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ORIGINAL RESEARCH

Multisystemic Effects of Elexacaftor–Tezacaftor–Ivacaftor in Adults with Cystic Fibrosis and Advanced Lung Disease

Pierre-Régis Burgel[1,2,3], Jean-Louis Paillasseur[4], Isabelle Durieu[5,6], Martine Reynaud-Gaubert[7], Rebecca Hamidfar[8], Marlène Murris-Espin[9], Isabelle Danner-Boucher[10], Raphaël Chiron[11], Sylvie Leroy[12], Benoit Douvry[13], Dominique Grenet[14], Laurent Mely[15], Sophie Ramel[16], Sylvie Montcouquiol[17], Espérie Burnet[2,3], El Hassane Ouaalaya[4], Philippe Sogni[18], Jennifer Da Silva[2,3], and Clémence Martin[1,2,3]; for the French Cystic Fibrosis Reference Network Study Group

Abstract

Rationale: Limited data exist on the safety and effectiveness of elexacaftor-tezacaftor-ivacaftor (ETI) in people with cystic fibrosis (pwCF) and advanced lung disease.

Objectives: To evaluate the effects of ETI in an unselected population of pwCF and advanced lung disease.

Methods: A prospective observational study, including all adults aged 18 years and older with percentage predicted forced expiratory volume in 1 second ($ppFEV_1$) ≤ 40 who initiated ETI from December 2019 to June 2021 in France, was conducted. PwCF were followed until August 8, 2022.

Results: ETI was initiated in 434 pwCF with a median $ppFEV_1$ of 30 (interquartile range, 25–35), including 27 with severe cystic fibrosis liver disease and 183 with diabetes. PwCF were followed for a median of 587 (interquartile range, 396–728) days after ETI initiation. Discontinuation of ETI occurred in 12 (2.8%) pwCF and was due mostly to lung transplantation ($n = 5$) or death ($n = 4$). Absolute increase in $ppFEV_1$ by a mean of +14.2% (95% confidence interval, 13.1–15.4%) occurred at 1 month and persisted throughout the study. Increase in $ppFEV_1$ in the youngest age quartile was almost twice that of the oldest quartile ($P < 0.001$); body mass index $< 18.5\ kg/m^2$ was found in 38.6% at initiation versus 11.3% at 12 months ($P = 0.0001$). Increases in serum concentrations of vitamins A and E, but not 25-hydroxy vitamin D_3, were observed. Significant reductions in the percentages of pwCF using oxygen therapy, noninvasive ventilation, nutritional support, and inhaled and systemic therapies (including antibiotics) were observed; insulin was discontinued in 12% of patients with diabetes.

Conclusions: ETI is safe in pwCF and advanced lung disease, with multisystem pulmonary and extrapulmonary benefits.

Keywords: real-word evidence; cystic fibrosis transmembrane conductance regulator modulators; severe cystic fibrosis liver disease

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A complete list of French Cystic Fibrosis Reference Network Study Group members may be found before the beginning of the References.

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This article has a related editorial.

This article has a data supplement, which is accessible at the Supplements tab.

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Cystic fibrosis (CF), is an autosomal-recessive disease caused by mutations in the gene encoding for the CFTR (CF transmembrane conductance regulator) protein (1, 2). Defective CFTR function, resulting in abnormal ion transport, leads to pulmonary disease characterized by mucus plugging, airway infection, and inflammation, with progressive development of bronchiectasis, destruction of bronchi, and loss in lung function, often leading to lung transplantation or death. The disease is also characterized by extrapulmonary manifestations, including pancreatic exocrine and endocrine insufficiency, leading to malnutrition and/or diabetes, and liver disease, which is severe in a subset of people with CF (pwCF).

The triple combination of CFTR modulators elexacaftor–tezacaftor–ivacaftor (ETI), which partially restores CFTR function (3), has become the new standard of care for pwCF carrying at least one F508del *CFTR* variant. Data from randomized clinical trials (4–6) revealed improvement in respiratory outcomes (respiratory symptoms, lung function, and exacerbations) and body mass index (BMI), which were largely confirmed in real-word studies (7). However, pwCF with advanced lung disease were excluded from clinical trials (4–6) and represented only a small number of participants in the large PROMISE (A Prospective Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function) real-word study (7). Although several real-world studies in patients with advanced lung disease using ETI have been reported (8–13), they were generally conducted among limited numbers of patients over short periods of time. These latter studies focused mostly on respiratory improvement after ETI initiation, and few data exist on the safety and effectiveness of ETI in patients with associated comorbidities (e.g., severe CF liver disease, diabetes), extrapulmonary manifestations, and evolution of concomitant therapies.

In France, pwCF are followed by a network of 47 pediatric and adults CF centers, and ETI is fully reimbursed. We took advantage of this network to launch a prospective study involving all adults (age $\geq$ 18 yr) treated with ETI at the 31 centers involved in adult care. Because most pwCF with advanced lung disease started ETI in an early access program that took place between December 2019 and June 2021, there is now an opportunity to describe the evolution of pwCF with advanced lung disease after the initiation of ETI over longer period of time, with special interest on specific subpopulations (e.g., severe CF liver disease).

Methods

Patient Population and Study Design

All French CF centers involved in adult care ($n = 31$) participated in a prospective, observational, before-and-after cohort study designed to obtain real-world data in CF adults (age $\geq$ 18 yr) with advanced lung disease who received ETI through the French early access program. Detailed information on the program has previously been published (14, 15). As previously described in prior work (15), patients received written information on the study's goals and design and on the use of their medical data before inclusion. In accordance with French laws, written consent was not required, and the study was approved by the Institutional Review Board of the French Society for Respiratory Medicine (Société de Pneumologie de Langue Française #2020-003).

Criteria for entering the adult early access program have been described previously (15) and were as follows: *1*) having at least one Phe508del mutation and *2*) having advanced respiratory disease characterized by a percentage predicted forced expiratory volume in 1 second ($ppFEV_1$) $<$40 and/or undergoing a pretransplant assessment (16). Lung transplantation candidates at the initiation of ETI were defined as patients already listed for lung transplantation or considered eligible for inclusion on the waiting list within the next 3 months by their referral physicians. All patients who started triple combination therapy were to have scheduled visits (including clinical assessment and pulmonary function tests) at treatment initiation, at 1, 3, 6, and 12 months after initiation, and every 6 months thereafter.

Data on demographic characteristics, *CFTR* variants, and pancreatic insufficiency were collected at treatment initiation. As previously described in prior work (15), clinical data collected at each visit included $ppFEV_1$, BMI, pulmonary bacterial colonization obtained using sputum culture, number of intravenous (i.v.) antibiotic days and hospitalization days since the last visit, comorbidities, maintenance medications, long-term oxygen therapy, and noninvasive ventilation (NIV). Severe CF liver disease was defined by the presence of portal hypertension (esophageal varices) and/or cirrhosis (17). Hemoptysis was recorded from medical records. The results of the recommended laboratory tests (alanine aminotransferase, aspartate aminotransferase, bilirubin, and creatine phosphokinase) were also collected, as were treatment-related adverse events (as documented in patients' charts by their referring physicians). Liver function testing and measurement of creatine phosphokinase were recommended before the initiation of ETI, at 1, 3, 6, and 12 months after the initiation of ETI, and every 6 months

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thereafter. Other blood measurements were recommended before the initiation of ETI and at annual visits. Results were analyzed according to the Grading of the common toxicity criteria for adverse events (CTCAE) (18). Lung transplantation candidate status (wait-listed, eligible, or no longer meeting criteria) was also recorded at each visit.

Statistical Analysis

Data are presented as number (percentage), median (interquartile range [IQR]), mean (95% confidence interval [CI]), or mean (standard deviation). Change from initiation in $ppFEV_1$ was examined using mixed model for repeated measures with covariates (age quartiles or sex). Changes in weight and BMI between treatment initiation and the end of the follow-up period were evaluated using the Wilcoxon signed rank test. The proportions of patients treated with long-term oxygen therapy and/or NIV and/or with chronic oral/inhaled therapies at initiation and at each time point during the 12 months after initiation were compared using the McNemar paired test. *P* values <0.05 were considered to indicate statistical significance in all analyses, which were performed using SAS 9.4 software (SAS Institute Inc.).

Results

Study Population

From December 24, 2019, and June 30, 2021, 435 adults (age $\geq$ 18 yr) with advanced CF initiated ETI at 31 CF centers. One patient had no data available at initiation or at any subsequent point. Characteristics of the 434 adults with advanced CF at the time of ETI initiation are shown in Table 1. The study population was composed of adults with low lung function (median [IQR] $ppFEV_1$, 30 [25–35]), with 40.6% treated with long-term oxygen therapy and 24.1% receiving NIV. Patients exhibited high rates of comorbidities, including severe CF liver disease in 27 (6.2%; Child-Pugh class A, $n = 24$; Child-Pugh class B, $n = 3$) and diabetes in 183 (43.8%). At ETI initiation, 30% of pwCF were treated with previous CFTR modulators (mostly lumacaftor–ivacaftor), and 70% were receiving no modulator therapy. Only 121 of 209 (57.8%) of Phe508del homozygous pwCF were receiving lumacaftor–ivacaftor at the time of ETI initiation, presumably because of high rates of discontinuation of lumacaftor–ivacaftor because of adverse events in pwCF and advanced lung disease (19).

Table 1. Characteristics of 434 adults with cystic fibrosis and advanced lung disease at elexacaftor–tezacaftor–ivacaftor initiation

Age, yr	31 (24–38)
Female sex	214 (49.3)
CFTR variants	
Phe508del/Phe508del	209 (48.2)
Phe508del/Others	225 (51.8)
Pancreatic insufficiency	409 (94)
$ppFEV_1$	30 (25–35)
BMI, kg/m^2	19 (18–21)
Chronic airway infection	
Pseudomonas aeruginosa	312 (72.9)
MSSA	139 (32.6)
MRSA	37 (8.6)
Burkholderia cepacia	14 (3.2)
Diabetes mellitus	
None	244 (56.2)
Insulin treated	154 (35.5)
Treated without insulin	36 (8.3)
Cirrhosis/portal hypertension	27 (6.2)
Child-Pugh class A	24 (5.5)
Child-Pugh class B	3 (0.7)
Previous liver transplantation	3 (0.7)
i.v. antibiotic days in the previous 12 mo	42 (14–66)
Hospitalization days in the previous 12 mo	6 (0–22)
Maintenance pulmonary medications at baseline	
Azithromycin	288 (66.4)
Inhaled antibiotics	300 (69.1)
Dornase alfa	246 (56.7)
Inhaled hypertonic saline	65 (15.0)
Inhaled corticosteroids	234 (53.9)
Oral corticosteroids	50 (11.5)
CFTR modulators at initiation	
Lumacaftor–ivacaftor	121 (27.9)
Tezacaftor–ivacaftor	5 (1.2)
Ivacaftor	4 (0.9)
None	304 (70.0)
Long-term oxygen therapy	176 (40.6)
Noninvasive ventilation	105 (24.1)
Enteral tube feeding	55 (12.7)
On waiting list for lung transplantation	18 (4.1)
Inclusion on waiting list for lung transplantation considered within the next 3 mo	51 (11.8)

Definition of abbreviations: BMI = body mass index; CFTR = cystic fibrosis transmembrane conductance regulator; i.v. = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; $ppFEV_1$ = percentage predicted forced expiratory volume in 1 second.
Data are presented as median (interquartile range) or *n* (%).

ETI was initiated at the standard recommended dose (morning dose: two elexacaftor 100-mg, tezacaftor 50-mg, and ivacaftor 75-mg tablets; evening dose: one ivacaftor 150-mg tablet) in 413 (95.2%) patients and at reduced doses in 21 (4.8%) patients because of liver disease ($n = 7$), drug–drug interaction ($n = 11$), low body weight ($n = 1$), or unspecified reasons ($n = 2$).

Lung Transplantation, Death, and Treatment Discontinuation

At the time of database extraction on August 8, 2022, 422 of 434 (97.2%) pwCF were continuing ETI and 12 of 434 (2.8%) had discontinued ETI. The median (IQR) follow-up duration from ETI initiation was 587 (396–728) days ($n = 434$ patients). Follow-up from ETI initiation was at least 12 months for 411 (94.7%) pwCF, at least 18 months for 306 (70.2%) pwCF, and at least 24 months for 198 (45.4%) pwCF.

Discontinuation of ETI was due to lung transplantation in five patients (1.2%), which occurred within days after the initiation of ETI in two patients and after 8, 17, and 21 months on ETI in the other three patients because of insufficient improvement with ETI. Discontinuation was due to death without transplantation in four patients

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(0.9%), which occurred at 2, 6, 19, and 21 months after the initiation of ETI and was related to acute respiratory failure in three cases and septic shock with multiple organ failure in one case. All four deceased patients had significant extrapulmonary comorbidities: severe CF liver disease with cirrhosis/portal hypertension ($n = 2$), severe chronic neurological disorder ($n = 1$), and severe psychiatric disease with poor adherence to all treatments ($n = 1$). None of these patients were listed for lung transplantation: three patients were considered to have contraindications to transplantation due to neurological or psychiatric disorders and/or poor adherence to medications, and the last patient was evaluated for lung and liver transplantation but was considered too sick to be listed. Finally, discontinuation was due to other causes in three patients (0.7%): pregnancy ($n = 1$), loss to follow-up after 12 months of ETI ($n = 1$), and myalgia and epilepsy after 2 months of ETI ($n = 1$). A flowchart is shown in Figure E1 in the data supplement.

Adverse Events

Adverse events possibly related to ETI were rare and mild and were managed without discontinuation of ETI. Localized cutaneous rash and/or acne occurred in 8.8% ($n = 38$ of 430 pwCF with follow-up data) and generalized cutaneous rash occurred within the first month of treatment in 3.5% ($n = 15$ of 430). Headache was reported in 9.8% ($n = 42$ of 430), gastrointestinal symptoms in 23.9% ($n = 103$ of 430), and myalgia in 17% ($n = 74$ of 430) of pwCF.

Liver enzymes were measured 1,790 times in 430 pwCF between initiation and 12 months on ETI. Elevated aspartate aminotransferase greater than 5 times the upper limit of normal (ULN; grade 3) occurred in 1.2% of patients ($n = 5$), including one patient with results $>20 \times$ ULN (grade 4). Elevated alanine aminotransferase ($\geq 5 \times$ ULN) occurred in 1.7% ($n = 6$; maximum $10 \times$ ULN). During the first 12 months of treatment with ETI, elevated creatine phosphokinase ($\geq 5 \times$ ULN; grade 3) were found in 16 of 430 (3.7%) pwCF, including 3 patients at $\geq 10 \times$ ULN (grade 4). Additional information on liver and muscular enzyme can be found in the data supplement.

Lung Function and Acute Respiratory Events

After the initiation of ETI, $ppFEV_1$ increased by a mean of +14.2% (95% CI, 13.1–15.4%) at 1 month, a difference that was sustained throughout the observation period (Figure 1A). Although most patients showed increases in $ppFEV_1$, the median (IQR) increase in $ppFEV_1$ was +12.0 (7.00–19.0), indicating high variability in the magnitude of the $ppFEV_1$ response. Age quartile was associated with absolute increase in $ppFEV_1$ (*see* the data supplement text and Tables E0 and E1), with younger age groups showing greater increases in $ppFEV_1$ after ETI initiation (Figure 1B). The increase in $ppFEV_1$ was twice greater in pwCF belonging to the youngest quartile (18–24 yr) than in those belonging to the oldest quartile (38 yr and older) ($P < 0.0001$). No significant difference in $ppFEV_1$ increase was found when comparing pwCF with no modulator therapy at initiation with those switching from other CFTR modulators ($P = 0.75$; Figure 1C). The increase in $ppFEV_1$ was not different in pwCF with or without severe CF liver disease ($P = 0.68$; Figure 1D).

In the year before ETI initiation, 88.5% of patients received i.v. antibiotics versus 26.5% during the first year of treatment with ETI ($P < 0.0001$; $n = 418$). In patients who received i.v. antibiotics, the median (IQR) duration of antibiotics was 42 (14–65) d/patient ($n = 377$) in the 12 months before ETI versus 14 (14–28) d/patient ($n = 110$) in the first year after ETI initiation ($P < 0.0001$). On the basis of these data and a recommended duration of i.v. antibiotics of 14 days, it appears that the reduction in i.v. antibiotics was related both to a reduction in the number of patients receiving i.v. antibiotics and a reduction by approximately 3 times in the exposure to i.v. antibiotics in those who received antibiotics. Similarly, the number of days spent in the hospital and the percentage of patients who were hospitalized were markedly reduced after ETI initiation. Available data on i.v. antibiotics and hospitalization over 24 months are presented in Figure 2. Clinically significant recurrent mild to moderate hemoptysis was present in 46 of 414 (11%) of patients in the year before ETI initiation, whereas it was recorded in only 10 of 414 (2.4%) in the first 12 months of treatment with ETI ($P < 0.0001$).

Weight and BMI

Increases in body weight and BMI occurred progressively within the first 12 months after the initiation of ETI and stabilized after 12 months of treatment with ETI (Figure 3). At 12 months of treatment with ETI, the median (IQR) increase in body weight was +6.0 (+3.6 to +9.0) kg, corresponding to a median (IQR) increase in BMI of +2.2 (+1.2 to +3.2) kg/m^2 ($n = 407$ pwCF).

A Sankey diagram showing the evolution of the percentage of pwCF belonging to BMI classes (underweight, normal weight, overweight, and obese) over the first 12 months of treatment with ETI is presented in Figure 4. Importantly, 38.6% of PwCF were underweight (BMI $< 18.5\ kg/m^2$) at ETI initiation versus 11.3% at 12 months of treatment with ETI ($P < 0.0001$); at that time, most pwCF had normal weight, and 14% had overweight; obesity was found in fewer than 2% of pwCF.

Blood Biology and Sputum Cultures

Results of blood biological measurements at ETI initiation and after 12 months of treatment with ETI are shown in Table 2. Neutrophils and platelets were elevated in a subset of patients at ETI initiation and decreased at 12 months; blood concentrations of vitamins A and E, but not in 25-hydroxy vitamin D_3 ($25OHD_3$), increased with ETI. Glycated hemoglobin (HbA_{1c}) decreased in pwCF with and those without diabetes.

Sputum cultures for bacteria, nontuberculous mycobacteria (NTM), and fungi were recommended at the initiation of ETI and at the four visits during the first year after ETI initiation. At initiation, the percentage of pwCF with available sputum samples cultured for bacteria, NTM, and fungi were 83.3%, 53.0%, and 65.8%, respectively. At the subsequent visits, each of these was decreased by approximately 20% in absolute value, which was related to the reduced ability of pwCF treated with ETI to produce spontaneous sputum samples. During the first year after the initiation of ETI, no sputum samples were available for 41 (9.5%) pwCF for bacterial culture, 54 (12.4%) for NTM culture, and 49 (11.3%) for fungal culture. Table 3 shows the comparison of microbial results during the 12 months before and the 12 months after ETI initiation. Most patients with positive sputum cultures for *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Haemophilus influenzae* or *Burkholderia cepacia* before ETI had positive cultures for these bacteria within the 12 months after the initiation of ETI. These were more important reductions in the percentage of patients with positive cultures for *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, NTM, and *Aspergillus fumigatus* when treated with ETI.

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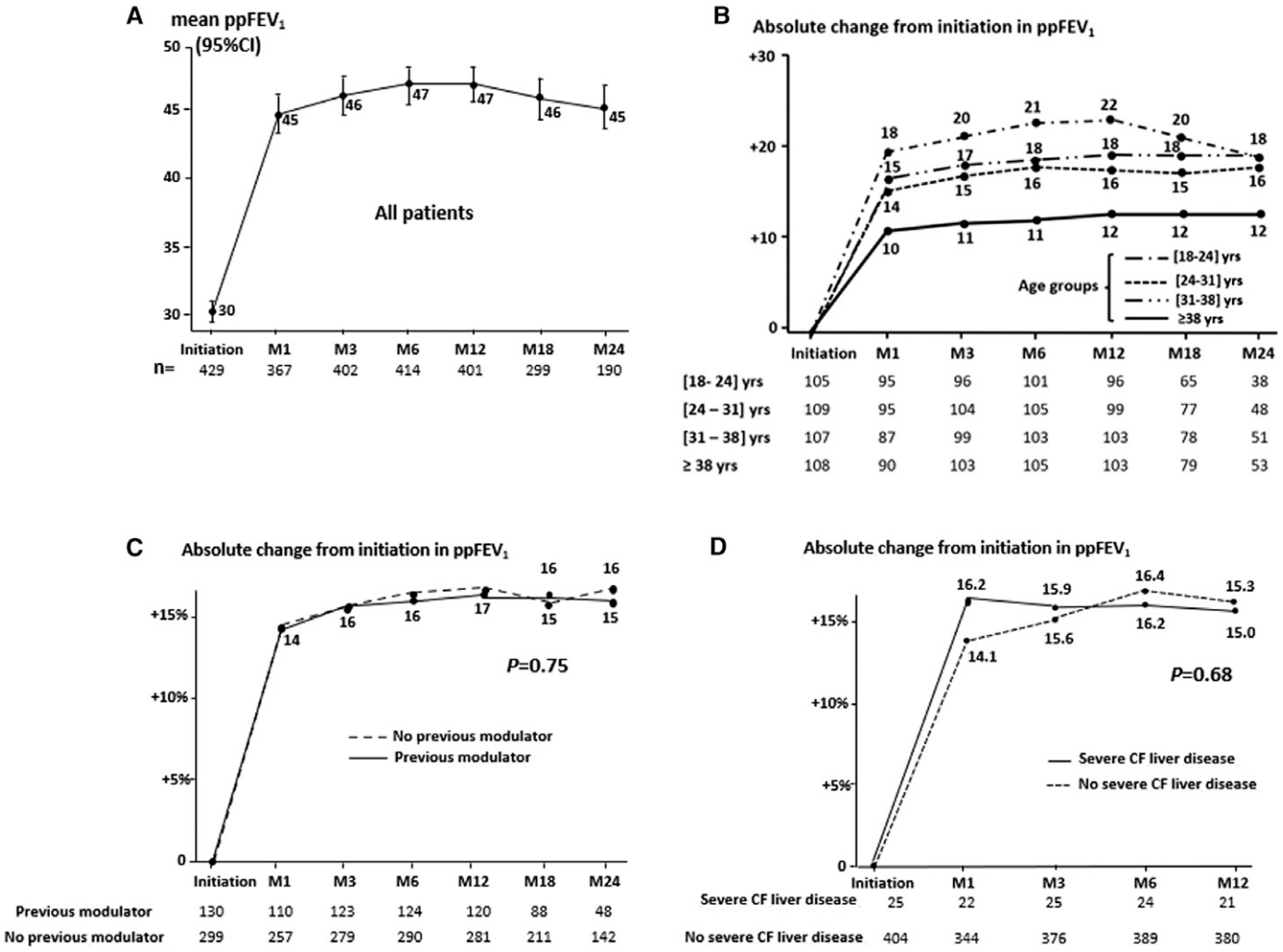

Figure 1. Absolute change in percentage predicted forced expiratory volume in 1 second ($ppFEV_1$) in people with cystic fibrosis (pwCF) and advanced lung disease after the initiation of elexacaftor–tezacaftor–ivacaftor (ETI). (*A*) All pwCF ($n = 430$). Data are shown as least squares means, and error bars show 95% CI. (*B*) Comparison of absolute change in $ppFEV_1$ by age quartiles. For all comparisons, $P < 0.001$ (*see* the data supplement for details). (*C*) Comparison of change in $ppFEV_1$ between pwCF treated with other cystic fibrosis transmembrane conductance regulator (CFTR) modulators and those with no CFTR modulator therapy at ETI initiation. No significant difference was found ($P = 0.75$) (*D*) Comparison of change in $ppFEV_1$ between pwCF with severe liver disease and those without severe liver disease; no significant difference was found ($P = 0.68$). Numbers of available data at each time point are indicated below the graphs. In (*D*), the analysis is limited to the first 12 months after ETI initiation because of small numbers in the group with severe CF liver disease after 12 months. CF = cystic fibrosis; CI = confidence interval; M = month.

Changes in Other Therapies

The percentage of pwCF who were prescribed long-term oxygen was 40.5% at ETI initiation and decreased to 13.8% and 5% at 12 and 24 months of treatment with ETI, respectively. The percentage of pwCF treated with NIV was 24.0% at ETI initiation and decreased to 10.9% and 9.6% at 12 and 24 months, respectively. The percentage of those prescribed enteral tube feeding was 12.6% at ETI initiation and decreased to 2.9% and 2.5% at 12 and 24 months, respectively. The kinetics of discontinuation of long-term oxygen, NIV, and enteral tube feeding over the first 24 months after ETI initiation are shown in Figure E2.

The percentages of pwCF who were prescribed inhaled or oral CF therapies at ETI initiation and at 12 months of treatment with ETI are shown in Table 4. At the 12-month visit, the percentage of pwCF who were prescribed inhaled antibiotics was reduced by 35–45% compared with initiation; prescription rates of mucolytics were reduced by 31.6% for dornase alfa and by 50% for hypertonic saline. The percentage of pwCF using oral therapies was reduced by 16.9% for azithromycin, by 30.6% for oral steroids, and by 53.5% for oral nutritional supplements. There were minimal or no changes in the percentage of pwCF who were being prescribed inhaled long-acting bronchodilators, inhaled corticosteroids, proton pump inhibitors, ursodeoxycholic acid, and pancreatic enzyme replacement therapy.

Of 416 pwCF with follow-up data at 12 months of treatment with ETI, 183 (44%) had diagnosed diabetes; insulin was

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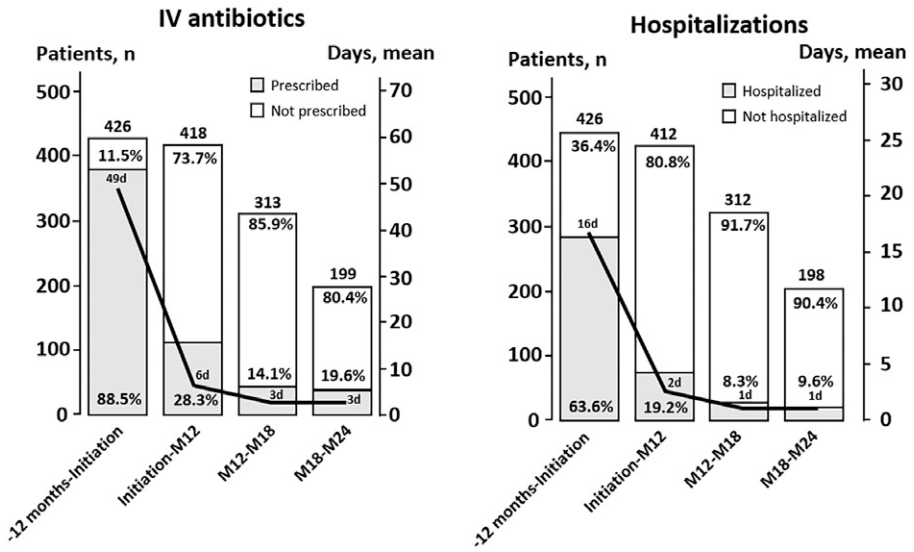

Figure 2. Use of IV antibiotics (left) and hospitalizations (right) in the 12 months before elexacaftor–tezacaftor–ivacaftor (ETI) initiation and in the 24 months after ETI initiation. IV = intravenous; M = month.

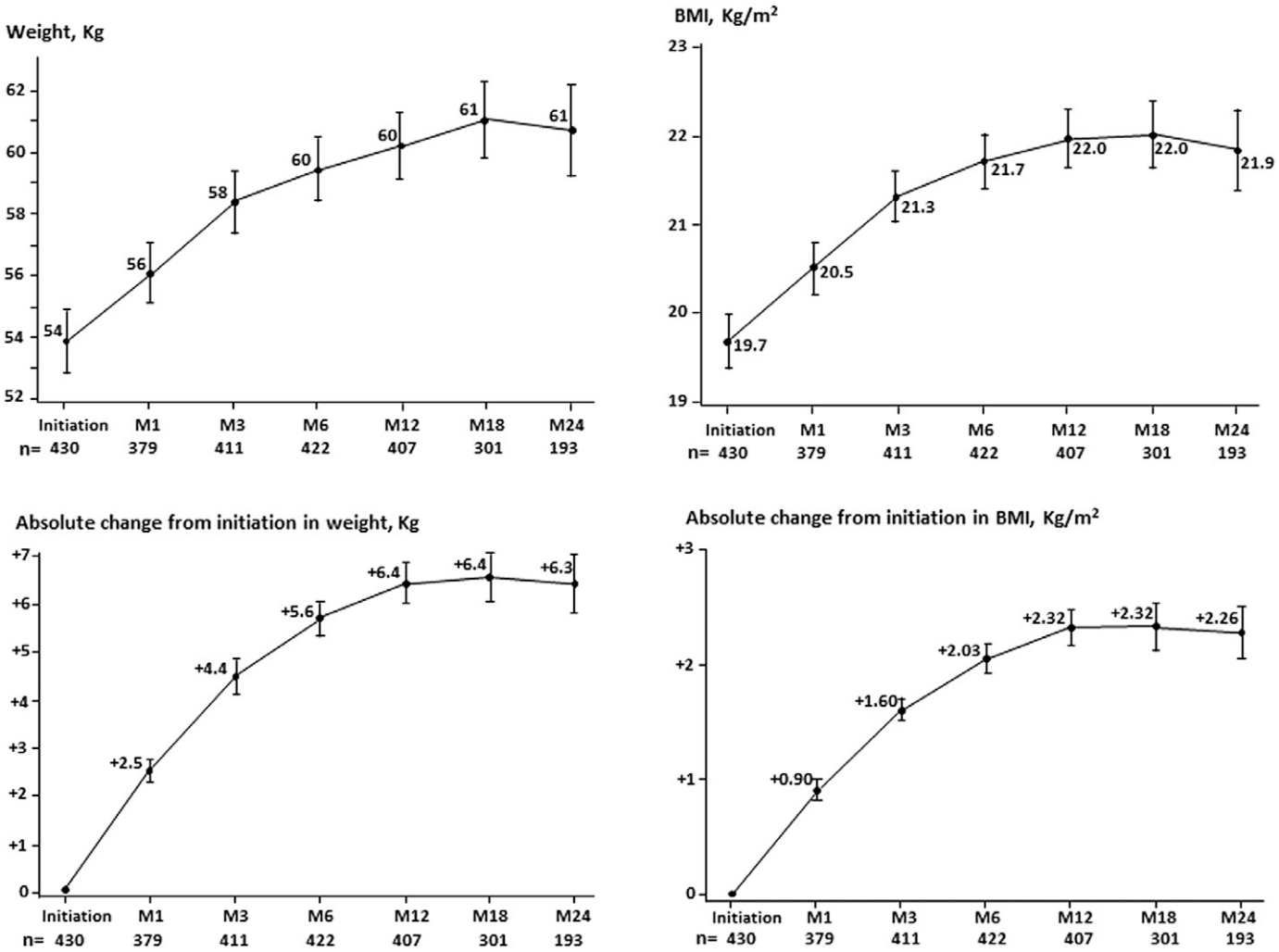

Figure 3. Evolution of body weight and BMI during the 24 months after the initiation of elexacaftor–tezacaftor–ivacaftor (ETI). Data are shown as absolute values (top) or absolute changes from ETI initiation (bottom). BMI = body mass index; M = month.

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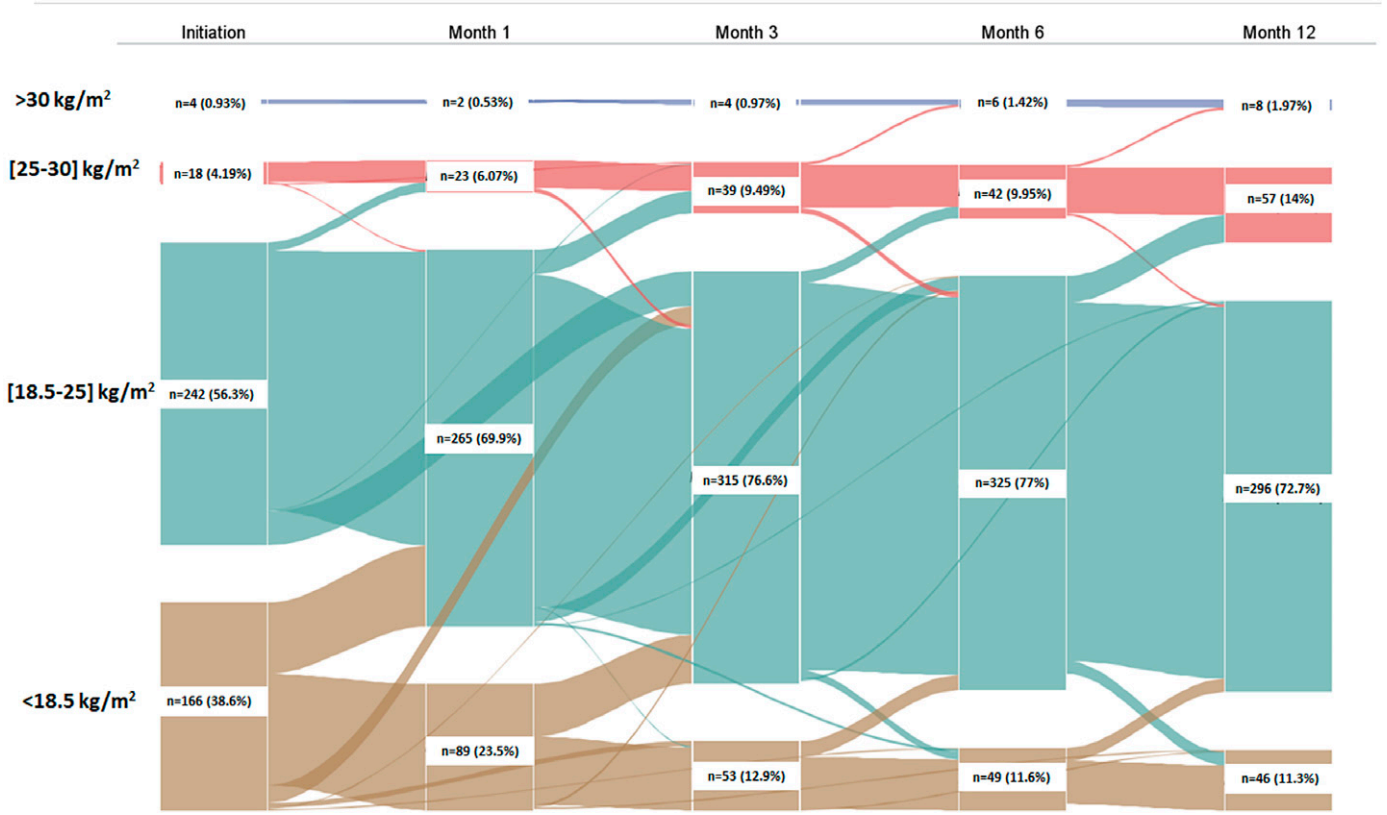

Figure 4. Sankey diagram depicting the evolution of the distribution of body mass index (BMI) classes in 430 people with cystic fibrosis and advanced lung disease during the first 12 months after elexacaftor–tezacaftor–ivacaftor initiation. BMI classes were underweight (<18.5 kg/m^2), normal weight (⩾18.5–25 kg/m^2), overweight (⩾25–30 kg/m^2), and obese (>30 kg/m^2). Percentages are calculated on the basis of the number of available data at each time point.

prescribed in 151 of 183 patients with diabetes (83%) at ETI initiation, whereas 32 (17%) had no insulin therapy. During follow-up, 4 (2%) patients with diabetes received new prescriptions for insulin and 22 (12%) patients discontinued insulin; of those who discontinued insulin, 10 patients were receiving low-dose insulin at initiation, which was stopped because of recurrent hypoglycemia; 12 patients stopped insulin on their own despite medical advice to continue insulin therapy.

Discussion

In the present study, we prospectively followed all adults with CF with advanced lung disease treated with ETI in France over a median time period of 19 months. Our data indicate sustained pulmonary effects, with improvements in lung function, low rates of i.v. antibiotics, decreases in the need for oxygen therapy and ventilatory support, and low rates of death and lung transplantation. The data further show multiple extrapulmonary effects, with increases in body weight, increases in vitamin A and E blood concentrations, reductions in blood inflammatory markers (e.g., leukocytes, platelets, serum immunoglobulin E), and decreases in HbA_{1c}. Reduced prevalence of certain pathogens seen in sputum microbiology are interpreted cautiously but are most notable for non-*Pseudomonas* bacterial species. Altogether, these data improve the characterization of pwCF with advanced lung disease treated with ETI.

Our data indicated rapid improvement in $ppFEV_1$ after the initiation of ETI in pwCF with advanced lung disease, confirming previous findings (10, 14). Importantly, there was marked heterogeneity in the magnitude of $ppFEV_1$ improvement after ETI initiation. Improvement in $ppFEV_1$ was greater in younger pwCF, compatible with the hypothesis that $ppFEV_1$ improvement in response to CFTR modulators is related to a decrease in mucus plugging (20, 21) and that irreversible lesions (e.g., small airway fibrosis and destruction) occur in older subjects (22), limiting the effect of modulators on lung function. In the PROMISE study, which included adolescents and adults with less advanced lung disease and less lung structural damage, no relationship was reported between age at initiation and improvement in $ppFEV_1$ after the initiation of ETI (7). Improvement in $ppFEV_1$ was not different when comparing patients with CFTR modulators (mostly lumacaftor–ivacaftor) at the initiation of ETI with those with no modulator therapy, contrasting with the results of randomized clinical trials (4) and observational studies (7). This result may not be surprising, as lumacaftor–ivacaftor induced no improvement in $ppFEV_1$ in patients with advanced lung disease (23). Further factors contributing to the variability in $ppFEV_1$ increase with ETI may include genetic factors (in both *CFTR* and gene modifiers), adherence, and differences in pharmacokinetics/pharmacodynamics. Finally, our data complement recent

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Table 2. Comparison of biological variables at ETI initiation and after 12 months of treatment

	ETI Initiation		12-mo ETI		Paired Difference		*P* Value*
Leukocytes, $\times 10^9$/L	$n = 386$	9.6 (7.4 to 12.4)	$n = 336$	7.1 (5.7 to 8.7)	$n = 325$	−2.3 (−4.9 to −0.3)	<0.0001
Hemoglobin, g/dl	$n = 385$	13.4 (12.5 to 14.5)	$n = 337$	14.2 (13.2 to 15.3)	$n = 325$	+0.6 (−0.4 to +1.5)	<0.0001
Platelets, $\times 10^9$/L	$n = 385$	337 (274 to 422)	$n = 336$	262 (217 to 316)	$n = 325$	−67 (−127 to −24)	<0.0001
HbA_{1c}, %							
All pwCF ($n = 434$)	$n = 270$	6.2 (5.8 to 6.6)	$n = 285$	5.6 (5.4 to 6.1)	$n = 212$	−0.4 (−0.7 to −0.1)	<0.0001
No diabetes at initiation ($n = 226$)	$n = 148$	5.9 (5.6 to 6.2)	$n = 159$	5.5 (5.2 to 5.7)	$n = 118$	−0.4 (-0.6 to −0.2)	<0.0001
Diabetes at initiation ($n = 178$)	$n = 122$	6.6 (6.2 to 7.3)	$n = 126$	6.2 (5.6 to 7.1)	$n = 94$	−0.4 (-0.9 to −0.1)	<0.0001
Vitamin A, μmol/L	$n = 234$	1.3 (0.9 to 1.7)	$n = 256$	1.8 (1.4 to 2.1)	$n = 175$	+0.4 (+0.1 to +0.8)	<0.0001
Greater than upper limit of normal, *n* (%)	2 (0.9)		5 (2.0)				0.45†
Vitamin E, μmol/L	$n = 233$	19.9 (14.4 to 26.9)	$n = 253$	21.5 (16.1 to 28.2)	$n = 172$	+1.6 (−1.9 to +6.4)	0.0006
Greater than upper limit of normal, *n* (%)	18 (7.7)		19 (7.5)				1†
$25OHD_3$, nmol/L	$n = 240$	59.0 (39.5 to 81.7)	$n = 263$	59.9 (37.1 to 78.0)	$n = 179$	0 (−13.0 to +14.6)	0.50
Greater than upper limit of normal, *n* (%)	0		0				
Total IgE	$n = 247$	63.0 (22.0 to 195.0)	$n = 270$	33.3 (11.6 to 98.8)	$n = 184$	−20.2 (−81.9 to −2.2)	<0.0001
Aspergillus IgE (M3)	$n = 230$	0.2 (0 to 3.0)	$n = 247$	0.1 (0 to 1.6)	$n = 168$	0 (−1.8 to 0)	<0.0001

Definition of abbreviations: $25OHD_3$ = 25-hydroxy vitamin D_3; ETI = elexacaftor–tezacaftor–ivacaftor; HbA_{1c} = glycated hemoglobin; IgE = immunoglobulin E; pwCF = people with cystic fibrosis.

Data are expressed as median (interquartile range) except as indicated. Normal values for vitamin concentrations are as follows: vitamin A, 1.55–3.30 μmol/L; vitamin E, 21–35 μmol/L; and $25OHD_3$, 25–137.5 nmol/L (recommended value >50 nmol/L).

*Data were analyzed using the paired McNemar test.

†Fischer exact test.

observations indicating improved $ppFEV_1$ in pwCF with less advanced lung disease over a 3-year period (24).

The initiation of ETI was associated with weight gain during the first year of treatment, which stabilized during the second year with ETI. The mean increase in body weight at 12 months was +6.4 kg, corresponding to a 2.32 kg/m^2 increase in BMI. The main effect was a reduction in the number of underweight subjects, with a corresponding increase in the size of the normal weight population. These effects occurred despite a decrease of ∼50% in the number of patients using nutritional oral supplements and the discontinuation of enteral tube feeding in most patients over the first year after ETI initiation. Overweight and obesity remained rare findings, although they increased with ETI in this population of French subjects with advanced lung disease. These findings are somewhat different from those reported by Petersen and colleagues, who reported marked increases in overweight and obesity (reaching 31.3% and 9.7%) in 134 adults with CF treated for 12 months at a single U.S. center (25). Differences are likely related to a population with less advanced disease in this latter study. Nevertheless, metabolic changes in ETI treated pwCF should be carefully monitored to prevent complications.

The initiation of ETI was associated with a substantial reduction in treatment burden. This reduction consisted of reductions in oxygen therapy, NIV, and enteral feeding, confirming our previous findings (14, 15). Therapies directed at improving mucociliary clearance, including dornase alfa (reduced by ∼30%) and hypertonic saline (reduced by ∼50%, but barely used in France), were also decreased. Our data further revealed a major decrease in antibiotic exposure characterized by a reduction in the prescription of inhaled and i.v. antibiotics and long-term azithromycin; the use of other oral antibiotics was not recorded. These data are in marked contrast with our present finding that *P. aeruginosa* persisted in most pwCF, which confirmed recent data obtained in pwCF with less advanced lung disease (26). The finding of a reduction in the positivity of sputum cultures for other bacteria (e.g., *S. maltophilia*, *A. xylosoxidans*, NTM) should be interpreted with caution, as it may represent a true reduction in bacterial infection and/or load but may also be related to a reduced number of available sputum samples in pwCF treated

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Table 3. Comparison of sputum cultures for bacteria, nontuberculous mycobacteria, and fungi between the 12 months before and the 12 months after ETI initiation

	12 mo before ETI	12 mo Treatment with ETI	*P* Value
Bacteria			
Number of samples/patient, median (IQR)	6 (4–8)	3 (2–4)	<0.0001*
Number of patients with at least one sample	426	365	<0.0001†
Number of patients with paired (before/treated with ETI) samples		364	
Percentage of patients with at least one positive sample in patients with paired samples			
Pseudomonas aeruginosa	81.9	73.4	<0.0001‡
MSSA	51.1	40.9	0.0002‡
MRSA	17.3	9.1	<0.0001‡
Achromobacter xylosoxidans	20.1	11.8	<0.0001‡
Stenotrophomonas maltophilia	17.0	2.8	<0.0001‡
Haemophilus influenzae	6.3	5.2	0.57‡
Burkholderia cepacia complex	3.0	2.8	1‡
Nontuberculous mycobacteria			
Number of samples/patient, median (IQR)	4 (2–6)	2 (1–3)	<0.0001*
Number of patients with samples	386	258	<0.0001†
Number of patients with paired (before/treated with ETI) samples		249	
Percentage of patients with at least one positive sample in patients with paired samples			
M. avium complex	3.6	0	§
M. abscessus complex	4.8	1.6	0.02‡
Other species‖	0.8	0.8	1.0‡
Fungi			
Number of samples/patient, median (IQR)	5 (3–7)	2 (1–3)	<0.0001*
Number of patients with samples	410	303	<0.0001†
Number of patients with paired (before/treated with ETI) samples		293	
Percentage of patients with at least one positive sample in patients with paired samples			
Aspergillus fumigatus	57.7	17.4	<0.0001‡

Definition of abbreviations: ETI = elexacaftor–tezacaftor–ivacaftor; IQR = interquartile range; *M. abscessus* = *Mycobacterium abscessus*; *M. avium* = *Mycobacterium avium*; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; pwCF = people with cystic fibrosis.

Data are presented as number of pwCF; median (IQR) number of sputum samples or percentage of pwCF with paired samples with at least one positive sputum culture in the year before ETI or in the year treated with ETI.

*Data were analyzed using the paired Wilcoxon test.

†Data were analyzed using the chi-square test.

‡Data were analyzed using the paired McNemar test.

§Not testable.

‖Other species included *Mycobacterium peregrinum*, *Mycobacterium xenopi*, *Mycobacterium llatzerense*, and *Mycobacteroides salmoniphilum*.

with ETI. Longer follow-up, which will allow an increased number of sputum samples in culture, will be necessary to fully understand the effects of ETI on lung bacterial infection. Future studies are needed in this area to determine whether pursuing high systemic and/or inhaled antibiotic exposure may lead to lesser decline in $ppFEV_1$ in pwCF treated with CFTR modulators.

PwCF with severe CF liver disease, who represent ~5–10% of the CF population (27), are usually excluded from clinical trials because of fear of increased adverse events. Our data, obtained in patients with Child-Pugh class A and a limited number with Child-Pugh class B cirrhosis, indicated that patients with severe CF liver disease derived comparable benefits with an acceptable safety profile. Two patients with liver cirrhosis died during follow-up, and one underwent lung and liver transplantation. Although these events were not ascribed to adverse effects of ETI, these data indicate that patients with advanced lung disease and severe liver disease remain at elevated risk of complication despite ETI.

Serum concentrations of vitamin A and E increased on ETI treatment, but it remains unclear whether these findings are indeed related to ETI. A new multivitamin supplement (DEKA; Callion Pharma) was made available for pwCF in France at the end of June 2022, which had a minimal impact on vitamin concentrations in this study, in which data were extracted on August 8, 2022. Importantly, serum concentrations of $25OHD_3$ remained unchanged. Maintaining a high concentration of $25OHD_3$, which is recommended for maintaining bone health (28), remains a challenge in the era of highly effective CFTR modulators. These results are somewhat different from those recently reported by Hergenroeder and colleagues in a retrospective study of vitamin concentrations obtained up to 4 years before ETI initiation and up to 2 years after ETI initiation in 264 pwCF aged 12 years and older (29). These authors reported significant increase sin vitamin A and D concentrations, but not in vitamin E. The reasons for these differences remain unclear, and further studies will be necessary to understand the effects of ETI on vitamin concentrations. HbA_{1c} improved in patients with and those without diabetes. This findings, which suggest improvement in glycemic control, could be related to a reduction in insulin

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Table 4. Prescriptions of long-term therapies at 12 months after the initiation of ETI

Therapy	At ETI Initiation	At 12 mo Treatment with ETI	Absolute Change	Relative Change	*P* Value*
Inhaled therapies ($n = 413$ patients)					
Inhaled antibiotics					
Any	70.2%	46.0%	−24.2%	−34.5%	<0.0001
Inhaled colistin	52.1%	32.9%	−19.2%	−36.9%	<0.0001
Inhaled tobramycin	31.8%	17.4%	−14.4%	−45.3%	<0.0001
Inhaled aztreonam lysine	11.9%	7.0%	−4.9%	−41.2%	0.0004
Dornase alfa	56.1%	38.3%	−17.8%	−31.6%	<0.0001
Hypertonic saline	14.7%	7.3%	−7.4%	−50.3%	<0.0001
Long-acting bronchodilators	70.0%	66.1%	−3.9%	−5.6%	0.08
Inhaled corticosteroids	49.1%	53.5%	+4.4%	+9.0%	0.05
Oral therapies ($n = 415$ patients)					
Oral steroids	10.8%	7.5%	−3.3%	−30.6%	0.03
Azithromycin	67.0%	55.7%	−11.3%	−16.9%	<0.0001
Pancreatic enzyme replacement therapy	92.8%	92.8%	0	0	1
Ursodeoxycholic acid	32.1%	30.8%	−1.3%	−4.0%	0.45
Oral nutritional supplements	46.0%	21.4%	−24.6%	−53.5%	<0.0001
Proton pump inhibitors	53.3%	50.1%	−3.2%	−6.0%	0.13
Insulin ($n = 181$ patients with diabetes)					
Insulin	81.2%	65.8%	−15.4%	−19.0%	0.0001

Definition of abbreviation: ETI = elexacaftor–tezacaftor–ivacaftor.
*Data were analyzed using the paired McNemar test.

resistance (e.g., due to decreased inflammatory status, as suggested by reductions in blood leukocyte counts) and/or to an improvement in CFTR-dependent insulin secretion (30). Most patients with diabetes treated with insulin at the initiation of ETI remained treated with insulin; daily doses of insulin were highly variable among and within patients with no specific pattern of evolution on ETI treatment. An unexpected finding was that 12% of patients with diabetes discontinued insulin during the first 12 months of ETI treatment; although insulin discontinuation was related to less need for insulin with the occurrence of hypoglycemia on insulin in about half of these patients, other patients sought to discontinue insulin despite the lack of evidence of improvement in diabetic control. These data indicate that ETI does not reverse established diabetes in most adults with CF and advanced lung disease. Of note, very few patients received new prescriptions for insulin, and further investigation will be necessary to determine the impact of ETI on preventing diabetes.

Strengths and Limitations

The present study has several strengths, including its prospective design with the inclusion of an unselected population composed of all adults with CF with advanced lung disease who initiated ETI in France. The relatively large number of patients made it possible to study subgroups and patients with concomitant rare comorbidities (e.g., severe CF liver disease). The evaluation process was standardized and followed recommendation from the French Cystic Fibrosis Society. However, the study was purely observational, with no control group, limiting the possibility of deriving definitive causality between ETI and measured outcomes. Although nearly all pwCF included in this study were White, no data were available on race/ethnicity, as these data were not collected at the beginning of the study because of legal restrictions in France. As part of the study was conducted during the initial phase of the coronavirus disease (COVID-19) pandemic, some of the data (especially those regarding exacerbation rates) may have been affected by the pandemic. There were some missing data, especially for biological measurements; missing data were minimal for most outcomes and had limited influence on our conclusions. Reductions in other treatments were based on physician prescriptions and may have underestimated the true reduction in treatment use by pwCF. Another limitation relates to the absence of exploratory outcomes (e.g., related to the infection/inflammatory process, glycemic control, or evaluation of lung imaging or liver structure and function) that are not used in daily practice.

Conclusions

The initiation of ETI was associated with multisystem pulmonary and extrapulmonary benefits in pwCF with advanced lung disease, but with persistent abnormalities, including incomplete recovery of lung function, limited clearance of chronic airway infection, and limited improvement in extrapulmonary comorbidities (e.g., diabetes and severe liver disease). These data indicate that CFTR modulators are not improving all aspects of established pulmonary and extrapulmonary disease and concur to promote the initiation of CFTR modulators earlier in the disease process. Although death without transplantation and lung transplantation were infrequent in the present study, their occurrence over a short period of observation indicates that pwCF and advanced lung disease treated with ETI should undergo careful long-term monitoring with the aim of preventing further deterioration of health status and proposing timely referral for lung transplantation in accordance with current recommendations (31–33). ■

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