achieved unprecedented results in modifying the respiratory management of CF.[6–9]

Improved lung function and reduced mucosal secretion and inflammatory exacerbation may require less time engaged in ACT, inhalation, and maintaining respiratory equipment. With the present study, we investigated patient and caregiver perceived changes in treatment burden at 1 year of ETI therapy, here operationalized as time engaged in routine RP. Our hypothesis was that ETI therapy would change the perceived burden by either shortening the amount of time needed for ACT or reducing the number of sessions.

Methods

This prospective observational study was carried out at the Centre for CF, Milan, Italy. Following the approval of ETI therapy in Italy in October 2021, people with CF (pwCF) who had been prescribed ETI therapy were consecutively recruited for this study. Exclusion criteria were diagnosis of *Burkholderia cepacia* infection, neurological disorders, or cognitive deficits.

During scheduled outpatient visits, demographics and clinical data were extracted from the participants' electronic health records before and then at 6 and 12 months into ETI therapy. The usual RP regimen remained unchanged during ETI therapy, as agreed between the CF care team and the pwCF. Twice daily ACT consisted generally of 10 repetitions of positive expiratory pressure (PEP) mask breathing for 1 min, followed by huffing, for a total 40 min/day. Continuous positive airway pressure (CPAP) was recommended[10] for pwCF experiencing difficulty in clearing their airways of mucus or with signs of respiratory fatigue during ACT. CPAP therapy entailed 2 min breathing at a given CPAP level, followed by autogenic drainage or a cycle of active breathing techniques, repeated 10 times twice or more often daily. Only hypertonic saline was to be discontinued during ETI therapy. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[11]

Treatment burden

To investigate the time participants and/or their caregivers were engaged in RP (preparation, execution, equipment maintenance) involving nasal irrigation, aerosol therapy, and ACT, two self-administered questionnaires were devised, one for the adult pwCF on ETI therapy and one for the caregivers of participants <18 years old. The questionnaires were created in three phases: phase I to identify the aim, the patient sample, and the areas of focus; phase II to select the type of question items and complete the first draft, which was reviewed by 11 clinical experts in CF (six physiotherapists, three paediatric physicians, two nurses); and phase III to test content validity based on a debriefing grid. The grid was evaluated by a group of five caregivers and 10 pwCF, consisting of both sexes and different ages, social backgrounds, and education levels. This was done to collect comments to further inform the content of the questionnaires.

The questionnaires were composed of three parts (available as Supplemental Material). The first collected demographics about master data, education level, and current employment status; the second investigated the perceived time engaged in RP; the third investigated the perceived burden of care, that is, time spent away from daily therapy and number of times the patient had to give up something in order to carry out the therapy session. A specific type of question item was designed for each part: closed-ended questions with response options for part 1; a mix of close-ended and open-ended question items for part 2; and a five-point Likert scale for part 3.[12] The questionnaires investigating the perceived time burden were processed by an investigator unfamiliar with the study, before contact with healthcare workers, to avert influencing the responses. The questionnaire took 10–15 min to complete.

Overall treatment burden was assessed according to the treatment burden subscale of the adolescent and the adult version of the Cystic Fibrosis Questionnaire (CFQ-R).[13] The respiratory domain of the CFQ-R was used to measure respiratory symptoms and the social subdomain to explore activity limitations. The severity of sinonasal symptoms was graded according to the overall score of the Sinonasal Outcome Test (SNOT-22) questionnaire.[14,15] The level of physical activity was determined according to the International Physical Activity Questionnaire (IPAQ),[16] a version of which is also available for children. The IPAQ[17] investigates duration, frequency, and intensity of physical activity converted into metabolic equivalent tasks (MET). CFQ-R, SNOT-22, and IPAQ were administered during scheduled visits to our Cystic Fibrosis centre.

Pulmonary measures

Forced expiratory volume in the first second (FEV_1) by spirometry was reported as a percentage of predicted values and as Z score according to Quanjer *et al.*'s equation.[18] Lung function was defined within the normal range when FEV_1 was above the -1.64 Z score (lower limit of normal at fifth centile). The lung clearance index (LCI), convective gas mixing in the conducting airways

(Scond*VT) and the diffusion–convection interaction within the acinus (Sacin*VT), was measured using an open-circuit multiple breath washout (MBW) hard- and software package with nitrogen as tracer gas (N_2MBW) (Exhalyzer® D and Spiroware 3.3.1 Ecomedics AG, Switzerland), as described elsewhere.[19] The LCI in the children was considered normal when below 7.1.[20]

Clinical measures

Clinical measures included participant age, genotype, anthropometrics, cystic-fibrosis-related diabetes (CFRD), pancreatic insufficiency, and colonization by *Pseudomonas aeruginosa*. A history of intravenous (IV) antibiotic therapy was recorded at baseline, in the 12 months before ETI therapy, and again at 6 and 12 months during the previous 6 months.

Statistical analysis

Variables are presented as mean and standard deviation (±1 SD) or count and percentage (%). Mixed-effect regression models were fitted to evaluate changes over time of the endpoints of interest (perceived time engaged in inhalation therapy, perceived time for lower and upper airway clearance and time perceived for cleaning and disinfecting personal respiratory equipment) at baseline, and then at 6 and 12 months after initiation of ETI therapy. The response variable consisted of the endpoint of interest, the covariate was time and age at ETI and FEV_1 as the adjusting factors. Only for the models investigating time engaged in inhalation therapy and time to clean and disinfect aerosol devices, we used the actual number of prescribed aerosol therapies as a further adjusting factor. One random effect for pwCF was included in each model to take into account the correlation of measurements taken on the same pwCF at the follow-up visits. The same approach was adopted to assess changes over time in the subdomain scores of the CFQ-R, METs derived from the IPAQ, and the SNOT-22 score, using age at ETI and FEV_1 as adjusting factors. Results are expressed as differences with 95% confidence intervals (CI). Changes in frequency were evaluated using Cochran's *Q* test. Bland–Altman analysis was performed to assess bias in the time perceived by the pwCF aged <18 years and their caregivers. A significance level of alpha 0.05 was set. Statistical analysis was performed using R software version 4.0.3, with package *childsds, lmerTest, emmeans*, and *blandr* added.[21]

Results

Between October 2021 and December 2022, a total of 184 pwCF started ETI therapy, of which 47 pwCF aged 21.4 (5.7) years and 29.8% (14/47) <18 years completed 12 months of ETI therapy and were entered into the present analysis. Our assumption is that a study of this size, with a desired significance of 0.05 and a desired power of 0.90, can reliably detect an effect size of about 0.48 (Cohen's *d*) between two timepoints.

Clinical characteristics of the study population are presented in Table 1. At baseline, the N_2MBW showed that ventilation inhomogeneity was impaired in 100.0% (14/14) of children and the FEV_1 was within the normal range in 21/47 (44.7%) pwCF; the mean LCI was 11.9 (3.0). Ventilation inhomogeneity was greater in the peripheral than the conductive airways (Table 2). Before beginning ETI therapy, 76.6% (36/47) pwCF had received one bout of IV antibiotic therapy in the previous 12 months.

Perceived time engaged in ACT was 66.7 (38.1) min/day. PEP mask breathing was the technique the pwCF used most often (38/47, 80.9%) and performed two times/day by 37/47 (78.7%), though some performed it more often (6/47, 12.8%) or used an advanced technique like CPAP (10/47, 21.3%). Half (50%) of pwCF performed aerosol therapy two or three times a day, for a total perceived time of 57.4 (44.8) min/day. The majority used a highly performant mesh nebulizer (36/47, 76.6%) or a pneumatic compressor (21/47, 44.7%) as second choice. Half (50%) of the pwCF spent between 7 and 30 min/day on cleaning and disinfecting their respiratory equipment.

At 6 and 12 months into ETI therapy, consistent improvement in clinical outcomes was noted (Table 2) as well as time engaged in routine RP (Table 3), which decreased with time. The difference between timepoints was not statistically significant (Table 4). The largest difference perceived by the pwCF was the time engaged in aerosol therapy at 1 year follow-up, with nearly 18 (95% CI −49.7 to 14.5) min/day gained. At 1 year of ETI therapy, 5/47 (10.6%) pwCF reported

Table 1. Cohort characteristics ($N = 47$).

No.	47
Age, years	21.4 (5.7)
Sex	
Female	23 (48.9)
Male	24 (51.1)
FEV_1, *Z* score	−1.7 (1.5)
FEV_1, % predicted	79.1 (17.7)
LCI, turnovers	11.9 (3.0)
BMI, *Z* score	−0.5 (0.9)
Chronic *Pseudomonas aeruginosa* infection	32 (68.1)
Pancreatic insufficiency	41 (87.2)
CFRD	6 (12.8)
Mutations	
Severe	41 (87.2)
Moderate	–
Unknown	6 (12.8)

Data are presented as mean and standard deviation (±1 SD) or count and percentage (%), FEV_1 denotes forced expiratory volume in 1 s as measured by spirometry; LCI lung clearance index; BMI body-mass index (weight in kg divided by height in m squared); and CFRD cystic-fibrosis-related diabetes.

they had discontinued PEP mask, none performed it more than twice a day, while 32/47 (68.1%) continued it as prescribed ($p < 0.001$).

At 12 months of ETI therapy, the overall mean CFQ-R score was increased by 5.2 (95% CI 1.9–8.5) points; the treatment burden and respiratory subdomain scores were increased by 17.0 (95% CI 9.9–24.2) and 14.1 (95% CI 9.5–18.7) points, respectively. Physical activity was increased by 1957.8 (95% CI 711.1–3205.8) MET-min/week. There was a decrease in sinonasal symptoms of 2.6 (95% CI: −5.4 to 0.1) points at 12 months of ETI therapy.

Comparison between the time perceived by children and that of their caregivers showed that the children perceived they spent less time on aerosol therapy compared to their caregivers; this difference was −21.2 (95% CI −49.4 to 6.9) min/day before ETI therapy and −10.5 (95% CI −34.5 to 13.5) min/day at 12 months. Similarly, the children's responses suggested that they spent a few minutes less on ACT than the responses by their caregivers, especially at 6 months (−12.7, 95% CI −25.6 to −0.1 min/day), whereas at 12 months, this difference was much smaller (−3.7, 95% CI −14.6 to −7.2 min/day).

In response to the questions about perceived time spared, 24/47 (51.1%) pwCF reported a satisfactory amount of time before initiating ETI therapy; at 1 year, the number of pwCF reporting a gain in spare time was increased to 35/47 (74.5%).

Table 2. Changes in clinical variables over time ($N = 47$).

Clinical variables	Baseline	6 months	1 year
FEV_1, *Z* score	−1.7 (1.5)	−0.3 (1.7)	−0.4 (1.5)
FEV_1, % predicted	79.1 (17.7)	96.1 (19.8)	94.6 (18.7)
LCI, turnovers	11.9 (3.0)	10.1 (3.2)	9.8 (3.6)
Sacin*VT	0.247 (0.182)	0.183 (0.134)	0.196 (0.171)
Scond*VT	0.113 (0.034)	0.086 (0.041)	0.097 (0.036)
BMI, *Z* score	−0.5 (0.9)	−0.1 (0.9)	−0.1 (0.9)
IV antibiotic therapy, no.	36 (76.6)	4 (8.5)	3 (6.4)

Data are presented as mean with standard deviation (±1 SD) or count and percentage (%). FEV_1 denotes forced expiratory volume in 1 s as measured by spirometry; LCI lung clearance index; Scond*VT convective gas mixing in the conducting airways; Sacin*VT diffusion–convection interaction within the acinus; BMI body-mass index (weight in kg divided by height in m squared).

Table 3. Time engaged in respiratory physiotherapy ($N = 47$).

Activities	Baseline	6 months*	1 year
Time engaged in aerosol therapy (min/day)	57.4 (44.2–70.5)	47.1 (22.1–72.1)	31.0 (22.5–39.5)
Time engaged in airway clearance therapies (min/day)	66.7 (55.6–77.9)	57.1 (43.7–70.5)	49.8 (40.0–59.6)
Time engaged in cleaning and disinfecting respiratory equipment (min/day)	28.1 (16.0–40.3)	17.9 (9.6–26.2)	13.5 (9.8–17.3)

Data are presented as mean with 95% confidence interval.

Table 4. Estimated difference and 95% CI between baseline and 1 year of ETI therapy.

Time engaged in aerosol therapy (min/day)*	Baseline – 6 months	−2.5 (95% CI: −32.9 to 27.8)
	6 months – 1 year	−15.0 (95% CI: −41.9 to 11.9)
	Baseline – 1 year	−17.6 (95% CI: −49.7 to 14.5)
Time engaged in airway clearance therapies (min/day)	Baseline – 6 months	−8.8 (95% CI: −25.9 to 8.3)
	6 months – 1 year	−7.4 (95% CI: −22.2 to 7.4)
	Baseline – 1 year	−16.2 (95% CI: −33.0 to 0.5)
Time engaged in cleaning and disinfecting respiratory equipment (min/day)*	Baseline – 6 months	−10.6 (95% CI: −26.5 to 5.3)
	6 months – 1 year	−5.3 (95% CI: −19.6 to 9.0)
	Baseline – 1 year	−15.9 (95% CI: −32.7 to 0.9)

*Model adjusted for the number of aerosol therapies.
Differences are presented as mean and 95% confidence interval: lower limit to upper limit.
ETI, elexacaftor–tezacaftor–ivacaftor.

There was no association between the amount of perceived time spared and the study timepoints (Table 5). Similarly, the CFQ-R social limitation subdomain score was increased by 3.0 (9% CI −2.5 to 8.5) points, whereas there was a statistically significant difference in the proportion of responses to the questionnaire items investigating having to give up something important in order to perform therapy across timepoints ($p = 0.004$).

Discussion

With this study, we wanted to gain a better understanding of the perceived burden of RP in pwCF on ETI therapy. Our findings indicate improved health and lower treatment burden in pwCF following therapy, together with less time engaged in RP, likely the result of self-management of ACT frequency and duration. Yet, aerosol therapy, cleaning and disinfecting respiratory equipment, and ACT still took up a considerable share of daily life, without meaningful changes in perceived time saved or social limitations.

During the first year of ETI therapy, neither the frequency nor the modality of ACT was changed; this decision was shared by other colleagues and caregivers from the CF community,[22] who agree upon the lack of short- and long-term evidence in favour of simplifying treatment. We believe that the rationale for time-consuming and low-grade evidence-based ACT is no longer tenable. Indeed, pwCF themselves[23] have stated that they would accept a 5% reduction in FEV_1 for treatment that reduced by 50% the time engaged in ACT. We found that few pwCF discontinued or reduced

Table 5. How much time matters to pwCF (*N* = 47).

	Baseline	6 months*	1 year	*p*-value
Amount of spare time				
Not at all/only a little	7 (14.9)	8 (17.4)	5 (10.6)	0.2061
To some extent	16 (34.0)	8 (17.4)	7 (14.9)	
Fairly much/very much	24 (51.1)	30 (65.2)	35 (74.5)	
Something important left undone				
Never/Very rarely	28 (59.6)	37 (80.4)	40 (85.1)	0.004
Occasionally	17 (36.2)	8 (17.4)	7 (14.9)	
Very frequently/Always	2 (4.3)	1 (2.2)	0 (0)	

Data are presented as count and percentage (%). PwCF denotes people with cystic fibrosis. *N=46.

ACT, whereas most continued with their routine as usual. Discontinuation and/or self-management of ACT resulted in approximately 16 min/day less devoted to ACT. Nevertheless, this gain in time is not reflected by the response concerning perceived time saved, which did not appear to have changed during the study period, nor by the scores on the CFQ-R subdomain investigating social limitations. Fifteen minutes might be too short to be perceived as spare time, and this fact alone could explain the lack of change.

There are other explanations for such findings. For example, the fact of having a chronic disease remained unchanged. The pwCF may have felt better while on ETI therapy, but they still had to manage a chronic respiratory illness that requires daily medications, especially for those with moderate-to-severe disease. In addition, changes in clinical condition while on CFTR modulator therapy may create uncertainty about the short- and long-term effects of this new medication, leaving the pwCF to deal with their chronic condition just as before. Adult pwCF may be more likely to harbour doubt about the effect of CFTR modulators, whereas the parents and the children seemed more optimistic as they experienced improved well-being first-hand.

Moreover, there is the wrong notion that ACT can be replaced by physical activity,[24–26] as if they were the same thing. While studies have reported that exercise may be as effective as a surrogate for airway clearance in some circumstances and for some outcomes, gaps in our understanding remain and further trials are needed.[27] The pwCF attending our centre are informed about the differences between the two types of intervention. People in good clinical condition usually perform only one ACT session on the days when physical activity is also planned. This combination is intended as a way to reduce treatment burden and encourage adherence. The greater amount of physical activity we reported could explain the lack of a gain in spare time as perceived by the pwCF on ETI therapy and the social limitation scores. We believe that the pwCF probably thought that by increasing their physical activity levels they could reduce the number of physiotherapy sessions, albeit without consulting their CF team. Basically, the pwCF just replaced one therapy with another, admittedly perhaps one that was more fun and experienced as *normal*.

The pwCF reported that they did not feel that they had to give up something important before initiating ETI therapy. This response merits comment, given the dramatic decrease in the number of pwCF receiving IV antibiotic therapy during the year. This meant less absenteeism from work or school and less hospitalization. It can be linked to the positive change in the overall treatment burden as measured by the CFQ-R score. Also, since loosening and removal of mucus secretion make up a big part of daily RP routine, these manoeuvres can serve as a guide for adjusting ACT frequency and duration. Our hypothesis is that the pwCF on ETI probably thought it was not worth giving up something important in order to perform ACT, which no longer gave them the

immediate effect of feeling the secretions had been removed. Indeed, the respiratory subdomain scores on the CFQ-R were increased.

We also wanted to investigate differences between the children with CF and their parents/caregivers in the perception of time, which was consistently less in the children compared to their parents for aerosol therapy and ACT, although above the 5% significance threshold. This may be related to the struggle caregivers go through when trying to motivate the children to perform daily treatment. In their study, Grossoehme *et al.*[28] found that parents reported feeling overwhelmed by the burden of daily care, challenged by the constant need to engage and to model responsible behaviour themselves (waking to an alarm) to ensure that the children carried out their daily routine. These findings may be related to participant age. As children get older, they comply less and less with treatment, particularly during adolescence.[29–32] This is a familiar stress factor for caregivers who want to be sure that therapy is done correctly and the adolescents who want to be independent. Parents need to start from the very beginning to establish a routine for children and develop it into effective self-management of the disease. Common strategies are telling stories, watching TV, or playing with electronic devices during ACT as an incentive or a distraction, which may make the routine easier for both the children and their caregivers alike.

Study strengths and limitations

This is the first study to estimate the burden of RP during ETI therapy measured as perceived time engaged in ACT, aerosol therapy, and cleaning and disinfecting respiratory equipment. Despite we only assumed that RP burden could be operationalized as time, the CF Italian Patient Centred Outcomes Research working group addressed time as a priority related to the patients' own experiences.[33] Validated questionnaires were administered to pwCF during ETI therapy; the responses were analysed and our findings generalized for comparison with other cohorts of pwCF.

The limitations are that the questionnaires investigating treatment burden were validated internally at our centre and that the sample involved a mixed of adult and paediatric population, enrolled according to a convenient approach without any formal sample size calculation. Furthermore, our assumption was that the adult pwCF would clean and disinfect their own respiratory devices, which could have created a response bias. The study revolves around how pwCF perceive their time, so it is challenging to set an external objective criterion as a benchmark. The only possible comparison is change over time in the perception of time in relation to lung function and other clinical parameters.

Conclusion

PwCF on ETI therapy may perceive less time burden engaged in their daily RP routine, although aerosol therapy, ACT, and maintenance of personal respiratory equipment still take a considerable share of a patient's day. Despite a remarkable clinical improvement over 1 year, social limitations and the amount of perceived spare time did not vary accordingly. Some pwCF discontinued or reduced their ACT in self-management.

The willingness of pwCF to work with healthcare professionals by engaging in lengthy procedures during observational trials on CFTR modulators is an opportunity to seek improvement in RP. Physiotherapists specialized in CF need to understand the role of ACT for people taking CFTR modulators, without medicalizing them to interventions such as physical activity masked as airway clearance intervention.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the local Ethics Committee Milano Area B (2396/2016). Written informed consent to participate in the study was obtained from the participants and/or from their legal guardian/next of kin.

Consent for publication

Not applicable.

Author contributions

Chiara Blardone: Conceptualization; Data curation; Investigation; Writing – original draft.

Simone Gambazza: Conceptualization; Formal analysis; Methodology; Writing – original draft.

Alessandra Mariani: Data curation; Investigation; Writing – original draft.

Rachele Galgani: Data curation; Investigation; Writing – original draft.

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Competing interests

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. SG received fees as a consultant for Viatris.

Availability of data and materials

The raw data supporting the conclusions of this study will be made available by the corresponding author, without undue reservation.

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Supplemental material

Supplemental material for this article is available online.

References

1. Elborn JS. Cystic fibrosis. *Lancet* 2016; 388: 2519–2531.
2. Lopes-Pacheco M. CFTR modulators: the changing face of cystic fibrosis in the era of precision medicine. *Front Pharmacol* 2020; 10: 1662–1729.
3. Raywood E, Shannon H, Filipow N, *et al.* Quantity and quality of airway clearance in children and young people with cystic fibrosis. *J Cyst Fibros* 2023; 22: 344–351.
4. Conway S, Balfour-Lynn IM, De Rijcke K, *et al.* European cystic fibrosis society standards of care: framework for the cystic fibrosis centre. *J Cyst Fibros* 2014; 13(Suppl 1): S3–22.
5. Saluzzo F, Riberi L, Messore B, *et al.* CFTR modulator therapies: potential impact on airway infections in cystic fibrosis. *Cells* 2022; 11: 1–22.
6. Heijerman HGM, McKone EF, Downey DG, *et al.* Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet* 2019; 394: 1940–1948.
7. Sutharsan S, McKone EF, Downey DG, *et al.*; VX18-445-109 study group. Efficacy and safety of elexacaftor plus tezacaftor plus ivacaftor versus tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for F508del-CFTR: a 24-week, multicentre, randomised, double-blind, active-controlled, phase 3b trial. *Lancet Respir Med* 2022; 10: 267–277.
8. Middleton PG, Mall MA, Dřevínek P, *et al.*; VX17-445-102 Study Group. Elexacaftor-Tezacaftor-Ivacaftor for cystic fibrosis with a single Phe508del Allele. *N Engl J Med* 2019; 381: 1809–1819.
9. Barry P, Mall M, Álvarez A, *et al.* Triple therapy for cystic fibrosis Phe508del –gating and –residual function genotypes. *N Engl J Med* 2021; 385: 815–825.
10. Gambazza S and Zuffo S. CPAP in cystic fibrosis: is It time to surrender yet? *Respir Care* 2013; 58: e116–e117.
11. von Elm E, Altman DG, Egger M, *et al.*; STROBE Initiative. The strengthening the reporting of

observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61: 344–349.

12. Likert RA. Technique for the measurement of attitudes. *Arch Psychol* 1932; 140: 1–55.
13. Quittner AL, Buu A, Messer MA, *et al.* Development and validation of the cystic Fibrosis Questionnaire in the United States. *Chest* 2005; 128: 2347–2354.
14. Mozzanica F, Preti A, Gera R, *et al.* Cross-cultural adaptation and validation of the SNOT-22 into Italian. *Eur Arch Otorhinolaryngol* 2017; 274: 887–895.
15. Hopkins C, Gillett S, Slack R, *et al.* Psychometric validity of the 22-item sinonasal outcome test. *Clin Otolaryngol* 2009; 34: 447–454.
16. Craig C, Marshall A, Sjöström M, *et al.* International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003; 35: 1381–1395.
17. Mannocci A, Masala D, Mei D, *et al.* International Physical Activity Questionnaire for Adolescents (IPAQ A): reliability of an Italian version. *Minerva Pediatr* 2021; 73: 383–390.
18. Quanjer PH, Stanojevic S, Cole TJ, *et al.*; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
19. Gambazza S, Ambrogi F, Carta F, *et al.* Lung clearance index to characterize clinical phenotypes of children and adolescents with cystic fibrosis. *BMC Pulm Med* 2022; 22: 122.
20. Kentgens A-C, Latzin P, Anagnostopoulou P, *et al.* Normative multiple-breath washout data in school-aged children corrected for sensor error. *Eur Respir J* 2022; 60: 2102398.
21. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. 2023. https://www.R-project.org.
22. Almulhem M, Harnett N, Graham S, *et al.* Exploring the impact of elexacaftor-tezacaftor-ivacaftor treatment on opinions regarding airway clearance techniques and nebulisers: TEMPO a qualitative study in children with cystic fibrosis, their families and healthcare professionals. *BMJ Open Respir Res* 2022; 9: 10.
23. Cameron RA, Office D, Matthews J, *et al.* Treatment preference among people with cystic fibrosis: the importance of reducing treatment burden. *Chest* 2022; 162: 1241–1254.
24. Rowbotham NJ, Daniels TE, Daniels E, *et al.* Airway clearance and exercise for people with cystic fibrosis: balancing longevity with life. *Pediatr Pulmonol* 2022; 57: S50–S59. DOI: 10.1002/ppul.25734
25. Rowbotham NJ, Smith S, Leighton PA, *et al.* The top 10 research priorities in cystic fibrosis developed by a partnership between people with CF and healthcare providers. *Thorax* 2018; 73: 388–390.
26. Saynor ZL, Cunningham S, Morrison L, *et al.* Exercise as airway clearance therapy (ExACT) in cystic fibrosis: a UK-based e-Delphi survey of patients, caregivers and health professionals. *Thorax* 2023; 78: 88–91.
27. Ward N, Morrow S, Stiller K, *et al.* Exercise as a substitute for traditional airway clearance in cystic fibrosis: a systematic review. *Thorax* 2021; 76: 763–771.
28. Grossoehme DH, Filigno SS and Bishop M. Parent routines for managing cystic fibrosis in children. *J Clin Psychol Med Settings* 2014; 21: 125–135.
29. Eakin MN, Bilderback A, Boyle MP, *et al.* Longitudinal association between medication adherence and lung health in people with cystic fibrosis. *J Cyst Fibros* 2011; 10: 258–264.
30. Daniels T, Goodacre L, Sutton C, *et al.* Accurate assessment of adherence: self-report and clinician report vs electronic monitoring of nebulizers. *Chest* 2011; 140: 425–432.
31. Shakkottai A, Kidwell KM, Townsend M, *et al.* A five-year retrospective analysis of adherence in cystic fibrosis. *Pediatr Pulmonol* 2015; 50: 1224–1229.
32. Bishay L and Sawicki G. Strategies to optimize treatment adherence in adolescent patients with cystic fibrosis. *Adolesc Health Med Ther* 2016; 7: 117–124.
33. Buzzetti R, Galici V, Cirilli N, *et al.* Defining research priorities in cystic fibrosis. Can existing knowledge and training in biomedical research affect the choice? *J Cyst Fibros* 2019; 18: 378–381.