Home physiotherapists assisting follow-up treatment in cystic fibrosis: a multicenter observational study

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Key words: Physiotherapy; home visit; aerosol; cystic fibrosis.

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Abstract

Inhaled therapies are relatively simple and easy to be managed however ineffective use of aerosols when self-administered may occur. We described variation of the number of clinic visits, lung function and number of antibiotic courses performed over 12 months in participants with cystic fibrosis (CF), when supervised or not by physiotherapists (PTs) at home. Participants in 8 Italian CF centers with a prescription of dry-powder antibiotic choose whether to be supervised at home (PT-FU) or not (non-PT-FU), in adjunct to routine clinic visits. PTs assisted participants with their inhaled therapies regimen and reviewed the airway clearance program in use. Mixed-effect regression models were fitted to evaluate the variation of selected endpoints over time. A total of 163 participants were included. Lung function declined over time in both groups, at higher extent in the non-PT-FU group at 6 months (-1.8, 95%CI: -4.4 to 0.7 % predicted), without reaching statistical significance, whereas in the PT-FU group only, nearly one visit less was recorded (p=0.027). Regardless the type of supervision adopted, the number of antibiotic courses did not change compared to the previous year. We counted 19/90 (21.1%) drop-out in the PT-FU, double compared to the group followed up at the clinics (p=0.065). Participants under a course of an inhaled antibiotic therapy showed a 1-year decline in lung function, whereas only the group receiving home supervision counted nearly one visit less at the CF center, whose clinical relevance should be further discussed.

Introduction

Daily management of lung disease and aggressive, time-consuming treatments of exacerbations are essential to preserve lung function in cystic fibrosis (CF) [1]. Considering that respiratory failure is yet the leading cause of death in CF, the improvement in life expectancy has also been achieved by increasing the efficacy of pulmonary medications. Particularly, inhaled antibiotics generate high levels dose coupled with limited toxicity and their particle

sizes offer the unique chance to be directed at the target site, i.e. small airways, with optimal deposition.

Inhaled therapies are relatively simple and easy to be managed, also considering the improvements made in both delivery devices and drug formulation, with dry-powder inhalers (DPI) showing the shortest administration time, minimum cleaning requirements and improved portability [2]. In the context of a chronic condition such as CF, this should favour patients' adherence to therapies, positively affecting treatment burden by shortening administration time and reducing device complexity. For example, nebulization of an antibiotic takes on average 15 mins and must be repeated twice a day, not counting the time needed for cleaning and disinfection procedures. By the contrary, administration via a DPI takes less than five minutes, requiring also minimum maintenance. However, there is a large body of evidence of sub-optimal or ineffective use of aerosols when self-administered [3,4], mainly due to lack of knowledge about proper technique and/or perceived lack of effects of medication [5].

The European Cystic Fibrosis Society practice guidelines suggest that patients should be reviewed regularly by specialist physiotherapists (PTs) in order to optimize aerosol regimen and review appropriate inhalation techniques [1]. It has been already documented that Italian PTs play a key role in the aerosol delivery management in CF centers, both performing inhaled therapies and educating patients and families to their use [6]. However, limited experience exists about the role of PTs outside CF centers in the care of patients with CF, especially when involved in the management of inhaled therapies directly at patients' home.

In 2013, an antipseudomonal DPI was brought to the Italian market coupled with the opportunity for patients to receive home visits by PTs, under the hypothesis that receiving support at home and providing specific education on individualized treatment would improve adherence and treatment efficacy, eventually. From the CF centres perspective, we wandered if such initiative could influence certain outcomes, relevant to the clinical course of patients with CF. Therefore, the aim of the present study is to evaluate whether individuals with CF under antibiotic therapy with a dry-powder inhaler differ in terms of the number of clinic visits, lung function and number of antibiotic courses, when supervised or not by PTs at home.

Methods

Study design

This study was a multicenter prospective observational study on individuals with a prescription of dry powder colistimethate sodium (Colobreathe®) therapy, referred to hereafter as colistimethate sodium DPI. This is a dry-powder formulation of micronized drug, which is administered via one capsule of 1.6625 MIU colistimethate sodium (equivalent to 125 mg) into the chamber of a hand-held inhaler (Turbospin®) [7]. Participants were prescribed twice a day with this inhaled antibacterial agent against *Pseudomonas aeruginosa* and received either continuous treatment or 28-day course followed by a 28-day off period (i.e. *on-off* regime), per medical decision, which is usually triggered by impaired adherence and/or bacteria colonization control.

Colistimethate sodium DPI was available to Italian patients with CF together with the opportunity to join a supervised program managed by Domedica Srl (Rome, Italy), consisting of personalized support at home delivered by respiratory physiotherapists. Patients and/or caregiver chose autonomously whether to take this inhaled antibiotic with (PT-FU) or without (non-PT-FU) being followed-up at home, in adjunct to routine visits at their own CF center. The costs for home visits were supported by Forest Laboratories Italy Srl (Milan, Italy), which distributed colistimethate sodium DPI in Italy at the time of the study. Drug cost was covered by the National Healthcare Service.

The program consisted in four home visits planned for each patient during the first year, and three during subsequent years. First contact at home was scheduled within 7 days from the first inhalation of colistimethate sodium DPI, which usually took place during an out-patient visit at CF center. After 30 days from the first home visit, patients could be reached by the same PTs for a second contact. After six months, a third visit occurred and the fourth was scheduled at 12 months. Afterwards, visits occurred every four months. However, home visits could be adapted to participants' needs and then changed in the number and frequency, accordingly. At home, PTs ran educational sessions, supporting patients and/or caregivers along their full range of inhaled therapy regimens. Most importantly, they kept training participants on the correct inhalation technique and on the proper cleaning and storage of the respiratory equipment. PTs were also available to review at home the airway clearance regimen in use and to correct errors in the techniques and/or adapt the regimen to the ongoing clinical situation, keeping in mind the exact timing between airway clearance and aerosol inhalation. Each PT was also equipped with a spirometer and with a pulse-oximeter, in order to check participants' condition and to report any abnormalities to the referral CF center.

Anthropometric, clinical data and outcomes reported in the present study were collected during out-patient visits at each CF centers, usually scheduled every four months. During routine clinic visits, patients also perform spirometry and PTs review the ongoing physiotherapy program, which can include their aerosol regimen.

Study participants

Eligible participants were individuals with a confirmed diagnosis of CF, who were prescribed with colistimethate sodium DPI. The study took place between 2016 and 2017 in the regional reference CF centers across Italy which agreed to propose this optional follow-up at home.

The study was approved by the research ethics boards at each center (598_2016), and participants were asked to complete a privacy rule written authorization, according to the current Italian legislation.

Pulmonary and anthropometric variables

Spirometry was performed according to ATS/ERS guidelines [8]. Forced Expiratory volume in the 1st second (FEV_1) percent predicted and z-score were calculated using the Global Lung Initiative equations [9]. Participants' lung function was considered in the normal range when FEV_1 was above the -1.64 z-score (lower limit of normal (LLN) at 5th percentile). Body mass index (BMI) was calculated as body weight in kg divided by height in m^2, expressed as z-score [10], and underweight was defined as a BMI below -1 z-score. Leeds criteria were used to categorize individuals as free, intermittent or chronic of a positive *Pseudomonas aeruginosa* culture in the previous 12 months [11]. Eventually, the number of out-patient visits and the number of antibiotic courses (both *per os* and intravenously (IV) administered) at baseline were

collected in the 12 months preceding the colistimethate sodium DPI initiation. Baseline FEV_1 was taken by the last available spirometry collected at the CF center.

Statistics

Demographic and clinical variables at baseline are reported according to the two groups of participants (PT-FU and non-PT-FU), as count and percentage for categorical variables and as median and interquartile range (IQR) for numerical variables. The data were compared using Fisher exact test for categorical variables and Wilcoxon test for numerical variables.

To evaluate the variation over time of the endpoints of interest (number of antibiotics courses, number of accesses to the center, value of FEV_1% predicted) mixed-effect regression models were fitted. The time-points selected for the number of antibiotics and clinic visits on which performing the analysis were the year before the initiation of colistimethate sodium DPI and the 12 months after, whereas baseline, 6 and 12 months were the time-points for the analysis of lung function. The response variable was the endpoint of interest, the covariates were program (PT-FU and non-PT-FU), time, the interaction between program and time and the following adjusting factors: age at spirometry, pancreatic status, *Pseudomonas aeruginosa* infection (chronic, intermittent *vs* free), type of treatment (on-off *vs* on-on), cystic fibrosis related diabetes (CFRD), sex, FEV_1 at baseline (below and above LLN) and BMI (below and above -1 z-score). Two random effects were included into the model: one for center, to take into account the correlation among different participants referring to the same center, and another one for participants, to take into account the correlation of measurements taken on the same subject at different time of follow-up. The results are expressed as differences, named *b* in the results session, with pertinent 95% confidence intervals and P-values. The statistical analysis was performed using R Core Team (2019), version 3.6.1, with packages *childsds*, *lmerTest*, *emmeans* added.

Results

Home support was offered to individuals with CF in eight Italian centers (1 pediatric, 2 adult centers and 5 mixed pediatric-adult centers). Only data collected during out-patient visits from 7 centers were used for the final analysis. One mixed pediatric-adult center could not contribute due to some delay with documents submission to ethics committee.

A total of 163 participants were included, with a median age of 26.5 (range 9.1 - 57.8) years. 29% (47/163) were homozygous for the F508del mutation and 46% (75/163) was compound F508del heterozygotes. Baseline demographic data are displayed in Table 1. The majority of participants (~73%) at the beginning of their therapy with colistimethate sodium DPI showed impaired lung function, with no significant difference between non-PT- and PT-FU (p=1.00). No other differences were detected at baseline between those individuals who joined the supervised program at home (90, 55.2%) and those who chose to attend only follow-up visits at CF center.

In terms of the number of antibiotic courses undertaken, the two groups expressed the same behavior across the considered time-points (p=0.784), and did not show any significant variation in the number of antibiotic courses performed in comparison to the previous year (Table 2). It is worth mentioning that participants with pancreatic insufficiency did more antibiotic courses (b=1.0, 95% CI: 0.1 to 2.0, p=0.038), as well as participants with a FEV_1 below the LLN (b=0.9, 95% CI: 0.1 to 1.6, p=0.021). Higher consumption of antibiotics was also associated with underweight (b=1.2, 95% CI: 0.5 to 1.9, p<0.001). Compared to the year before, participants experienced a reduction in the number of clinic visits in the PT-FU group only (Table 2), however no difference between groups over time was

Table 1. Participants' characteristics at baseline, stratified by the type of supervision chosen.

	Total (n=163)	non-PT-FU (n=73)	PT-FU (n=90)	p-value*
Age, n (%)				
<18 years	25 (15.3%)	9 (12.3%)	16 (17.8%)	0.387
≥18 years	138 (84.7%)	64 (87.7%)	74 (82.2%)	
Sex, n (%)				
Male	91 (55.8%)	44 (60.3%)	47 (52.2%)	0.343
Female	72 (44.2%)	29 (39.7%)	43 (47.8%)	
Pancreatic insufficiency, n (%)	135 (82.8%)	56 (76.7%)	79 (87.8%)	0.094
CFRD, n (%)	43 (26.4%)	14 (19.2%)	29 (32.2%)	0.074
Pseudomonas aeruginosa, n (%)				
Chronic	114 (69.9%)	49 (67.1%)	65 (72.2%)	0.497
Intermittent	49 (30.1%)	24 (32.9%)	25 (27.8%)	
Burkholderia cepacia, n (%)	7 (4.3%)	4 (5.48%)	3 (3.33%)	0.701
FEV_1 z-score, n (%)				
< -1.64	120 (73.6%)	54 (74.0%)	66 (73.3%)	1.000
≥ -1.64	43 (26.4%)	19 (26.0%)	24 (26.7%)	
FEV_1 % predicted, median (IQR)	62.00 (42.95 - 81.15)	59.48 (48.27 - 81.36)	64.63 (40.26 - 80.79)	0.534
BMI z-score, median (IQR)	-0.33 (-1.02 - 0.24)	-0.36 (-1.04 - 0.13)	-0.28 (-0.90 - 0.26)	0.658
Treatment type, n(%)				
on-on	98 (60.1%)	44 (60.3%)	54 (60.0%)	1.000
on-off	65 (39.9%)	29 (39.7%)	36 (40.0%)	

Data are displayed as median (interquartile range, IQR) or as count (percentage) according to the variables distribution; FEV1, Forced Expiratory volume in the first second. *Fisher test was used to compare categorical variables whereas Wilcoxon test was used to compare median for continuous data.

detected (p=0.416). Females (b=0.7, 95% CI: 0.2 to 1.3, p=0.008) and individuals underweight (b=1.1, 95% CI: 0.5 to 1.1, p=0.001) were in the need of more visits.

Lung function, expressed as FEV_1% predicted, declined over time (Figure 1), regardless participants were in non-PT- or PT-FU group (p=0.909). At 6 months, non-PT-FU participants' lung function declined of 1.8 points %predicted (p=0.153) while in the PT-FU group it was observed an average decline of 1.1 points %predicted (p=0.331). At 12 months, the average decline was almost the same between the two groups (Table 2). Again, older participants (b=-0.74, 95%CI: -1.18 to -0.39, p=0.001) and those with pancreatic insufficiency (b=-20.3, 95% CI: -30.5 to -10.2, p<0.001) and individuals underweight (b=-3.88, 95% CI: -7.31 to -0.49, p=0.024) exhibited lower FEV_1% than their counterparts. Overall, we counted 19/90 (21.1%) participants stopping the inhaled therapy in the PT-FU, more than double compared to the group only followed up at the clinics (p=0.065). Drop-out classified as related to the ongoing antibiotic therapy (i.e. due to bronchospasm, chest tightness, cough) were mostly detected in the PT-FU group (11/90, 12.2%) and between the 7th and 12th months (7/90, 7.8%). Participants in the non-PT FU group recorded one drop-out related to the ongoing treatment (1/73, 1.4%). However, these differences are not statistically significant.

Eventually, 16.4% (12/73) participants in the non-PT FU resulted free from *Pseudomonas aeruginosa* at 12 months, compared to 25.6% (23/90) in the group followed up at home (p=0.233).

Table 2. Estimate difference and 95%CI of study outcomes between time points.

		Total* (n=163)	non-PT-FU (n=73)	PT-FU (n=90)
Antibiotic courses,# n		0.2 (95% CI: -0.2 to 0.6)	0.1 (95% CI: -0.5 to 0.7)	0.2 (95% CI: -0.3 to 0.7)
Clinic visits,# n		-0.4 (95% CI: -0.9 to -0.1)	-0.3 (95% CI: -0.9 to 0.3)	-0.6 (95% CI: -1.2 to -0.03)
FEV1, %predicted	0-6 months	-1.5 (95% CI: -3.5 to 0.6)	-1.8 (95% CI: -4.4 to 0.7)	-1.1 (95% CI: -3.3 to 1.1)
	6-12 months	-1.4 (95% CI: -3.6 to 0.7)	-1.2 (95% CI: -3.8 to 1.5)	-1.7 (95% CI: -4.0 to 0.7)
	0-12 months	-2.9 (95% CI: -5.1 to -0.7)	-3.0 (95% CI: -5.6 to -0.4)	-2.8 (95% CI: -5.2 to -0.4)

Data are displayed as mean and 95% Confidence Interval (CI): lower limit to upper limit. #Differences are between the year of follow-up and the previous year; *marginal estimates obtained from the mixed effects model.

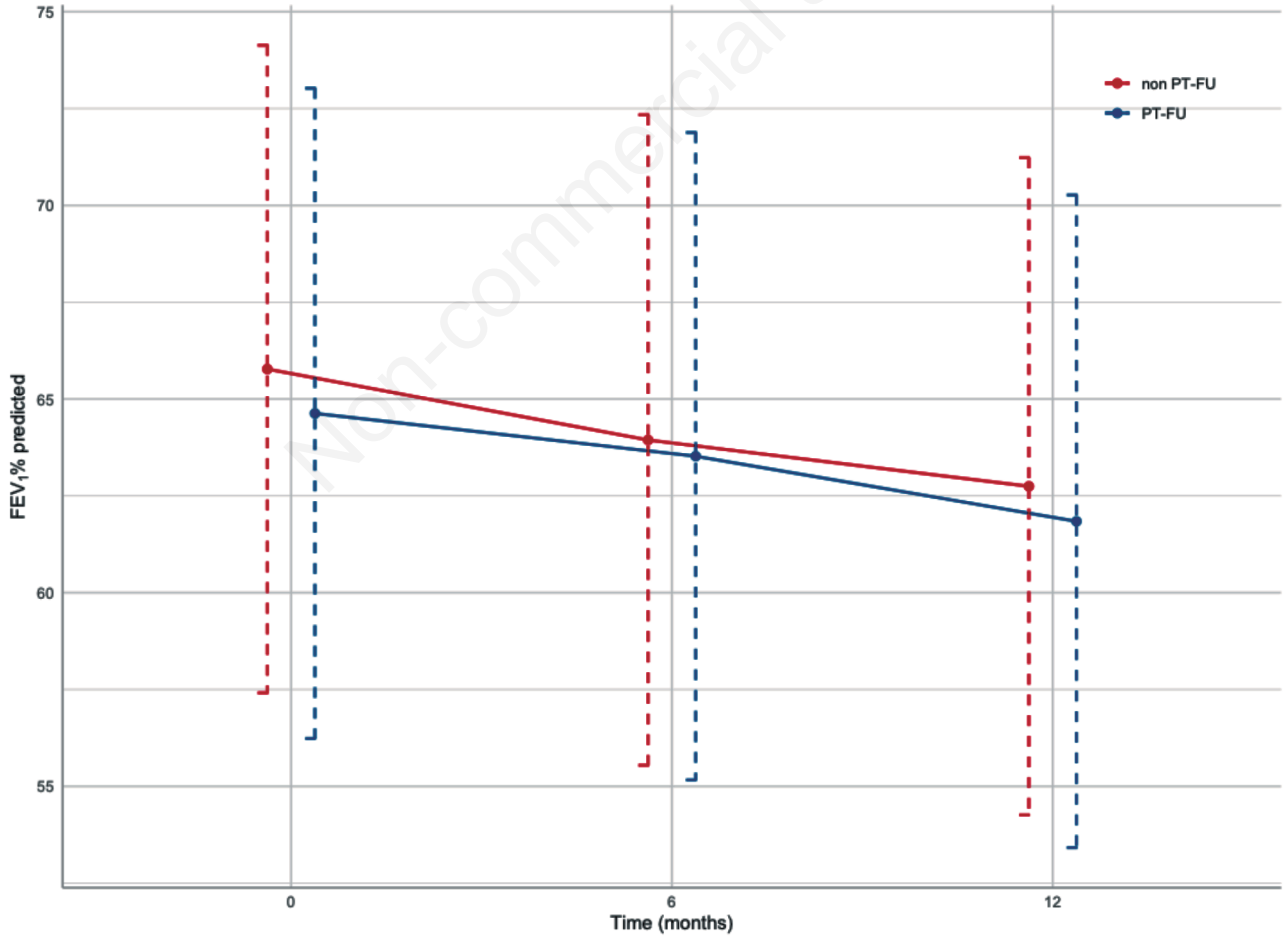

Figure 1. Plot of estimated marginal means for FEV1 %predicted at baseline, after 6 and 12 months. Dashed bars denote 95% confidence intervals.

Discussion

Overall adherence to standard CF therapies is generally low, and widely ranges for airway clearance techniques and inhaled medications [12], often perceived as time-consuming, burdensome, and poorly effective. Considering that poor adherence to long-term therapies severely compromises the effectiveness of treatments [13], as CF health professionals we positively valued the idea of supporting patients through home visits, combining the novelty of this initiative under the Italian CF scenario with the chance to enhance adherence to the whole physiotherapy care at home. The present findings show a 1-year reduction in the number of clinic visits for the group followed-up at home, compared to the previous year.

Literature describing home-based respiratory physiotherapy in cystic fibrosis is scant. The few experiences available are mainly focused on exercise training or on the whole rehabilitative approach on small groups of patients [14], including also dietetic supervision [15]. Whether to implement changes to treatment plans or to optimize physiotherapy treatments during IV treatments, community/home care services are poorly mentioned, maybe because the model of care for physiotherapy is meant to be hospital-based [16] in most countries yet. This will likely change in near future, considering the important lesson learnt during coronavirus pandemic, which demonstrate how hospital-based care may not be enough to cover needs of patients with chronic diseases.

However, as a matter of fact, home visits delivered by specialized PTs are not currently sustainable in the majority of Italian CF centers. Appropriate staff numbers represent an issue in Italian CF centers, some of them striving to provide comprehensive care sometimes. While the European Cystic Fibrosis Society recommends at minimum 2 full time physiotherapists per 50 pediatric patients or 2 full time PTs/100 adult patients [17], the staffing levels at each CF center included in the present study, for example, represent a barrier to implement any initiative that favors patients' care at home. Indeed, 50% of centers included in this project had no full-time PTs at the time of the study. Therefore, services that could bridge CF centers to specialized support in the community, outside hospital, might be considered positively. In a country like Italy, where distance does not represent an issue to access CF care, home physiotherapy might become part of wider telemedicine programs. Current monitoring for patients with CF generally occurs every 2-3 months at CF clinics, and home visits could just represent a complementary strategy to the surveillance of CF disease.

Furthermore, home visits could be more appreciated than frenetic visits at clinic, at least for those patients who feel such initiative as a help rather than a mere control over their health condition, facilitating also educational processes. Tipping et al. found that parents felt overwhelmed by physiotherapy-related educational processes, although authors' research focus was the post initial diagnosis and the transition from infant to toddler period [18]. However, it is intuitive to consider that a more relaxed environment favors attention and might help patients and/or caregiver to discuss issues more easily, not feeling overload by the information received by each professional of the multidisciplinary team during one visit. As outlined by Byrne *et al.* in a survey performed on families resident in the north east of England who had access to community physiotherapy and home visits, the degree of satisfaction was high and a significant number of families requested additional home visits [19]. Interestingly, it was not only the appointment time that positively influenced families' satisfaction, but also the quality of care received.

Theoretically, home visits would benefit all the patients and their caregiver, in terms of days absent from work or school, nosocomial infection and cross infection, being potentially less likely to occur. Also, home visits could be economically advantageous to the health system. Twelve-months intensive out-patient physiotherapy program showed that weekly outreach physiotherapy and exercise could reduce healthcare costs and requirements for intravenous antibiotic treatment in 14 children (range 4-15 years) with moderate-severe CF [20]. In this study only some patients were assessed at home when parents reported an exacerbation, however, the key finding seem to be that monthly review of optimal airway clearance and mucolytic inhalation therapy need to be taken into account as well when designing effective intervention. Practice and repetition in chronic care are profoundly associated with adherence, whose promotion is among our duties as healthcare professionals.

In our study, participants presented a non-statistically significant decline in lung function over the first 6 months, at larger extent in the group not supervised at home by respiratory physiotherapists. Whether it is clinically relevant or not, this finding may bring to light an important effect, which we should always maximize in our clinical practice and consider for future studies involving physiotherapy. Placebo effect is a psychobiological phenomenon, whose mechanisms involved are expectancy and motivation mainly [21]. Participants who chose to adhere to home-visit supervision were perhaps more prone to change their behaviour towards their care, maybe more concerned about their health status or just more adherent. Whichever was the case, they were more motivated to follow PTs' suggestions and so they expected better clinical outcomes from the new initiative. Although placebo has no direct effect on objective measures in a repetitive and consistent way but does have on subjective symptoms in some respiratory conditions (*e.g.* asthma) [22], participants could have been pushed into any action whose short-term consequence was a slower decrease in FEV_1. We might speculate if three home visits in the first six months compared to one only in the months left could have had any impact, also considering the number of drop-out occurred in the same period. In fact, higher detection of drug-related adverse events in participants followed up at home might support the advantages of a strict monitoring during exposure to a new aerosolized medication, potentially explaining the smaller decline in lung function seen in the PT-FU group. Nevertheless, the two groups expressed the same rate of lung function decline at one year.

Generally, we are reporting no evidence of variation in the number of antibiotic courses and the same rate of lung function decline in one large cohort of individuals with CF undergoing an extra pulmonary treatment with colistimethate sodium DPI, compared to the previous year. Nearly one visit less at the CF clinic occurred in the group of participants who decided to be followed-up at home, although this result was obtained through four visits at home by specialized PTs.

To the best of our knowledge, this is the first study reporting the CF respiratory physiotherapist as a case manager along inhaled medication practice at home. Several new drug formulations and inhalation devices have been developed so far for CF, considering the importance of treating the lungs directly with smaller doses, resulting in fewer side effects than oral delivery. Therefore, it is crucial that patients perform this therapy properly. Errors with the inhalation technique and problems with aerosol devices reduce the effectiveness of inhaled therapies, and negatively impact adherence. For example, an incorrect use of one aerosol device or misunderstanding with the prescribed medication may lead to ineffective lung deposition, resulting in perceived lack of effect. Patient training and educa-

tional interventions are recognized as effective strategies to improve adherence [23], and CF respiratory physiotherapists are indeed positioned to assist patients and families with inhalation therapies [6]. As conceived by the home-care provider, a more relaxed environment like home might be the right setting for supervising aerosol therapy and sustaining educational interventions.

Given the observational approach which came after the launch of this initiative from Forest Laboratories Italy Srl and considering that the study was not designed to ascertain the effectiveness of home-supervised physiotherapy, no other major conclusions can be drawn. Despite more than 50% of participants decided to join this supervised physiotherapy program, they did not express peculiar characteristics of the CF disease. However, it is worth mentioning that participants with lower BMI are in the sub-group who might benefit at most of a closer clinical supervision, together with females.

Among the limitations, as regards to the internal validity, we acknowledge that some participants deliberately chose to receive PTs supervision at home, however no statistical difference between groups emerged at baseline, thus no potential confounding could be identified. In any case, estimates obtained in the present study were adjusted for the effects of other included variables, including age. Moreover, only eight Italian CF centers accepted to adhere to this initiative coupled with the prescription of colistimethate sodium DPI. These centers might have welcomed this initiative for different reasons, and the simplest could be related to the presence of home assistance delivered by the homecare provider around the territory. Anyway, the present sample contained the professional practice of at least one large center in the north of Italy (579 patients), one from the central territory (515 patients) and one from the south (260 patients) of the Country, making the results quite generalizable. Overall, these potential sources of variability (centers and patients) were taken into account in the proposed analysis as random effects within the longitudinal model.

Future studies should carefully standardize the contents of PTs' intervention, both delivered at home and during out-patient visits. For example, as designed by the home-care provider, spirometry was not mandatory at each home-visit and some PTs may have performed more spirometric tests than others, thus recording adverse-drug reactions otherwise not detectable. By the contrary, physicians or nurses perform spirometry in some Italian CF centers, and PTs may had met patients on colistimethate sodium DPI therapy for other reason than their inhaled ongoing therapy during clinic visits.

Unfortunately, no participants' satisfaction was recorded by the CF centers' personnel and no adherence to inhaled medication was recorded by the home-care provider.

Conclusions

Based on the results of this study, individuals with CF lung disease under a course of colistimethate sodium DPI therapy showed an overall 1-year decline in lung function, accompanied by the same number of antibiotic courses, in comparison to the previous year. These outcomes did not show evidence of variation between individuals receiving additional home visits on top of regular follow-up visits at CF centers. The group receiving home supervision counted nearly one visit less at the CF center, whose clinical relevance should be further discussed.

By adopting more rigorous prospective study design, some questions may be answered, including long-term cost-effectiveness, sustainability and a comprehensive evaluation of the impact of such programs on exigency and pattern of patients' lifestyle.

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