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Original Article

Effect of discontinuation and reduction of respiratory cotherapies on the effectiveness of CFTR modulators

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ABSTRACT

Background: We evaluated whether the initiation of CFTR modulators led to a concomitant reduction in or discontinuation of respiratory cotherapies in French pwCF treated with IVA or LUM/IVA and determined whether the reduction in or discontinuation of respiratory cotherapies led to decreased effectiveness of CFTR modulators on clinical status.

Methods: We conducted a national retrospective cohort study using data from the French CF Registry (FCFR) linked to the French National Health Data System (SNDS), including all French pwCF aged 6 years and older who initiated IVA or LUM/IVA between 2012 and 2020 and who were treated for at least six months. Exposure to respiratory cotherapies was defined as at least one dispensing event of azithromycin, RhDNase, or inhaled antibiotics (aztreonam, colistimethate, or tobramycin).

Results: In total, 1378 pwCF were included in the study, with >90% of the population treated with LUM/IVA. Dornase alpha was discontinued in 25% of adults and 17% of children. Azithromycin was discontinued in 19% of adults and children. For inhaled antibiotics, discontinuation of the three treatments was observed in almost 40% of adults. No effect of the discontinuation of respiratory cotherapy was detected on the FEV1%, number of intravenous antibiotic courses or number of total antibiotic courses (0.13, 95% CI (-1.44; 1.70)); the values were -0.03 (-0.18; 0.13) and 0.04 (-0.25; 0.32), respectively.

Conclusion: This real-world study revealed a high rate of respiratory cotherapy discontinuation or reduction during the year following LUM/IVA or IVA initiation, without measurable clinical impact.

1. Introduction

During the past decade, the emergence of CFTR modulator treatments, which improve lung function and reduce pulmonary exacerbations, represents important hope for pwCF. Whether the use of CFTR modulators allows the elimination of some standard treatments while maintaining beneficial effects on lung function remains to be demonstrated, and current standards of care recommend the continuation of routine therapy, as the long-term efficacy of CFTR modulators on disease progression remains to be confirmed [1]. In pivotal randomized control trials demonstrating the beneficial effects of CFTR modulators, other standard CF therapies used by patients were maintained, without modifications during the study [2–4]. Several real-life studies have confirmed clinical benefits [5] and improved quality of life [6]; others have shown a decrease in the use of symptomatic respiratory therapies following the initiation of CFTR modulators, particularly inhaled therapies [7–10]. These studies focused mainly on ivacaftor (IVA) and elexacaftor/tezacaftor/ivacaftor (ETI) but rarely on lumacaftor/-ivacaftor (LUM/IVA), while LUM/IVA is usually associated with a lower benefit on lung function. No evaluation of the impact of stopping routine treatments on the effectiveness of CFTR modulators was performed.

The aims of our study were, first, to evaluate whether the initiation of CFTR modulators leads to a concomitant reduction in or discontinuation of respiratory cotherapies in French pwCF treated with IVA or LUM/IVA

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and, second, to determine whether dose reduction or discontinuation of respiratory cotherapies leads to decreased effectiveness of CFTR modulators on clinical status.

2. Methods

2.1. Study design

We conducted a national retrospective cohort study using data from the French CF Registry (FCFR) linked to the French National Health Data System (SNDS). The FCFR is based on an annual review of pwCF followed by one of the 47 CF centres in France and gathers information on medical history, treatments, and clinical and microbiological data [11]. The linkage method used between the FCFR and SNDS is described in detail in our previous publications [12,13].

2.2. Population study and outcomes

We included all French pwCF aged 6 years and older who initiated IVA or LUM/IVA between 2012 and 2020—since 2012 for IVA and 2015 for LUM/IVA—and who were treated for at least six months. Patients were followed from one year prior to CFTR modulator initiation (index date) to two years after initiation. Patients with inconsistent data (discordance between the CF registry and the SNDS regarding the dispensing dates and quantities of CFTRm dispensed) or who died before the end of the follow-up period were excluded from the population study.

To investigate whether the discontinuation or reduction of respiratory cotherapies leads to a decrease in the effectiveness of IVA and LUM/IVA on clinical status, we included patients who were treated with respiratory cotherapies during the 6 months prior to IVA and LUM/IVA initiation.

Exposure to respiratory cotherapies was defined as at least one dispensing event of azithromycin (ATC code: J01FA10), RhDNase (R05CB13), or inhaled antibiotics (aztreonam J01DF01, colistimethate J01XB01, tobramycin J01GB01). Data on hypertonic saline were not available for the study because this treatment has only been reimbursed in France since 2021, which did not allow exposure to be measured. PwCF were divided into two groups based on whether they discontinued or reduced their respiratory cotherapies. PwCF who discontinued at least one respiratory cotherapy during the year after the index date compared with the 6 months before the index date of use were classified into the discontinuation group.

PwCF for whom a dose reduction of at least half was observed in dispensing for at least one respiratory cotherapy (including a 100% dose reduction corresponding to discontinuation) during the year after the index date, compared with the 6 months before the index date, were identified in the dose reduction group. These two groups were compared with pwCF without discontinuation or reduction of respiratory cotherapies during the year after the index date, compared with the 6 months before the index date.

To evaluate the changes in the clinical status of pwCF, we compared the best annual forced expiratory volume in 1 s, expressed as a percentage of the predicted value (FEV1%), the number of intravenous antibiotic courses and the total number of antibiotic courses (intravenous and oral) between the year following the index date and year preceding CFTRm initiation:

2.3. Data sources

Sociodemographic characteristics extracted from the SNDS database for the year preceding the index date included age, sex, and socioeconomic status, i.e., complementary health insurance and the FDep index categorized into quintiles, of which the fifth quintile (Q5) represents 20% of the population living in the most deprived areas [14]. CFTRm type (IVA or LUM/IVA), the data for exposure to respiratory cotherapies, defined as the presence of at least one dispensing event of azithromycin (ATC code: J01FA10), RhDNase (R05CB13), or inhaled antibiotics (aztreonam J01DF01, colistimethate J01XB01, and tobramycin J01GB01), were extracted from the SNDS database, as well as the presence of CF-related diabetes (CFRD), defined as the presence of at least one dispensing event of antidiabetic treatment during the year before the index date (insulin and oral antidiabetic treatment).

Clinical data obtained annually on a calendar-year basis from the FCFR during the study period included the following: the best annual FEV1%, bronchial colonization with *Pseudomonas aeruginosa*, the number of intravenous and oral antibiotic courses, nutritional status (underweight defined by a Z score<0 for children and adolescents and a body mass index (BMI) <18.5 for adults), and CF centre size (defined by the number of pwCF treated in one CF centre at the index date).

2.4. Statistics

First, we described population characteristics at the index date, respiratory cotherapies dispensing during the 6 months before the index date and the change in respiratory cotherapies dispensing (discontinuation and reduction) the year after the index date. To explore whether the reduction in or discontinuation of respiratory cotherapies led to a decrease in the effectiveness of CFTRm on clinical status, we performed propensity score-based analyses using the inverse probability of treatment weighting (IPTW) method to balance the distribution of measured potentially confounding factors among the groups in which pwCF was discontinued or reduced [15]. We derived weights from the propensity score, which was estimated as the predicted probability of a patient reducing or discontinuing cotherapies, using a logistic regression model that included sociodemographic and clinical pwCF characteristics. IPTW was stabilized with a marginal incidence of discontinuation or reduction of cotherapies [16]. We used standardized differences to assess the degree of balance between groups during the index year [17]. An absolute standardized difference (ASD) ≤ 0.10 was chosen to indicate a negligible difference in the mean or prevalence of a variable between groups. We also assessed the balance for continuous variables using graphical methods (side-by-side boxplots, empirical cumulative distribution functions, and empirical QQ plots) to compare the distributions across the two groups. We examined the distribution of the weights derived from the specifications of the propensity score models to ensure that there was no evidence of nonpositivity or misspecification of the propensity score models: we calculated the mean, standard deviation, minimum and maximum of the stabilized weight. We ultimately provided estimations with confidence intervals (CIs) between therapies for discontinuation or dose reduction from linear regression models with IPTW assigned to each patient. We also stratified this analysis between adults and children and performed a sensitivity analysis focusing only on IVA patients. All analyses were two-sided, and a p value <0.05 was considered to indicate statistical significance. All CIs were calculated at 95%, and the statistical test results are presented at the 5% threshold. Data manipulation and analyses were performed using Statistical Enterprise Guide software (SAS Institute, Cary, NC, USA).

2.5. Ethical considerations

In accordance with national legislation and institutional requirements, the CESREES (Comité d'Expertise pour les Recherches les Etudes et les Evaluations dans le domaine de la Santé) and the National Commission for Data Protection and Freedom of Information (Commission Nationale Informatique et Liberté or CNIL) approved this study, which is registered as a MODUCO study (n°DR-2022–224). The patients included received a written information leaflet about the study and confirmed nonopposition for study participation. All methods were performed in accordance with the relevant guidelines and regulations.

3. Results

3.1. Population characteristics at index date

A total of 1378 pwCF were included in the study (Fig. 1), mostly children (N = 798; 57.9%; Table 1). >90% of the population were treated with LUM/IVA; the mean FEV1% was 67.4% for adults and 95.7% for children, and 17.1% of adults were chronically colonized with *Pseudomonas aeruginosa*. More than half of the children were underweight. One-quarter of the adults were treated for CFRD. A total of 1378 pwCF were included in the study. In this group, 1171 pwCF had at least one respiratory co-therapy. Among these 1171 pwCF, 75 had missing FEV1% data and only 1096 pwCF were included in the analyses to explore whether the reduction or discontinuation of respiratory cotherapies led to a decrease in the effectiveness of CFTRm on clinical status.

3.2. Changes in respiratory cotherapies

During the 6 months before the index date, 85.0% of pwCF (N = 1171) had at least one respiratory cotherapy (Table 2). Among these patients, 57.0% reduced their cotherapy use in the year after the index date compared with the previous 6 months, including 43.4% who discontinued it. Discontinuation or dose reduction of at least one

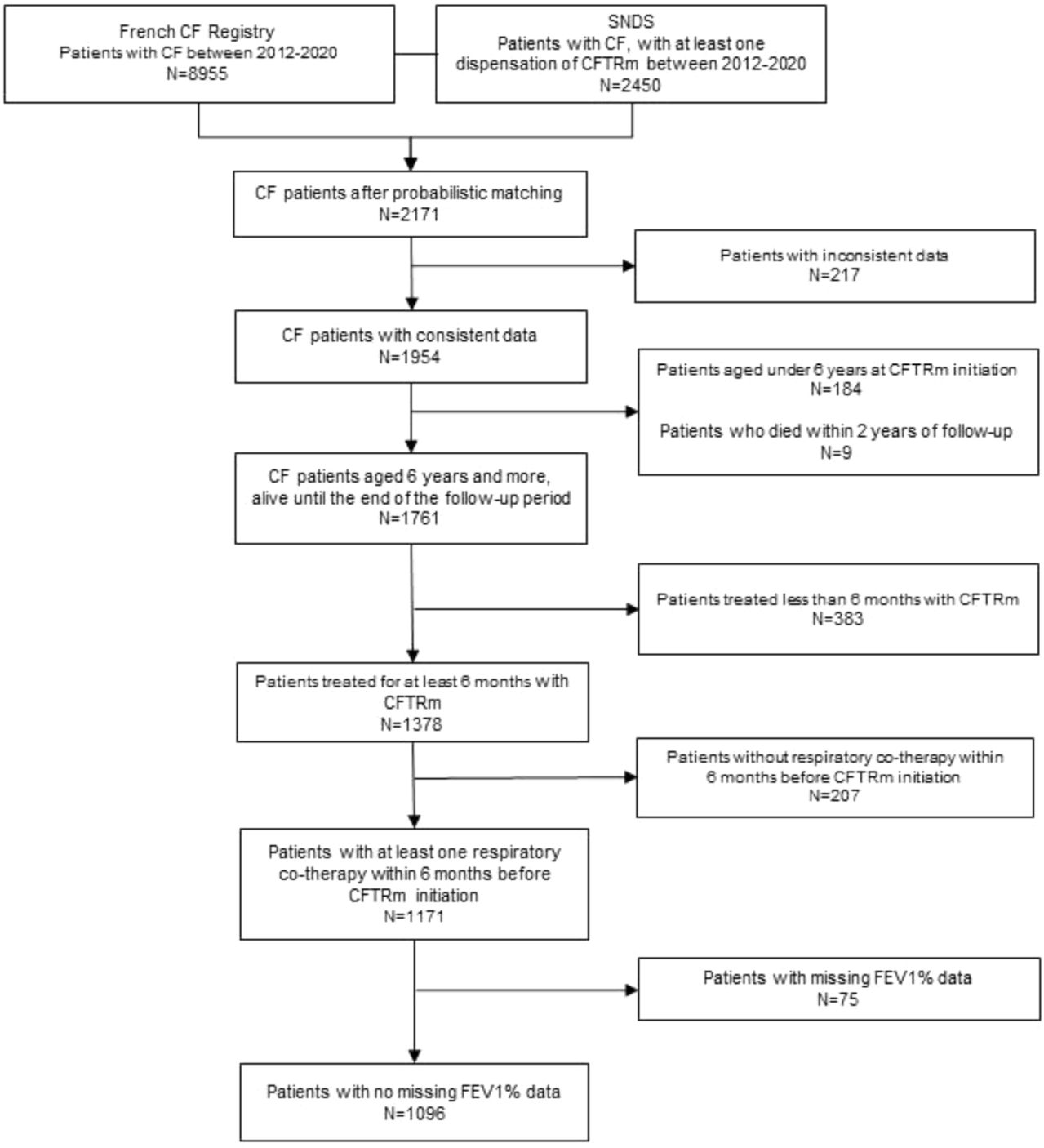

Fig. 1. Study flow chart.

Table 1
Characteristics of the population at the time of CFTR modulator initiation (index date).

	Adults N = 580	Children N = 798	Total N = 1378
Men, n (%)	333 (57.4)	392 (49.1)	725 (52.6)
Age years, mean ± SD	29.6 ± 8.9	11.6 ± 3.1	19.2 ± 10.8
French Deprivation index, n (%)			
Missing data	12 (2.1)	22 (2.8)	34 (2.5)
Q1 *(least deprived)*	116 (20.0)	147 (18.4)	263 (19.1)
Q2	140 (24.1)	180 (22.6)	320 (23.2)
Q3	131 (22.6)	171 (21.4)	302 (21.9)
Q4	100 (17.2)	146 (18.3)	246 (17.9)
Q5 *(most deprived)*	81 (14.0)	132 (16.5)	213 (15.5)
Complementary solidarity health insurance, n (%)	31 (5.3)	122 (15.3)	153 (11.1)
CFTRm type, n (%)			
IVA	52 (9.0)	45 (5.6)	97 (7.0)
LUM/IVA	528 (91.0)	753 (94.4)	1281 (93.0)
Best FEV1% the year before the index date, mean ± SD	67.4 ± 22.7	95.7 ± 19.8	83.8 ± 25.3
***P. aeruginosa* colonization, n (%)**	99 (17.1)	47 (5.9)	146 (10.6)
Nutritional status the year before the index date			
Z score, mean ± SD	-	−0.2 ± 1.5	-
BMI, mean ± SD	21.1 ± 2.8	-	-
Underweight (Z score < 0 or BMI < 18.5), n (%)	100 (17.2)	455 (57.0)	555 (40.3)
Treated CFRD, n (%)	162 (27.9)	47 (5.9)	209 (15.2)

BMI: body mass index, CFRD: cystic fibrosis-related diabetes, CFTRm: CFTR modulator, FEV1: forced expiratory volume in 1 s, IVA: ivacaftor, LUM/IVA: lumacaftor/ivacaftor, Q: quintile, SD: standard deviation.

respiratory cotherapy was greater among adults than among children (48.1%vs. 39.9% and 61.2% vs. 54.0%, respectively). Dornase alpha was reduced in 37.0% of adults and 29.3% of children, including 25.3% of adults and 17.7% of children who discontinued treatment. Azithromycin was reduced in 27.1% of adults and 33.3% of children, including 19.0% of adults and 19.9% of children who discontinued it. For inhaled antibiotics, dose reduction was observed in >50% of patients for the three types of inhaled antibiotics.

3.3. Description of pulmonary function and antibiotic courses

The best FEV1 increased from 83.8% to 85.5% between the year before and after the index date, representing a 2.6% increase in the best FEV1, whereas the mean number of antibiotic courses decreased from 3.7 years before to 2.9 to the year after the initiation of the CFTRm, representing a 25.6% decrease in the mean number of antibiotic courses (Fig. 2). These trends were similar in children and adults.

3.4. Effect of reduced respiratory cotherapies on the effectiveness of CFTRms

Among the 1096 pwCF and after the IPTW method was performed, patient characteristics were well balanced between the dose reduction and no dose reduction groups (see Supplement, Table 1).

Respiratory cotherapy dose reduction had no effect on pulmonary function, number of intravenous antibiotic courses or number of total antibiotic courses (0.69 (−2.25; 0.87), −0.01 (−0.16; 0.14), and −0.03 (−0.31; −0.25), respectively; Table 3). Results were consistent between adults and children (Supplement Table 11 to 14).

Table 2
Description of respiratory cotherapies in the 6 months before CFTRm initiation (index date) and their discontinuation or dose reduction in the year after the index date compared with the previous 6 months.

Respiratory cotherapies	Adults N = 580	Children N = 798	Total N = 1378
At least one respiratory cotherapy*, n (%)			
6 months before the index date	495 (85.3)	676 (84.7)	1171 (85.0)
Discontinuation the year after	*238 (48.1)*	*270 (39.9)*	*508 (43.4)*
Dose reduction the year after	*303 (61.2)*	*365 (54.0)*	*668 (57.0)*
Dornase, n (%)			
6 months before the index date	292 (50.3)	570 (71.4)	862 (62.6)
Discontinuation the year after	*74 (25.3)*	*101 (17.7)*	*175 (20.3)*
Dose reduction the year after	*108 (37.0)*	*167 (29.3)*	*275 (31.9)*
Azithromycin, n (%)			
6 months before the index date	336 (57.9)	312 (39.1)	648 (47.0)
Discontinuation the year after	*64 (19.0)*	*62 (19.9)*	*126 (19.4)*
Dose reduction the year after	*91 (27.1)*	*103 (33.0)*	*194 (29.9)*
Aztreonam, n (%)			
6 months before the index date	225 (38.8)	196 (24.6)	421 (30.6)
Discontinuation the year after	*92 (40.9)*	*70 (35.7)*	*162 (38.5)*
Dose reduction the year after	*123 (54.7)*	*99 (50.5)*	*222 (52.7)*
Tobramycin, n (%)			
6 months before the index date	169 (29.1)	192 (24.1)	361 (26.2)
Discontinuation the year after	*70 (41.4)*	*108 (56.3)*	*178 (49.3)*
Dose reduction the year after	*96 (56.8)*	*135 (70.3)*	*231 (64.0)*
Colistimethate, n (%)			
6 months before the index date	36 (6.2)	10 (1.3)	46 (3.3)
Discontinuation the year after	-	-	*19 (41.3)*
Dose reduction the year after	-	-	*25 (54.3)*

* Dornase, Azythromycin, Aztreonam, Tobramycin and Colistimethate.

Discontinuation the year after was defined as the discontinuation of the considered respiratory cotherapy during the year after the index date compared with the previous 6 months.

Dose reduction the year after was defined as a reduction of at least 50% in the dose of the study respiratory cotherapy during the year after the index date compared with the previous 6 months.

Numbers were not presented when at least one of the variables' categories was <10.

3.5. Effect of discontinuation of respiratory cotherapies on the effectiveness of CFTRms

Among the 1096 pwCF and after the IPTW method was performed, patient characteristics were well balanced between the discontinuation and no discontinuation groups (Supplement Table 2).

Respiratory cotherapy discontinuation had no effect on pulmonary function, number of intravenous antibiotic courses or number of total antibiotic courses (0.13 (−1.44; 1.70), −0.03 (−0.18; 0.13), and 0.04 (−0.25; 0.32), Table 4. Results were consistent between adults and children (Supplement Table 7 to 10).

We have conducted a sensitivity analysis on the LUM/IVA group corresponding to 1035 pwCF treating with LUM/IVA with at least one respiratory co-therapy within 6 months before CFTRm initiation and no missing FEV1% data, excluding patients treated with IVA. The results remain inconclusive regarding treatment de-escalation (Supplement Tables 3 to 6).

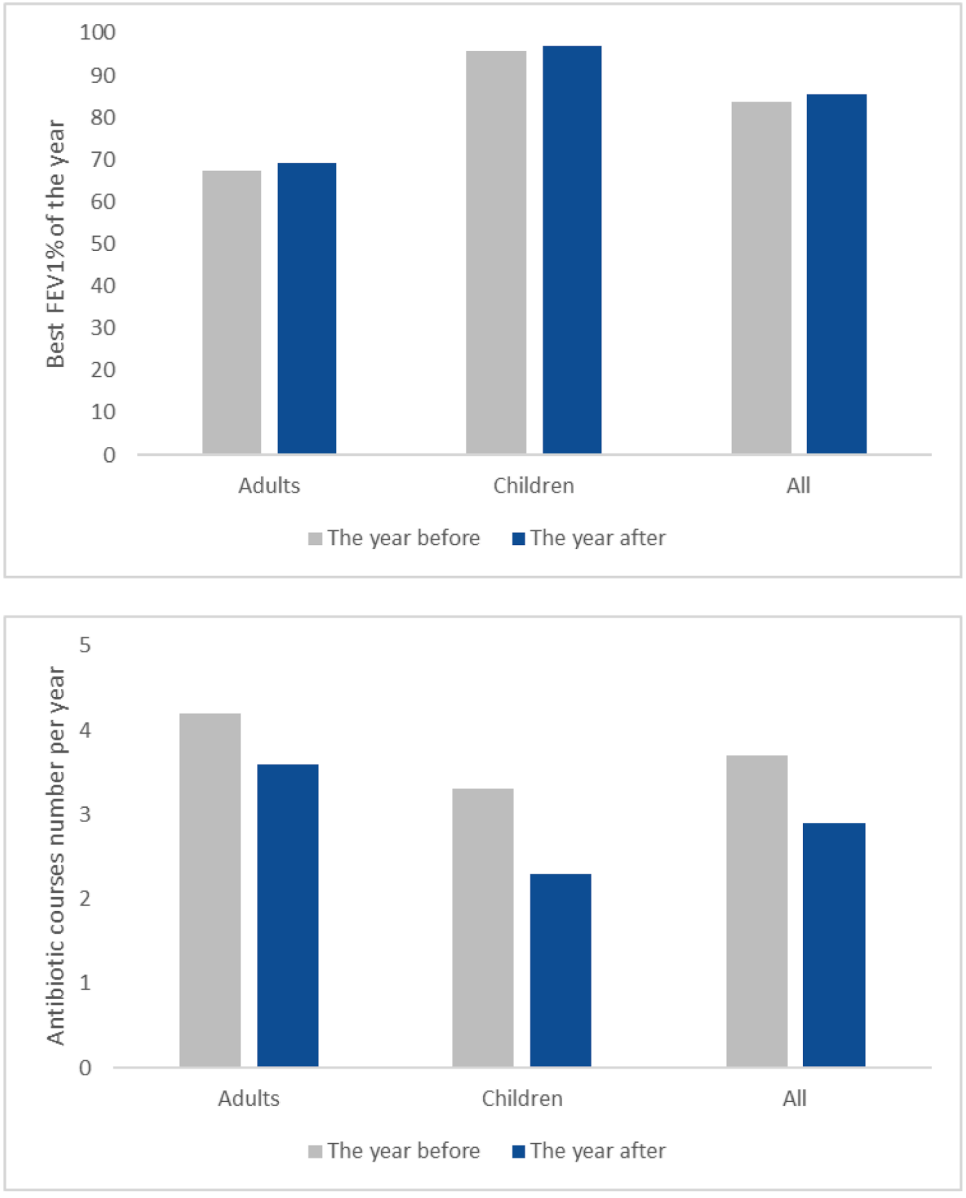

Fig. 2. Description of the best FEV1 expressed as the % predicted value and the mean number of antibiotic courses per year, including intravenous and oral courses, the year before and the year after CFTRm initiation.

Table 3
Effect of dose reduction of respiratory cotherapies in the year following CFTRm initiation (index date) on the effectiveness of CFTRms compared with the year before.

	Respiratory cotherapy dose reduction			
	No	Yes	Estimate (IC 95%)	*P* value
FEV1% difference	1.71 ± 13.36	1.02 ± 12.33	−0.69 (−2.25; 0.87)	0.384
Number of IV antibiotic courses, difference	−0.21 ± 1.21	−0.22 ± 1.26	−0.01 (−0.16; 0.14)	0.886
Number of total antibiotic courses, difference	−0.75 ± 2.22	−0.79 ± 2.35	−0.03 (−0.31; −0.25)	0.809

Table 4
Effect of discontinuation of respiratory cotherapies in the year following CFTRm initiation (index date) on the effectiveness of CFTRms compared with the year before.

	Respiratory cotherapy discontinuation			
	No	Yes	Estimate (95% CI)	*P* value
FEV1% difference	1.14 ± 13.39	1.27 ± 12.54	0.13 (−1.44 ;1.70)	0.870
Number of IV antibiotic courses, difference	−0.20 ± 1.19	−0.23 ± 1.40	−0.03 (−0.18 ;0.13)	0.772
Number of total antibiotic courses, difference	−0.79 ± 2.27	−0.75 ± 2.47	0.04 (−0.25 ;0.32)	0.788

4. Discussion

To our knowledge, this study is the first to evaluate the discontinuation or dose reduction of respiratory cotherapies in pwCF treated with IVA or LUM/IVA based on a solid linkage between a clinical database and a dispensing database. In 93% of the included cases, PwCF

were treated with LUM/IVA.

As expected and confirmed in real-life studies, the impact of introducing LUM/IVA on pulmonary function was low, with a 1% increase in FEV1% and a small decrease in the total number of antibiotic courses.

We first confirmed that a large portion of our cohort stopped or reduced respiratory cotherapies during the year after the first year of use of LUM/IVA, with 20% of dornase alpha and azithromycin discontinuation and almost half of patients who stopped one of the 3 inhaled antibiotics.

Second, we did not observe a significant deleterious effect of discontinuation or dose reduction of respiratory cotherapies on the effectiveness of LUM/IVA or IVA in terms of pulmonary function and antibiotic use despite the slight beneficial effect of LUM/IVA and considering potential confounding factors such as age, sex, socioeconomic status, pseudomonas colonization, CFRD, FEV1 and BMI at the index date. Only one British study reported this trend in a survey of IVA, LUM/IVA and TEZA/IVA [18].

More recently, many studies have focused on the modification of respiratory cotherapies after the initiation of ETI [10,19–21]. All of them confirmed significant reductions in their use. Their methodologies were based on self-reports [19] or index calculations such as the medication possession ratio [20] and prescription refill rate [21] or the national pharmacy registry [10]. In all of them, ETI was associated with a reduction in other chronic respiratory cotherapies, without affecting the effectiveness of ETI. Sagel et al. [19] reported that the maintenance of $\geq$ 2 cotherapies was associated with older age and poor lung function. Considering only mucus clearance therapy, a randomized Simplify study concluded that the discontinuation of hypertonic saline or dornase alfa for 6 weeks in pwCF on ETI did not result in a significant difference in lung function compared with continuing treatments [22]. The short- and long-term trajectories of the study period should be explored when respiratory cotherapy discontinuation is considered, but long-term reductions in inflammation and maintenance of clinical improvement are encouraging [23]. The recent study CF Storm in UK including pwCF on ETI for at least 3 months, and a minimum of FEV1% of 40% found that, on average, stopping nebulised mucoactive therapies did not negatively impact lung function over a period of 12 months compared with continuing nebulised mucoactive therapies. The main difference is that the beneficial effects of ETI on lung function and bronchial exacerbation rates are greater than those of LUM/IVA.

Despite a robust methodology owing to the linkage between the French CF Registry (FCFR) and the French National Health Data System (SNDS), we were not able to identify whether pwCF who experienced a greater initial clinical response to LUM/IVA were more likely to reduce their use of respiratory cotherapies. Using a propensity score-based method, we nevertheless considered some of the main confounding factors between the groups. However, we cannot rule out the possibility that the pwCF included in the analysis were those who continued the modulator, particularly LUM/IVA, because they benefited the most from it. Burgel et al. reported a high rate of LUM/IVA discontinuation, particularly among adults and those with severe disease [24].

Our study has several limitations. The data source used to identify medication reduction or discontinuation is the French national database of medication reimbursement. Even if dispensing and reimbursement data are a high-quality assessment of respiratory cotherapy use, they are not a direct measure of adherence, as redeemed drugs might not be ingested. Consequently, the treatment reduction rate may be underestimated. Additionally, treatment adherence to LUM/IVA or other medications and other factors (time burden, side effects, discussion between patients and clinicians) that may have influenced the decision to discontinue or reduce respiratory cotherapy may influence outcomes. A high adherence rate was observed in pwCF who continued LUM/IVA at 12 months [25] but was not specifically measured in our cohort. Our methodology did not allow us to explore the exact reasons for treatment discontinuation or reduction. Chest physiotherapy or other mucus clearance techniques were not used in our study because the reimbursement database does not provide sufficient information. Even if several confounding factors have been considered using propensity score analysis, a clinical response to LUM/IVA cannot be ruled out. The FEV1% and the number of antibiotic courses do not perfectly reflect long-term lung damage, we were not able to evaluate sputum colonization especially Pseudomonas and the results should be confirmed over a longer period. More sensitive markers exist to explore pulmonary function, such as CT scans known to evolve positively in cases of treatment with LUM/IVA [26], which could allow precise evaluation over longer follow-up periods.

This study has several strengths. Most important is the size of the studied population, which is based on a national registry. Adding the French CF Registry clinical data to the claims recorded in the SNDS provides a more exhaustive profile of pwCF, including its phenotypic parameters, and allows the clinical impact of medication discontinuation to be measured.

In summary, although our findings on LUM/IVA may offer limited novelty, two important factors merit particular consideration. The first concerns methodological originality. By utilizing two carefully matched real-world databases, we were able to simultaneously assess treatment adherence and its impact on clinical parameters, thereby circumventing the operational complexity and resource demands typically associated with randomized controlled trials. This approach provides a pragmatic framework for evaluating therapeutic interventions in routine care settings. The second relates to the clinical implications of our observations. To our knowledge, this is the first demonstration that LUM/IVA use has already influenced patterns of concomitant therapies without inducing measurable clinical deterioration in a subset of patients. These findings suggest that LUM/IVA may have indirect effects on treatment strategies, which could have broader implications for patient management and health care resource allocation.

Future work will extend these analyses to ETI to confirm and expand upon these preliminary insights and to better understand the evolving therapeutic landscape in cystic fibrosis care.

Declaration of competing interest

None

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2026.05.007.

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