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Improvement of iron status with elexacaftor tezacaftor ivacaftor therapy is associated with the correction of systemic inflammation and improvement of lung function: a one-year prospective study

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Iron deficiency (ID) is frequent in adult patients with cystic fibrosis (pwCF). The effect of elexacaftor-tezacaftor-ivacaftor (ETI) on iron metabolism has rarely been reported. We aimed to study the trends and variables associated with iron store modulation under ETI. We conducted a prospective adult cohort in two referral centres for pwCF. Iron supplementation during the follow-up was an exclusion criterion. Clinical, biological data and pulmonary function tests were collected prospectively at ETI initiation (V0) and after 1 year of ETI (V12). The presence of *Pseudomonas aeruginosa* in forced sputum was assessed at V0 and V12. 220 (87 women) pwCF among the 278 screened were included. At V0, ID prevalence was 58% and was significantly associated with female sex and lower forced expiratory volume (FEV1). At V12, ID prevalence decreased significantly from 58 to 31% ($p = 0.001$). A significant decrease of C reactive protein and total globulins was found at V12. 60% of patients with ID at V0 achieved normalization of iron status at V12 with a significant association with the increase of FEV1 (moderate size effect: 0.68). A lower decrease of C reactive protein was significantly associated with the onset of ID in a small sample of patients ($p < 0.001$). The disappearance of *Pseudomonas aeruginosa* in sputum at V12 was not correlated to the evolution of iron status under ETI. ETI was associated with a decrease of ID prevalence, and improvement of pulmonary function and a correction of systemic inflammation.

Cystic fibrosis (CF) is an autosomal recessive disease due to mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene[1,2], impairing the expression and/or function of CFTR protein acting as a chloride and bicarbonate channel. Abnormal ion transport, airway surface liquid dehydration and inflammation result in tissue damage responsible for the CF multisystem severe phenotype.

Iron deficiency (ID) is common in patients with cystic fibrosis (pwCF)[3,4] with a prevalence ranging from 19 to 83% in the adult population of pwCF according to the biological thresholds used to define ID[5]. ID is either absolute by the decrease of the total body iron stores, and/or functional in patients with inflammation withholding iron from the plasma leading to inadequate erythropoiesis. Systemic inflammation induces an increase of hepcidin level reducing ferroportin transcription, thus limiting iron supply to the plasma causing functional ID[6,7]. Systemic inflammation is assumed to be one of the main pathways leading to the onset of ID

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in pwCF, highlighted by the increase of hepcidin level typically occurring after pulmonary exacerbation[8,9,10]. Reciprocally, it has been demonstrated that the treatment of pulmonary exacerbation waning the systemic inflammation induces a decrease of hepcidin level in pwCF[8]. Several other mechanisms may contribute to the onset of absolute ID including the malabsorption of micronutrients in the setting of exocrine pancreatic insufficiency and increase of iron loss via sputum[11].

Elexacaftor Tezacaftor Ivacaftor (ETI) is the first triplet of CFTR modulators, demonstrating significant benefits for pwCF including improved lung function and quality of life[12]. The decrease of pulmonary infections under ETI therapy[13,14] could restore normal iron metabolism in pwCF in line with the improvement of nutritional status[15]. In our previous study before the wider use of ETI, we found a high prevalence of ID in adult pwCF with no influence of the use of a double CFTR modulator (mostly Ivacaftor - Lumacaftor)[5].

The aim of the present study was to prospectively assess the prevalence of ID in adult pwCF before and after one year of ETI, and to study its relation with clinical and nutritional status, pulmonary function, and biological markers.

Patients and methods

We conducted a one-year prospective bi-centric study in two adult referral centres for CF between 1st January 2021 and 31st January 2023. We included adult patients (age ≥ 18 years) with genetically proven CF who underwent a full iron store blood assessment at their ETI initiation visit (V0) and after 1 year of treatment (V12). Exclusion criteria were: (i) Clinically apparent exacerbation of CF during the 7 days before each visit, (ii) the use of iron supplements during the study period, (iii) solid organ transplantation during the follow-up, (iv) discontinuation of ETI treatment before V12.

Clinical and biological data

We prospectively collected the following data at baseline (V0) and at V12:

- Clinical data: age, sex, genotype; body mass index (BMI); the use of pump proton inhibitors (PPI); the use of CFTR modulators, Pseudomonas *aeruginosa* bronchial positivity with forced sputum samples after bacterial culture examination; Cystic Fibrosis Related Diabetes (CFRD) status.
- Biological markers including: iron store markers (serum ferritin: SF, transferrin saturation: TSAT), C reactive protein, full blood count, total globulins on serum protein electrophoresis, vitamin D level, oral glucose tolerance test (OGTT) including insulin and glucose levels at 0, 60 and 120 min.
- Pulmonary function tests (PFT) including forced expiratory volume in one second (FEV1) and forced vital capacity (FVC).

The primary outcome was the changes of iron status at V12 (after 1 year of ETI treatment). ID was defined by serum ferritin (SF) ≤ 20 (women) or 30 (men) µg/L or ≤ 100 µg/L in the case of systemic inflammation (CRP ≥ 10 mg/L) and/or transferrin saturation (TSAT) ≤ 16% similar to our previous cohort study[5] which is also recommended for the assessment of iron status in chronic inflammation[7,16,17]. Normalization of iron stores was defined by the shift from ID at V0 to no ID at V12. Anaemia was defined according to the WHO thresholds for adult patients: haemoglobin < 120 g/L (women) or 130 g/L (men)[18].

To further explore the potential underlying mechanism associated with iron status variations with ETI treatment, we included as secondary outcomes the study of PFT values variations, HOMA indices, prevalence of *Pseudomonas aeruginosa* bronchial positivity in forced sputum at V0 and V12, vitamin D levels, CRP level, and globulin level.

HOMA indices are validated methods for assessing insulin-resistance and β-cell function, requiring a single plasma assay[19]. β-cell function (HOMA-%β) and insulin resistance (HOMA-IR) were calculated from fasting plasma insulin and glucose plasma levels obtained from OGTT with the following formulas: HOMA-%β = [(fasting insulinemia (mUI/L) x 20) / (fasting plasma glucose (mmol/L) – 3.5)]; HOMA-IR = [(fasting insulinemia (mUI/L) x fasting plasma glucose (mmol/L)) / 22.5][20].

Statistical analysis

Categorical data were described with numbers (percentages). Continuous data were expressed as median and interquartile range, according to the statistical distribution. The assumption normality of the data was assessed using the Shapiro-Wilk test.

The comparisons between independent groups (such as (i) men vs. women, (ii) according to iron status course under ETI) were performed using analysis of variance (ANOVA) or the Kruskal-Wallis test when the assumptions to apply ANOVA were not met. The homoscedasticity (equality of variances) was assessed using the Bartlett test. The two by two post-hoc comparisons correcting type I error were conducted using Tukey-Kramer test after ANOVA and Dunn test after Kruskal-Wallis.

To assess changes between visits (i.e. baseline vs. after 1 year of ETI), statistical paired tests were performed using the paired Student t-test or Wilcoxon test if the assumptions of the t-test were not met. Pitman's test was used to analyse the equality of variances. For categorical data, McNemar test was performed to analyse the evolution of ID prevalence between V0 and V12.

The relationships between continuous variables (i.e. between nutritional status and PFT at 12 months) were analysed using correlation coefficients (i.e. Pearson or Spearman according to the statistical distribution). Statistical analyses were performed using Stata software (version 15, StataCorp, College Station, US). All statistical tests were two-sided, with a type I error set at 5%. Emphasis was given to assessing the magnitude of differences using Hedge's effect sizes (ES) and 95% confidence intervals (95% CI), and these were interpreted according to Cohen's recommendations defining ES as small (≥ |0.2|), medium (≥ |0.5|), and large (≥ |0.8|)[21].

Ethics

The study protocol was registered on clinicaltrials.gov (NCT04584489). Written informed consent was obtained from each participant. The research was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee (International Review Board, Hospices Civils de Lyon, IRB number: 69HCL20_0793).

Results

Among 278 patients who initiated ETI treatment between 1st January 2021 and 31st January 2023, 220 (87 women, 39.6%) were included. The main reasons for exclusion were the absence of interpretable iron data at V0 ($n=10$) or V12 ($n=16$), the use of iron treatment during follow-up ($n=9$) and follow-up endpoint (V12) not reached when the study was closed to recruitment ($n=17$). Five additional patients moved during the study (follow-up carried out in a non-participating centre) and one patient discontinued the ETI treatment due to side effects.

At V0, median age was 29.3 [IQR 23.6; 35.9]. 51 patients (23.5%) had CFRD, 84 (38.7%) used pump proton inhibitors, and 45 (20.5%) were treated by CFTR modulators before ETI, mostly Ivacaftor-Lumacaftor (96%).

Iron status at baseline (V0)

Table 1 show the main characteristics of the population at V0. ID prevalence was 58%, significantly associated with female sex (78% *versus* 44%, $p<0.001$). ID was associated with lower FEV1% (FEV1p: 53 [41; 73] vs. 70 [52; 83], $p<0.001$). In the gender subgroup analysis, a similar but non-significant trend was found. BMI and age were lower in ID patients (20.4 ± 4.1 kg.m^{-2} vs. 21.1 ± 4.7 kg.m^{-2} and 29.7 ± 9.2 kg.m^{-2} vs. 31.9 ± 9.3 kg.m^{-2} respectively, $p=0.003$) but the difference did not reach statistical significance. *Pseudomonas aeruginosa* colonization, diabetes mellitus and PPI use were not associated with ID. CRP was higher in patients with ID (17.8 ± 29.1 mg/L vs. 5.1 ± 8.5 mg/L, $p<0.001$). We found no association between HOMA indexes and iron deficiency.

Iron status after 1 year of ETI (V12)

At V12, the prevalence of ID decreased significantly from 58 to 31% ($p=0.001$). At V12 after 1 year of ETI treatment, 60% of patients who had ID at V0 normalized their iron status. In the gender subgroup analysis, the decrease of ID prevalence was significant for females (78% to 44%, $p=0.03$) while we observed a non-significant trend for males (44% to 23%). Serum ferritin (SF) increased significantly (46 µg/L [26.5; 85.5] to 53 µg/L [30.3; 97.8], $p=0.002$, size effect 0.25) as well as TSAT (17% [12; 24] to 24% [17; 29.8], $p=0.001$, size effect 0.57). Table 2 shows the evolution of the main characteristics of the population between V0 and V12.

	Men ($n=133$)	Women ($n=87$)	p
Age (years, median [Q1;Q3])	29.7 [23.9; 37.3]	28.5 [23.2; 35.2]	0.15
Genotype F508del homozygote (n, %) F508del heterozygote (n, %) Other genotypes (n, %)	77 (57.9%) 55 (41.4% 1 (0.8%)	49 (56.3%) 37 (42.5%) 1 (1.1%)	0.95
BMI (kg.m^{-2}, median [Q1;Q3])	21.2 [19.4; 23.4]	20.0 [18.6; 21.9]	0.27
Diabetes (n, %)	26 (19.7%)	25 (29.4%)	0.09
PPI use (n, %)	52 (39.4%)	32 (37.6%)	0.79
Pseudomonas aeruginosa positivity (n, %)	86 (64%)	57 (65%)	0.96
Haemoglobin (g/dL, median [Q1;Q3])	15.1 [14.5; 15.8]	12.9 [12.2; 14]	< 0.001
Anaemia (n, %)	7 (5.4%)	20 (24.1%)	< 0.001
Iron deficiency (n, %)	59 (44%)	68 (78%)	< 0.001
Ferritin (µg/L, median [Q1;Q3])	63 [35; 110]	27.5 [14; 53]	< 0.001
TSAT (%)	21 [15; 26]	14 [9; 18]	< 0.001
CRP (mg/L)	5 [1.8; 11.1]	5.7 [2.3; 16.5]	0.14
FEV1p (median [Q1;Q3]	66 [50; 81]	52.5 [40; 72.3]	< 0.001
FEV1 (n, %) - > 69% - 50–69% - 30–49% - < 30%	57 (44.2%) 40 (31%) 28 (21.7%) 4 (3.1%)	25 (29.8%) 20 (23.8%) 33 (39.3%) 6 (7.1%)	0.01

Table 1. Baseline characteristics at ETI initiation visit.

	V0 ($n=220$)	V12 ($n=220$)	p
Iron deficiency (n, %)	126 (58%)	68 (31%)	0.001
BMI (kg.m^{-2}, median [Q1;Q3])	20.8 [19; 22.9]	22.1 [20.5; 23.7]	< 0.001
Diabetes (%)	24%	22%	ns
Glycaemia (mmol/L)	5.1 [4.6; 5.4]	5 [4.6; 5.3]	ns
PPI use (n, %)	84 (38%)	77 (35%)	0.38
Pseudomonas aeruginosa colonization (n, %)	143 (64%)	95 (43%)	< 0.001
Haemoglobin (g/dL, median [Q1;Q3])	14.4 [13.1; 15.4]	14.6 [13.6; 15.4]	ns
Anaemia (n, %)	27 (12.7%)	11 (5.1%)	0.006
Ferritin (µg/L, median [Q1;Q3])	46 [26.5; 85.5]	53 [30.3; 97.8]	0.002
TSAT (%)	17 [12; 24]	24 [17; 29.8]	< 0.001
CRP (mg/L)	5.3 [2; 13.8]	1 [0.4; 2.7]	< 0.001
Globulin (g/L)	12.7 [10.6. 15]	10.9 [9.4; 12.6]	< 0.001
Vitamin D (ng/mL)	60.5 [39.3; 75.9]	70 [51.3; 88]	< 0.001
FEV1p (%, median [Q1;Q3]	59 [44; 77]	80 [61; 96]	< 0.001
FEV1 (n, %) - > 69% - 50–69% - 30–49% - < 30%	82 (38.5%) 60 (28.2%) 61 (28.6%) 10 (4.7%)	141 (66.2%) 46 (21.6%) 23 (10.8%) 3 (1.4%)	< 0.001

Table 2. Variations of the main characteristics after one year of ETI.

	ID-/ID- ($n=76$)	ID+/ID- ($n=75$)	ID-/ID+ ($n=17$)	ID+/ID+ ($n=50$)	p
Age (years, median [Q1;Q3])	32.7 [25.5; 39.2]	29.1 [22.6; 33.2]	28.4 [21; 31.9]	30.9 [23.1; 35.1]	0.03
Female sex (%)	20%	44%	23.5%	66%	< 0.001
BMI at V0 (kg.m^{-2}, median [Q1;Q3])	21.2 [19.7; 23.7]	20.0 [18.4; 22.2]	20.5 [18.7; 21]	21.4 [18.8; 23.2]	0.003
BMI variations at V12 (%)	4.9 ± 7.3	7.2 ± 9	6.9 ± 9.8	6.6 ± 9.6	0.02
CFRD at V0 (n, %)	13%	22%	41%	34%	0.01
PPI use (n, %)	36%	34%	47%	48%	ns
Pseudomonas aeruginosa positivity at V0 (%)	56%	73%	76%	60%	ns
Absence of Pseudomonas aeruginosa at V12 in patients with positive sputum at V0 (%)	29%	40%	16%	16%	ns
Haemoglobin at V0 (g/dL, median [Q1;Q3])	15.9 [14.3; 15.8]	14.1 [13.2; 14.9]	14.9 [14.4; 16]	13.1 [12.2; 14.2]	< 0.001
Haemoglobin variations at V12 (%)	-0.01 ± 12.2	4.9 ± 9.3	-0.8 ± 6.3	2.3 ± 14.3	0.02
CRP at V0 (mg/L)	2.4 [1.2; 6]	9.7 [4.1; 21.2]	2.7 [1.5; 6.2]	7.6 [2.9; 19.9]	< 0.001
CRP variations at V12 (%)	− 72 [− 88; − 31]	− 88 [− 96; − 77]	− 50 [− 74; − 94]	− 78 [− 90; 0]	< 0.001
Globulin at V0 (g/L)	11 [9.8; 13.5]	13.5 [11.8; 15.9]	12.8 [10.6; 13.9]	13 [11.9; 16.3]	< 0.001
Globulin variations at V12 (%)	− 12 [-17.5; -2.4]	-15.2 [-24; -7.2]	-19.8 [-25.2; -1.5]	-17.1 [-27.5; -5.7]	ns
Vitamin D at V0	62 [42; 78]	61 [39; 75]	59 [47; 73]	52 [35; 74]	ns
Vitamin D variations at V12 (%)	16 [-7; 60]	18 [-10; 56]	25 [2.6 : 58]	15.8 [-6; 48]	ns
FEV1 variations at V12 (%)	17.4 [9.7; 30.1]	37.1 [17.2; 52.8]	23.6 [6.2; 45]	26.1 [15.4; 45]	< 0.001

Table 3. Characteristics of patients according to the evolution of iron status under ETI.

Subgroup analysis by iron store trend after 1 year of ETI therapy

We conducted a subgroup analysis to describe covariates associated with the changes of iron status under ETI. The main results are showed in Table 3. Two patients were excluded from this subgroup analysis because of missing data on BMI and pulmonary function tests at V12.

We identified 4 subgroups: (i) patients without ID before and after ETI therapy (group 1, ID-/ID-); (ii) patients with ID before ETI and without ID after ETI (Group 2, ID+/ID-); (iii) patients without ID before ETI experiencing ID after ETI (group 3, ID-/ID+); and (iv) patients with ID before and after ETI (group 4, ID+/ID+).

FEV1% variations were significantly correlated with the evolution of iron status among the subgroups ($p < 0.001$). The FEV1 increase was significantly higher in group 2 (ID+/ID-) *versus* group 1 (ID- (37% vs. 17% respectively, moderate size effect − 0.68 (CI95% -1.02; -0.34), $p < 0.001$), suggesting that ID correction under ETI

was associated with a better improvement of pulmonary function. Sex ratio was statistically different among groups ($p < 0.001$) with a higher proportion of women in group 4 (ID+/ID-) compared to group 1 (66% *versus* 20% respectively, $p = 0.001$), compared to group 2 (66% *versus* 44% respectively, $p = 0.02$) and compared to group 3 (66% *versus* 23.5%, $p = 0.004$). This may suggest that ID persistency may be associated to female gender under ETI therapy. Age was statistically different between groups (ID-/ID+, 28.4 ± 9.8 years, $p = 0.03$), but no paired subgroup analysis was statistically significant.

The disappearance of *Pseudomonas aeruginosa* in sputum between V0 and V12 was not significantly correlated to the evolution of iron status. CRP decrease was significantly different between groups ($p < 0.001$) but no paired subgroup analysis was statistically significant. The increase of BMI was significantly different between groups ($p = 0.018$); no paired subgroup analysis was statistically significant.

Discussion

We present here the results of the largest prospective cohort study on iron metabolism in adult pwCF treated with ETI, finding a high prevalence of ID of 58%, in line with previous reports[3,22-25]. ID was associated with female sex and lower lung function, but not with PPI use or *Pseudomonas aeruginosa* colonization. The high prevalence of ID in men with pwCF (44%) compared to the prevalence of ID in the general male population[26] highlights the specific underlying mechanisms of ID in CF. The robustness of our study lies in the use of stringent criteria for ID diagnosis based on the adjustment of ferritin threshold levels to systemic inflammation[17], the exclusion of iron fortification use during the follow-up and the large sample size of our population.

Our results are in agreement with the retrospective cohort study by James et al.[27]. In this retrospective cohort characterized by a prolonged follow-up of 2 years, the authors studied the variations of biological iron markers under ETI treatment in 127 adult pwCF. While ID was not the main outcome, the authors reported a significant increase in ferritin and transferrin saturation even after adjustment for covariates (age, sex, BMI, diabetes, lung function and *P.aeruginosa* colonization). Interestingly, the authors included patients receiving iron therapy, which was an exclusion criterion in our cohort and reported that the increase in iron was not significantly different between patients taking iron supplementation and those without iron supplementation. Thus, the improvement of iron was mainly due to ETI treatment and not by iron supplementation, which is in line with our findings.

Ferritin is a well-recognized acute phase-reactant produced in response to the secretion of pro-inflammatory cytokines[28]. Among the 128 patients with ID, the use of adjusted ferritin threshold (≤ 100 µg/L) according to the level of systemic inflammation allowed us to diagnose 18 additional patients with ID. This diagnosis strategy is recommended in patients with chronic diseases characterized by recurrent or chronic inflammation, which is a hallmark of cystic fibrosis due to repeated infections[29]. In the most recent review focusing on ID diagnosis, the ferritin threshold for absolute ID in case of inflammation is 70–100 µg/L combined with a TSAT ≤ 20% [7]. Jia et al. reported a retrospective cohort study of ID in adult pwCF treated with ET using the TSAT threshold ≤ 20% [30]. Interestingly, among the 18 patients who were diagnosed with ID at baseline in our cohort using the inflammation corrected ferritin threshold ≤ 100 µg/L, only 7 wouldn't have been classified as ID with the definitions used in the study by Jia et al. However, the mean ferritin level in this small subgroup was 60 µg/L (min 34, max 82), which was lower than the lowest threshold (≤ 70 µg/L) discussed by Pasricha et al.[7].

In our previous cohort, we found no association between the use of Lumacaftor-Ivacaftor and the correction of iron status compared to patients receiving no CFTR modulators[5]. These results were confirmed in the present cohort as well as in the report from Jia et al. showing a mild improvement of iron biomarkers in patients receiving moderately effective modulator therapy[30]. ETI has demonstrated numerous benefits for pwCF, including the improvement of nutritional status, illustrated by the significant increase of BMI during the follow-up in our cohort. We found a clear improvement of lung function (increase of 16% of FEV1) consistent with previous randomized trials regardless of patient genotype[31]. These two parameters were significantly improved at V12 but we found significant correlations with the evolution of iron status only for FEV1p, with a moderate size effect for patients who normalized their iron status under ETI. These results are in line with Jia et al. study who also reported a higher increase of iron markers in patients with lower FEV1p.

A major pathway of iron metabolism disorders in CF may be the systemic inflammation due to the recurrence of infectious events, inducing hepcidin secretion which in turn blocks iron absorption and bioavailability[32]. In a paediatric study focusing on iron metabolism in children with CF, it has been showed that hepcidin is decreased in case of ID, allowing to increase nutritional iron absorption and iron availability for erythropoiesis[9]. In adult pwCF, hepcidin level has been showed to be directly correlated to the number and severity of pulmonary exacerbation in a longitudinal study[33]. Similar findings were reported in children pwCF, with an increase of hepcidin in case of inflammation[34]. Even though we did not measure hepcidin in our study, the higher CRP level in baseline ID and the significant association between ID correction and the improvement of inflammatory parameters under ETI support the hypothesis that inflammation correction may be a significant contributing factor of the normalization of iron stores in pwCF. We did not collect the number of exacerbations requiring antibiotic treatment in our study, but numerous reports showed a drastic reduction of these events under ETI[12]. However, under ETI we observed a significant decrease of globulins whose high levels may indicate prolonged or repeated immune system stimulation due to bronchial infections[35]. These results are also in favour of the correction of inflammation as a cofactor of iron store normalization and were confirmed in a recent retrospective cohort study[14]. We found a decrease of *Pseudomonas aeruginosa* sputum positivity at V12 but did not find a significant link with the correction of ID. Increased iron excretion through sputum is presumed to play a pivotal role in ID genesis for pwCF[25]. Airway cells expressing the ΔF508-CFTR increase iron availability promoting *Pseudomonas aeruginosa* biofilm formation[36]. Our results cannot support this hypothesis but the study of bronchial positivity through sputum bacterial culture may not be a highly reliable criterion as the collection of sputum is more difficult owing to the reduced volume of bronchial secretion under ETI.

A small sample of patients developed ID under ETI. This subgroup (ID-/ID+) was characterized by a lower decrease of CRP at V12. Our study was observational with no controlled group, which cannot allow identifying causal relationship between ETI treatment and ID onset. We did not identify any correlation between covariables and ID onset under ETI, and further studies are required to fully understand the underlying mechanisms of iron metabolism disorders. This subgroup was characterized by a greater increase of BMI (7%). An increase of erythropoiesis consuming iron stores in response to the increase of body mass might be a hypothesis[37], but further studies are required to fully understand the pathways involved in this specific evolution of iron under ETI.

The study by James[27] highlighted that both patients with and without iron fortification improved the level of ferritin and TSAT under ETI treatment. The improvement of iron status under ETI may probably reduce the requirement for iron fortification, for which debate still exists with regard to the risk of infection and exacerbations of CF after iron treatment[33,38].Some additional parameters would be of interest in further studies to investigate the mechanisms underlying iron deficiency correction under ETI, such as iron levels in sputum and nutritional iron absorption.

Conclusion

ETI therapy in a large prospective cohort study is associated with the improvement of iron status, and with the correction of systemic inflammation. Nutritional status was partly correlated to the improvement of FEV1p but was not directly linked to the improvement of iron status. Further studies are required to identify the driving processes leading to the onset of ID in CF, particularly in patients who become ID notwithstanding ETI treatment.

Data availability

The datasets generated and/or analysed during the current study are not publicly available due to local regulation constraints but are available from the corresponding author on reasonable request.

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H.L. : Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing - Original Draft, Writing - Review & Editing.B.P. : Formal analysis, Writing - Review & EditingM.R. : Investigation, Resources, Writing - Review & Editing, Visualization, M.RP. : Investigation, Resources, Writing - Review & Editing, Visualization, I.D. : Conceptualization, Methodology, Resources, Writing - Review & Editing, Visualization, Supervision, Q.R. : Conceptualization, Methodology, Resources, Investigation, Writing - Review & Editing, Visualization, Project administration.

Declarations

Competing interests
Prof. Isabelle Durieu reports a relationship outside this work with the French Ministry of Health and with the Non Profit Organization "Vaincre la mucoviscidose" that includes: funding grants from Zambon outside this work that includes: travel reimbursement. Prof. Isabelle Durieu reports a relationship with Vertex that includes: board membership outside this work. The other authors reports no conflict of interest.

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