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Elexacaftor/tezacaftor/ivacaftor—real-world clinical effectiveness and safety. A single-center Portuguese study

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ABSTRACT

Objective: To evaluate the effectiveness of treatment with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) and to characterize its safety profile in cystic fibrosis (CF) patients in a real-world clinical setting. **Methods:** This was a prospective observational study carried out in a CF referral center in Portugal involving adult CF patients who started treatment with ELX/TEZ/IVA. Clinical characteristics of the patients were collected, and effectiveness and safety data were evaluated. **Results:** Of the 56 patients followed in the center at the time of the study, 28 were eligible for ELX/TEZ/IVA treatment in accordance with the Portuguese National Authority for Medicines and Health Products at the time of the study. Of these, 24 met the follow-up time requirement to be included in the clinical effectiveness analysis. The mean follow-up time was 167.3 ± 96.4 days. Adverse events were generally mild and self-limited. Significant improvements in lung function, BMI, sweat chloride concentration, and number of pulmonary exacerbations were observed. No significant differences in outcomes between F508del homozygous and heterozygous patients were found. The effectiveness of this new CFTR modulator combination also applied to patients with advanced lung disease. **Conclusions:** Treatment with ELX/TEZ/IVA showed effective improvement in real-world clinical practice, namely in lung function, BMI, sweat chloride concentration, and number of pulmonary exacerbations, with no safety concerns.

Keywords: Cystic fibrosis; Cystic fibrosis transmembrane conductance regulator; Membrane transport modulators; Treatment outcome.

INTRODUCTION

Cystic fibrosis (CF) is a rare genetic autosomal recessive disease caused by mutations on the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene and, consequently, dysfunction of its protein, leading to multiorgan involvement, namely progressive lung disease and early death.[1] Although there are more than 2.000 *CFTR* mutations described, the most common mutation worldwide, the F508del mutation, is found in nearly 90% of CF patients, of which approximately 50% are homozygous.[2]

The emergence of new CFTR modulator therapies was a turning point in the treatment of CF. In clinical trials of CF patients with at least one F508del mutation, the new CFTR modulator combination, elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) showed significant improvement in clinical outcomes of patients, such as lung function, sweat chloride concentration, and nutritional status.[3,4] These remarkable results and its potential impact on prognosis have led to ELX/TEZ/IVA approval by the U.S. Food and Drug Administration in October of 2019 and by the European Medicines Agency in August of 2020.

Patients with advanced lung disease (FEV_1 < 40% of the predicted value) were excluded from clinical trials, leading to drug approval; however, preliminary data on these patients suggest that they present with significant clinical improvement with ELX/TEZ/IVA as well.[5,6]

In Portugal, the National Authority for Medicines and Health Products (Infarmed) approved ELX/TEZ/IVA on July 22, 2021 for CF patients ≥ 12 years of age and homozygous for the F508del mutation or heterozygous for the F508del mutation and a minimal function mutation.[7]

Real-world data regarding ELX/TEZ/IVA effectiveness are limited, and, although these new CFTR modulators have been well tolerated in clinical trials,[3-5,8] there is also scant real-world data about their adverse events of these new CFTR modulators.

In this study we aimed to identify the clinical and functional outcomes of patients who started treatment with the ELX/TEZ/IVA combination in order to evaluate its effectiveness and safety. Additionally, we intended to characterize the effects of ELX/TEZ/IVA on the CF population with advanced lung disease. The present study also compared the effects of ELX/TEZ/IVA on lung function, BMI, and sweat chloride concentration in F508del homozygous patients vs. F508del heterozygous patients with a minimal function mutation.

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METHODS

We conducted a prospective, observational, single-center study of adult CF patients at the Cystic Fibrosis Center of the Santa Maria Hospital, located in the city of Lisbon, Portugal, who started treatment with ELX/TEZ/IVA. The drug combination was administered in accordance with the general approval of the Infarmed[7] or in specific situations based on early access to a program that Infarmed approved.

All adult patients meeting the requirements of Infarmed for use of this drug combination, as stated before, and who agreed starting treatment with ELX/TEZ/IVA were eligible for inclusion. However, only patients who had at least a minimum of 12 weeks of follow-up after treatment initiation were considered for the clinical effectiveness analysis.

Clinical and functional data were collected at treatment initiation, and then at 4, 12, and 24 weeks after treatment initiation or in a medical visit out of that timeframe (for example, if an exacerbation or side effects due to treatment occurred). The relevant medical history of patients was assessed through revision of their medical records. All data were documented and processed anonymously, a written informed consent was obtained from all patients, and the institutional research ethics committee approved the study (Protocol no. 155/22).

The data collected included age; sex; BMI at baseline and 24 weeks after treatment initiation; *CFTR* genotype; date of treatment initiation; history of treatment with CFTR modulators; baseline lung function (FEV_1) and after 12 to 24 weeks of treatment; laboratory data at baseline (most recent results before ELX/TEZ/IVA treatment initiation) and during follow-up, including sweat chloride test (24 to 48 weeks after baseline), transaminases, and creatine kinase (worst value registered during monitoring every 2-4 weeks after treatment initiation); reported side effects; and occurrence of pulmonary exacerbations.

The study was carried out between March 10, 2021 and February 28, 2022, and all eligible patients evaluated in our center during that period were included in the study, forming a convenience sample.

Statistical analysis was performed with the IBM SPSS Statistics software package, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean and standard deviation, whereas categorical variables were expressed as absolute and relative frequencies. We used t-tests for independent and paired samples, as well as the Wilcoxon test. Significance was set at $p < 0.05$.

RESULTS

During the study period, 56 patients were being treated in the clinic, and 28 were eligible for ELX/TEZ/IVA therapy in accordance with the Infarmed recommendations.[7] Of these, 4 patients were excluded from the clinical effectiveness comparative analysis for not meeting the minimum 12-week follow-up period required.

Figure 1 presents the flow chart of patient recruitment, enrollment, and follow-up. Table 1 summarizes demographic and clinical characteristics of the patients.

At the time of data extraction and analysis on February 28, 2022, the mean follow-up time after treatment initiation was 167,3 ± 96,4 days. Only 9 patients (37.5%) had a history of treatment with lumacaftor/ivacaftor, which is another CFTR modulator combination previously approved in Portugal for CF homozygous F508del patients.

Of the 28 patients in the study, 20 (71.4%) reported having adverse events, mostly during the first week of treatment. Adverse events were headaches, in 12 (42.6%); cutaneous rash, in 6 (21.4%); gastrointestinal symptoms, such as epigastric pain and diarrhea, in 5 (17.6%); neurological symptoms, including vision and sensorial alterations and paresthesia, in 4 (14.3%); new-onset psychiatric disorders, namely depression, dysphoric mood, depersonalization, and bipolar syndrome, in 4 (14.3%); wheezing, in 3 (10.7%); testicular tenderness, in 2 (7.1%); and recurrent bacterial infections, namely tonsillitis, chalazion, and bartholinitis, in 3 (10.7%).

Seven patients had asymptomatic changes in blood tests. Elevated liver transaminases greater than twice the upper limit of normal were seen in 4 (14.3%), but were normalized in up to 3 months, and there was no need for treatment interruption or dose reduction in any of these patients. Creatine kinase levels were increased twice the upper limit of normal in 2, (7.1%), and elevated total bilirubin occurred in 1 (3.6%).

One patient had severe intracranial hypertension and had to be hospitalized, at which point an undiagnosed congenital malformation (Budd-Chiari syndrome) was found that led to an unfavorable clinical course and death. Apart from that patient, adverse events were generally mild and self-limited even in patients with advanced lung disease, neither requiring specific interventions nor dose adjustments of the medication.

Because of the COVID-19 pandemic, several in-person visits and lung function tests could not safely take place as expected and had to be postponed. For that reason, 2 patients were unable to have a lung function revaluation, and 7 were unable to have a sweat chloride test reassessment by the time data were collected.

Significant improvements in terms of lung function, BMI, and sweat chloride concentration were observed, as shown in Table 2. After 12-24 weeks of ELX/TEZ/IVA treatment, FEV_1 in % of predicted and in L, respectively, improved 15.23% (95% CI, 10.51-19.95; $p < 0.001$) and 0.54 L (95% CI, 0.36-0.72; $p < 0.001$). The mean increase in BMI after 24 weeks of treatment was 1.31 kg/m^2 (95% CI, 0.84-1.78; $p < 0.001$). There was also a significant mean decrease

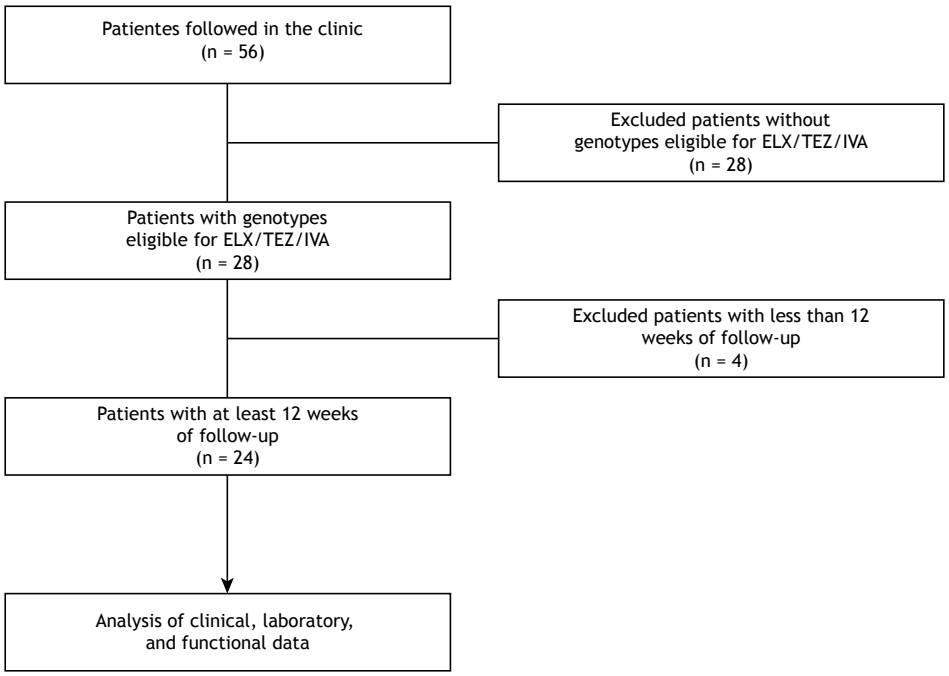

Figure 1. Flow chart of patient recruitment, enrollment, and follow-up.ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor.

Table 1. Clinical and demographic characteristics of the patients included in the study (N = 24).[a]

Characteristic	Result
Sex	
Female	11 (45.8)
Male	13 (54.2)
Age, years	26.9 ± 7.7
BMI, kg/m^2	19.3 ± 1.5
Follow-up time, days	167.3 ± 96.4
CFTR genotype	
Homozygous F508del	13 (54.2)
Heterozygous	11 (45.8)
F508del/R334W	6 (25.0)
F508del/G85E	3 (12.5)
F508del/R1066C	2 (8.3)
Prior CFTR modulator therapy	9 (37.5)
Advanced lung disease[b]	8 (33.3)

CFTR: cystic fibrosis transmembrane conductance regulator. [a]Values expressed as n (%) or mean ± SD. [b]Defined as FEV_1 < 40% of the predicted value.

in sweat chloride concentration (−35.94 mmol/L; 95% CI, −49.65 to −22.24; p < 0.001).

Although FEV_1 improvement was interestingly greater in heterozygous F508del patients when compared with homozygous F508del patients (16.36 vs. 14.10% and 0,58 L vs. 0.50 L), these differences were not statistically significant (p = 0.630 and p = 0.658, respectively; Figure 2). The same was observed for sweat chloride concentration, which had a greater decrease in the heterozygous group than in the homozygous group (−39.56 mmol/L vs −31.88 mmol/L; p = 0.570). However, both groups had the same improvement in BMI (1.31 kg/m^2).

There were 8 patients who were considered as having advanced lung disease, defined as FEV_1 < 40% of predicted, and they were demographically similar to patients with FEV_1 ≥ 40%. These patients also had significant improvements in FEV_1, both in % of predicted (13.28%; 95% CI, 3.97-22.58%; p = 0.012) and in L (0.42 L; 95% CI, 0.16-0.68 L; p = 0.006), as well as in BMI (2.13 kg/m^2; 95% CI, 1.27-2.98; p = 0,001; Table 2). Although there was also a decrease in sweat chloride concentration, that was not statistically significant (−28.83 mmol/L; 95% CI, −63.05 to +5.38; p = 0.083). Moreover, of the 3 patients in the transplantation waiting list, 1 had such a significant improvement with ELX/TEZ/IVA that the indication for lung transplantation was suspended.

Regarding pulmonary exacerbations (Table 3), there were only 3 patients who had pulmonary exacerbations after starting ELX/TEZ/IVA treatment during the study period, only 1 having advanced lung disease who needed hospitalization, compared with 29 patients in the previous year before ELX/TEZ/IVA treatment (p = 0.001), of whom 14 required hospitalization (p = 0.016).

DISCUSSION

Although we have found adverse events more frequently than in previous clinical trials,[3,4,9] most appeared in the first week of treatment and were only minor, self-limited, with no impact on treatment in contrast to what occurred in other studies, in which treatment had to be interrupted.[8] However, 1 of our

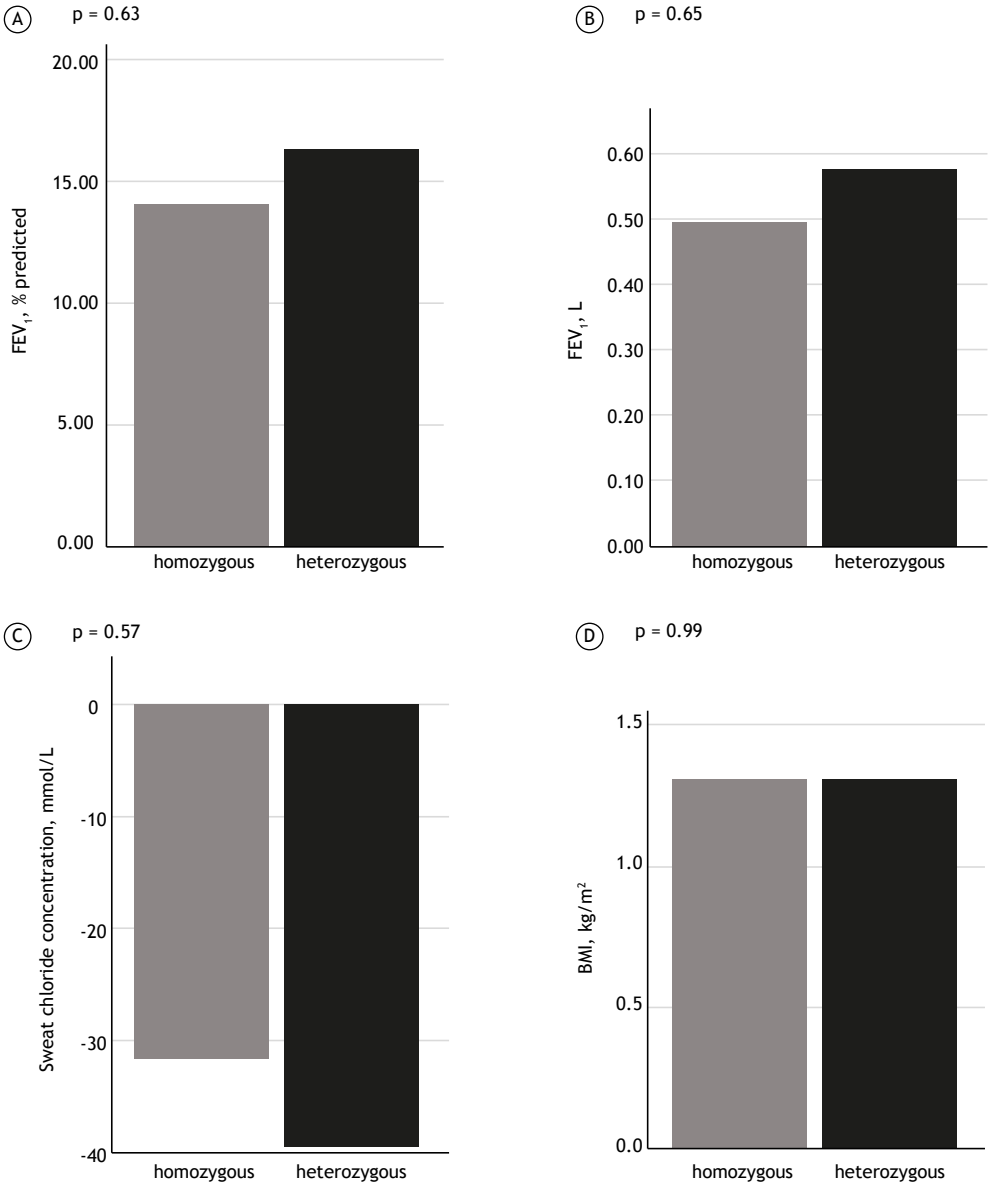

Figure 2. Differences in outcomes between F508del homozygous patients and F508del heterozygous patients with a minimal function mutation, in terms of changes after treatment initiation: in A, FEV_1, % predicted; in B, FEV_1, L; in C, sweat chloride concentration, mmol/L; and in D, BMI, kg/m^2.

patients who had a congenital cranial malformation had severe intracranial hypertension and died. There are some case reports of severe intracranial hypertension following ELX/TEZ/IVA treatment, mainly related to hypervitaminosis A toxicity,[10,11] but with good prognosis despite continuation of treatment with ELX/TEZ/IVA, supporting our belief that our patient's unknown congenital malformation was determinant for the negative outcome.

Blood test alterations have frequently been described[12,13] and the same was seen in our study; however, these changes were all asymptomatic and normalized in up to 3 months without any intervention.

Our results provided clear evidence of ELX/TEZ/IVA effectiveness on lung function in a real-world clinical setting, as shown by an improvement in FEV_1 of 15.23% of predicted and of more than 500 mL within just 12-24 weeks of treatment. Some studies suggested that improvements were larger in those naive for modulators, albeit substantial in all groups,[14] but we did not perform this analysis since only 9 patients in our study had undergone previous treatment with CFTR modulators. Likewise, we found a significant decrease in sweat chloride levels (−35.94 mmol/L) and a significant increase in BMI (1.31 kg/m^2), reflecting the CFTR functional improvement and its association with nutritional status, similarly to other studies.[14-16]

Table 2. Effects of elexacaftor/tezacaftor/ivacaftor treatment on lung function, BMI, and sweat chloride concentrations at baseline and at the end of the follow-up period of the study.

Sample or subgroup	Outcome	Baseline	End of follow-up	Mean difference	p
Overall (n = 24)	FEV_1, % predicted	50.36 (42.27-58.46)	65.60 (56.14-75.05)	15.23 (10.51-19.95)	< 0.001
	FEV_1, L	1.75 (1.41-2.10)	2.29 (1.87-2.71)	0.54 (0.36-0.72)	< 0.001
	Sweat chloride, mmol/L	71.59 (56.29-86.88)	35.65 (25.89-45.40)	−35.94 (−49.65 to −22.24)	< 0.001
	BMI, kg/m^2	19.72 (18.98-20.45)	21.03 (20.23-21.82)	1.31 (0.84-1.78)	< 0.001
Homozygous (n = 13)	FEV_1, % predicted	51.82 (39.52-64.18)	65.92 (51.62-80.22)	14.10 (5.33-22.87)	0.005
	FEV_1, L	1.79 (1.27-2.31)	2.29 (1.66-2.92)	0.50 (0.18-0.82)	0.006
	Sweat chloride, mmol/L	67.88 (40.49-95.26)	36.00 (17.14-54.86)	−31.88 (−55.42 to −8.33)	0.015
	BMI, kg/m^2	19.46 (18.26-20.65)	20.76 (19.51-22.03)	1.31 (0.71-1.90)	< 0.001
Heterozygous (n = 11)	FEV_1, % predicted	48.91 (36.15-61.67)	65.27 (50.23-80.32)	16.36 (10.96-21.77)	< 0.001
	FEV_1, L	1.72 (1.18-2.26)	2.30 (1.62-2.97)	0.58 (0.10-0.33)	< 0.001
	Sweat chloride, mmol/L	74.89 (53.07-96.71)	35.33 (22.60-48.07)	−39.56 (−59.84 to −19.27)	0.002
	BMI, kg/m^2	20.03 (19.07-20.99)	21.34 (20.22-22.46)	1.31 (0.43-2.19)	0.008
Advanced lung disease[a] (n = 8)	FEV_1, % predicted	32.98 (27.81-38.14)	46.25 (32.31-60.19)	13.28 (3.97-22.58)	0.012
	FEV_1, L	1.07 (0.93-1.20)	1.49 (1.12-1.86)	0.42 (0.16-0.68)	0.006
	Sweat chloride, mmol/L	62.50 (33.87-91.13)	33.67 (16.02-51.31)	−28.83 (−63.05 to 5.38)	0.083
	BMI, kg/m^2	18.83 (17.48-20.18)	20.96 (19.43-22.49)	2.13 (1.27-2.98)	0.001

[a]Defined as FEV_1 < 40% of the predicted value.

Table 3. Pulmonary exacerbations twelve months before elexacaftor/tezacaftor/ivacaftor treatment initiation and during the follow-up period of the study.

Sample/subgroup	Outcome	Before	During	p
Overall	Exacerbation, n	29	3	0.001
	Hospitalization, n	14	1	0.016
Advanced lung disease[a]	Exacerbation, n	9	1	0.041
	Hospitalization, n	5	1	0.068

[a]Defined as FEV_1 < 40% of the predicted value.

We also acknowledge that the mean changes were not statistically different between homozygous F508del patients and heterozygous F508del patients with a minimal function mutation, even though the rates of improvements in FEV_1 and sweat chloride concentrations were interestingly greater in the heterozygous group. These results might suggest that other patients with different mutations might also benefit from ELX/TEZ/IVA.

Pulmonary exacerbations rates were also significantly smaller after starting treatment when compared with the 12 months before ELX/TEZ/IVA therapy; nevertheless, it must be noted that the mean follow-up time of this study was approximately 6 months, which might have underestimated these results.

Regarding advanced lung disease patients, our data contradict previous studies that suggested that CFTR modulators were less effective in this group of patients and that lung damage was irreversible.[17] In fact, we found a significant improvement in FEV_1 of 13.28% of predicted over a period of 12-24 weeks of treatment, which is similar to the results reported in a recent French study by Burgel et al.[6] Of note in that study[6] is that a significant smaller proportion of patients with advanced lung disease required long-term oxygen therapy or noninvasive ventilatory support after 1-3 months of treatment with the triple CFTR modulator therapy. Likewise, an increase in nutritional status, inferred by BMI improvement, was also seen in this population as previously described. In terms of sweat chloride concentrations, our results were not as expressive, which could be related to the small sample, given the lack of results at the time of data collection, as mentioned before.

Importantly, 1 of our 3 patients in the transplantation waiting list was excluded from that list because of such a clinical improvement that transplantation was no longer indicated. This has also been reported in another study,[6] in which there was a two-fold decrease in lung transplantations. Moreover, there were no special safety concerns in this group of patients when compared with patients with less severe disease.

There are some limitations in our study that need to be noted. First, the official approval of ELX/TEZ/IVA in Portugal occurred only in July of 2021, which implied a short follow-up period. Also, the COVID-19 pandemic interfered with and prevented some in-person visits, including spirometry evaluations, in 2 patients, and sweat chloride tests, in 7 patients, who were not included in this study. It should also be noted this was an observational, non-randomized, single-center study that involved a limited number of patients in the analysis. Notwithstanding, the Cystic Fibrosis Center of the Santa Maria Hospital is the largest adult

CF center in Portugal, following about one-third of adult CF patients in the country, which allows us to contextualize our results within the national reality.

Other treatments, such as inhaled antibiotics or mucolytic agents, were not considered in this analysis, and whether they impact effectiveness of ELX/TEZ/IVA is unclear. Furthermore, we did not evaluate whether ELX/TEZ/IVA allow discontinuation of these classic baseline CF treatments, hence we have to wait for the results of studies evaluating those outcomes to understand whether ELX/TEZ/IVA would lead to significant reductions in the use of supportive therapies.

We found effective benefits of ELX/TEZ/IVA treatment in real-world clinical practice, even in patients initially not included in clinical trials, such as those with advanced lung disease, with improvements in FEV_1, BMI, sweat chloride concentrations, and number of exacerbations, and no significant differences were seen between F508del homozygous patients and F508del heterozygous patients with a minimal function mutation.

Overall, treatment with ELX/TEZ/IVA was well tolerated, and our data support the safety of ELX/TEZ/IVA, even in patients with advanced lung disease; above all, our results reflect the life change that this treatment brought to life expectancy of our CF patients.

AUTHOR CONTRIBUTIONS

PA: study conception and design. KL, CC, CL, RB, and PA: patient follow-up. KL, CC, RB, and PA: data collection. KL and CC: statistical analysis and drafting of the manuscript. All of the authors revised the manuscript and approved the final version as submitted and agree to be accountable for all aspects of the work.

CONFLICTS OF INTEREST

None declared.

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