Check for updates

Received: 9 October 2022 | Accepted: 29 May 2023

DOI: 10.1002/ppul.26535

ORIGINAL ARTICLE

WILEY

Patients with cystic fibrosis who could not receive the CFTR modulator treatment: What did they lose in 1 year?

Salih Uytun MD[1] | Güzin Cinel[1,2] | Sanem Eryılmaz Polat MD[1] | Satı Özkan Tabakçı MD[1] | Nural Kiper[3] | Ebru Yalçın[3] | Dilber Ademhan Tural[3] | Beste Özsezen MD[3] | Velat Şen[4] | Hadice Selimoğlu Şen[5] | Derya Ufuk Altıntaş[6] | Haluk Çokuğraş[7] | Ayşe Ayzıt Kılınç[7] | Azer Kılıç Başkan MD[7] | Hakan Yazan MD[8] | Abdulhamit Çollak MD[8] | Selçuk Uzuner MD[8] | Gökçen Ünal MD[9] | Aslı İmran Yılmaz MD[9] | Hanife Tuğçe Çağlar MD[9] | Ebru Damadoğlu[10] | İlim Irmak[10] | Esen Demir[11] | Gökçen Kartal Öztürk MD[11] | Ayşen Bingöl[12] | Erdem Başaran[12] | Nihat Sapan[13] | Yakup Canıtez[13] | Ayşe Tana Aslan[14] | Pelin Asfuroğlu MD[14] | Koray Harmancı[15] | Mehmet Köse[16] | Melih Hangül[16] | Ali Özdemir[17] | Nazan Çobanoğlu[18] | Gizem Özcan MD[18] | Özlem Keskin[19] | Hasan Yüksel[20] | Şebnem Özdoğan MD[21] | Erdem Topal[22] | Gönül Çaltepe[23] | Demet Can[24] | Pervin Korkmaz Ekren[25] | Mehmet Kılıç[26] | Nagehan Emiralioğlu[3] | Tuğba Şişmanlar Eyüboğlu[14] | Sevgi Pekcan[9] | Erkan Çakır[8] | Uğur Özçelik[3] | Deniz Doğru[3]

Correspondence
Salih Uytun, MD, Division of Pediatric Pulmonology, Ankara City Hospital, Ankara, Turkey.
Email: salihuytun@gmail.com

Abstract

Background: Cystic fibrosis (CF) is an autosomal recessive disorder caused by CF transmembrane conductance regulator (CFTR) genetic variants. CFTR modulators improve pulmonary function and reduce respiratory infections in CF. This study investigated the clinical and laboratory follow-up parameters over 1 year in patients with CF who could not receive this treatment.

Methods: This retrospective cohort study included 2018 and 2019 CF patient data from the CF registry of Turkey. Demographic and clinical characteristics of 294 patients were assessed, who had modulator treatment indications in 2018 but could not reach the treatment.

Results: In 2019, patients younger than 18 years had significantly lower BMI *z*-scores than in 2018. During the 1-year follow-up, forced expiratory volumes (FEV1) and FEV1 *z*-scores a trend toward a decrease. In 2019, chronic

For affiliations refer to page 2511.

 © 2023 Wiley Periodicals LLC.

Staphylococcus aureus colonization, inhaled antipseudomonal antibiotic use for more than 3 months, oral nutritional supplement requirements, and oxygen support need increased.

Conclusions: Patients who had indications for modulator treatments but were unable to obtain them worsened even after a year of follow-up. This study emphasized the importance of using modulator treatments for patients with CF in our country, as well as in many countries worldwide.

KEYWORDS

body mass index, CFTR modulator, cystic fibrosis, forced expiratory volume, *z*-scores

1 | INTRODUCTION

In recent years, cystic fibrosis (CF) treatment has progressed from therapies aimed at treating the consequences of organ damage to therapies aimed at modifying the CF transmembrane regulator (CFTR) function, known as CFTR modulators. CFTR modulators are classified as potentiators (such as ivacaftor [IVA]), correctors (such as lumacaftor [LUM], tezacaftor [TEZ], and elexacaftor [ELX]), and amplifiers. IVA is a CFTR potentiator whose action is to prolong the duration of the opening of the CFTR channel and thereby improve chloride transport. LUM, TEZ, and ELX are correctors that alter the conformational deformation and allow *CFTR* to move to its correct position on the cell surface (trafficking).[1,2]

Previous studies demonstrated that CFTR modulators improved weight, body mass index (BMI), and *z*-scores, reduced sweat chloride concentrations, increased predicted forced expiratory volumes (FEV1) and quality of life, and decreased pulmonary symptoms.[3] It is well known that initiating modulator therapies early in the course of CF can slow or even prevent the progression of pulmonary and extrapulmonary complications.[4] Over the past decade, the number of mutations in the *CFTR* gene, which is a modulator treatment indication, has increased, as has the number of patients with indications for modulator therapy, and the age at which patients start modulator therapy has decreased rapidly.[5]

These modulator drugs are currently licensed and used in many countries for patients with CF. However, the annual cost of these drugs has ranged between $270,000 and $310,000. These drugs are costly for almost all countries. Therefore, modulators are inaccessible to many patients unless covered by health system insurance.[6] In our country, Turkey, many patients with CF cannot obtain CFTR modulators because they are not covered by insurance. Therefore, we aimed to evaluate the clinical and laboratory characteristics of patients with CF who had indications for CFTR modulator therapy but were unable to receive it over a 1-year follow-up period. We hypothesized that at the 1-year follow-up, patients with CF who could not receive the CFTR modulator treatment would have lower BMI, BMI *z*-scores, FEV1 and FEV1 *z*-scores, and increased CF-associated complications.

2 | METHODS

2.1 | Study participants and procedures

This is a retrospective cohort study that includes data from patients in the CF registry of Turkey (CFRT) from 2018 to 2019. No patient in our country had access to modulatory treatment during these years. Data from patients in 2018 and 2019 who did not access modulatory treatment despite being indicated for treatment were compared.

Data were analyzed regarding demographic and clinical characteristics, including sex, current age, BMI and BMI *z*-scores, spirometry results, medications, presence of microorganisms, complications, and transplants.

BMI was calculated as weight in kilograms divided by height in square meters (kg/m^2), and BMI-for-age *z*-scores were calculated using the World Health Organization (WHO) anthropometric calculator (AnthroPlus v.1.0.4), which is based on the WHO Child Growth Standards and Growth Reference data. BMI *z*-scores were calculated for patients under the age of 18. Spirometry indices were analyzed using the European Respiratory Society/European Community for Steel, and Coal/Knudson reference values.[7]

The modulator therapy indications and age groups of the patients were determined according to Clinical and Functional Translation of CFTR in 2018 (cftr2.org).[8] The following criteria were used to determine eligibility for modulator drugs: LUM/IVA for patients aged 2 years or older with two copies of the *F508del* mutation; TEZ/IVA for those aged 6 years or older with two copies of the *F508del* mutation or a single copy of one of the 26 specific mutations (*A455E*, *A1067T*, *D110E*, *D110H*, *D579G*, *D1152H*, *D1270N*, *E56K*, *E193K*, *F1052V*, *F1074L*, *K1060T*, *L206W*, *P67L*, *R74W*, *R117C*, *R347H*, *R352Q*, *R1070W*, *S945L*, *S977F*, *711+3A>G*, *2789+5G>A*, *3272-26A>G*, *3849+10kbC>T*, and *E831X*); IVA for those aged 6 months or older with a single copy of one of the TEZ/IVA-approved mutations or 12 other specific mutations (*G178R*, *G551D*, *G551S*, *G1069R*, *G1244E*, *G1349D*, *R117H*, *R1070Q*, *S549N*, *S549R*, *S1251N*, and *S1255P*); and ELX/TEZ/iVA for those aged 12 years or older with a single copy or two copies of the *F508del* mutation. Our national data shows that Turkish patients with CF have various CFTR mutations due to our country's geographic location, historical background, and

10990496, 2023, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ppul.26535 by Balikesir University, Wiley Online Library on [02/09/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

the high prevalence of consanguineous marriages. The most common mutations are *F508del*, followed by *G542X*, *1677delTA*, *N1303K*, and *2183AA- >G* in 2018 in CFRT.[9]

The need for lung transplantation was assessed following the CF Foundation recommendations.[10] We defined chronic colonization with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *and Burkholderia cephacia* according to the "modified Leeds criteria" as applied in the ECFSPR guideline; >50% of the samples collected over 12 months (sputum/others) should be positive; at least four samples should be collected.[11]

CFRT database, use of inhaled tobramycin, inhaled colistin, the status of need for oxygen and noninvasive mechanical ventilation, and the use of oral nutritional supplements are based on their consecutive and continuous use for at least 3 months or more in a year.

Pulmonary function tests in the CFRT database show the best value of the year obtained during the patients' healthy period. Each center annually recorded data of patients in a software program that was specially developed for the CFRT. Totally 15 demographic and 79 annual data compatible with ECFS Patient Registry were recorded in the CFRT, consisting of demographic features, diagnostic tests, pancreatic sufficiency/in-sufficiency status, complications, colonization status, treatments, and transplantation status. At the end of each year, data cleaning was undertaken by the board members, and a private company performed statistical analysis. Perform a descriptive cross-sectional analysis was performed for statistical analysis. Missing data were excluded from the analysis.[12] This study was conducted in accordance with the amended Helsinki Declaration, and our local ethics committee approved all procedures involving human participants. Before being registered in the registry system, the patients and their families provided informed consent. A total of 1488 patients were enrolled in CFRT. Among these patients, 294 patients who have genetic mutations and indications for modulatory treatment and have data for both the 2018 and 2019 years were included in the study. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart is depicted in Figure 1.

2.2 | Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences software (IBM SPSS statistical package; version 23.0) and Prism (GraphPad Software Inc). In descriptive statistics, categorical variables were expressed as numbers and percentages, while continuous variables were expressed as medians (minimum [min]−maximum [max]). The homogeneity of variables was assessed using the Kolmogorov−Smirnov test. The two dependent groups were compared using the Wilcoxon signed-rank test for the non-normally distributed data and the paired Student's *t*-test for the normally distributed data. The categorical variables were compared between dependent groups using the McNemar tests. The changes in FEV1 and FEV1 *z*-score by years, as well as the effect of age categories, were analyzed using the repeated measures analysis of variance (ANOVA) test. When the sphericity assumption was violated, the Greenhouse−Geisser correction was applied. A *p*-value of less than 0.05 was considered statistically significant.

3 | RESULTS

In the registry, 294 out of 351 patients had data for both the 2018 and 2019 years (Table 1). In 2018, their mean age was 10.11 ± 6.1 years (min−max: 1−43) 2018. Among all patients, 147 patients (50%) were female, and 147 (50%) were male. BMI *z*-scores of patients under the age of 18 decreased significantly in 2019 compared to 2018. However, in the 1-year follow-up of patients over the age of 18, there was a decrease in BMI *z*-scores, but it was not statistically significant. Three new patients were added to the BMI group under 18.5. It shows that 3 out of 14 patients' BMI scores had shifted to a low level. Comparisons of BMI for patients older than 18 years between the 2018 and 2019 follow-ups are shown in Figure 2.

The respiratory sample colonization statutes, complications, new support, and treatments of patients are shown in Table 2. In 2019, chronic *S. aureus* colonization, inhaled antipseudomonal antibiotic use for more than 3 months, and oral nutritional supplement requirements, use of inhaled DNase, hypertonic saline, and oral azithromycin increased. Furthermore, the need for oxygen support increased significantly in (*p*:0.004) 2019, while the need for noninvasive mechanical ventilation increased but did not reach statistical significance.

FEV1 and FEV1 *z*-scores were evaluated by categorizing the patients into three age groups: 5−12, 12−18, and over 18 years. It was found that as the age group of patients increased for both the 2018 and 2019 years, FEV1 and FEV1 *z*-scores a trend toward a decrease. At the 1-year follow-up, there was a decrease in FEV1 and FEV1 *z*-scores for the 12−18 years, but it was not statistically significant (Table 3).

The changes in FEV1 and FEV1 *z*-score were analyzed over time, as well as the effect of age categories, using the repeated measures ANOVA test, and the results revealed that age categories had no statistically significant effect on FEV1% and FEV1 *z*-score decline ($p = 0.2$ and 0.68, respectively). However, the number of patients with an FEV1% of less than 50% increased significantly (Table 4).

Among the patients with indications for modulator therapy, three patients died in 2018, two died in 2019, and two underwent lung transplantation in 2018.

4 | DISCUSSION

The present study demonstrates that the clinical characteristics of patients with indicated CFTR modulators worsened even after a 1-year follow-up when CFTR modulators were not available. In detail, we demonstrated that the number of patients who require oxygen support and those who must be referred to a lung transplantation center increased due to having FEV1% less than 50%.

10990496, 2023, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ppul.26535 by Balikesir University, Wiley Online Library on [02/09/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

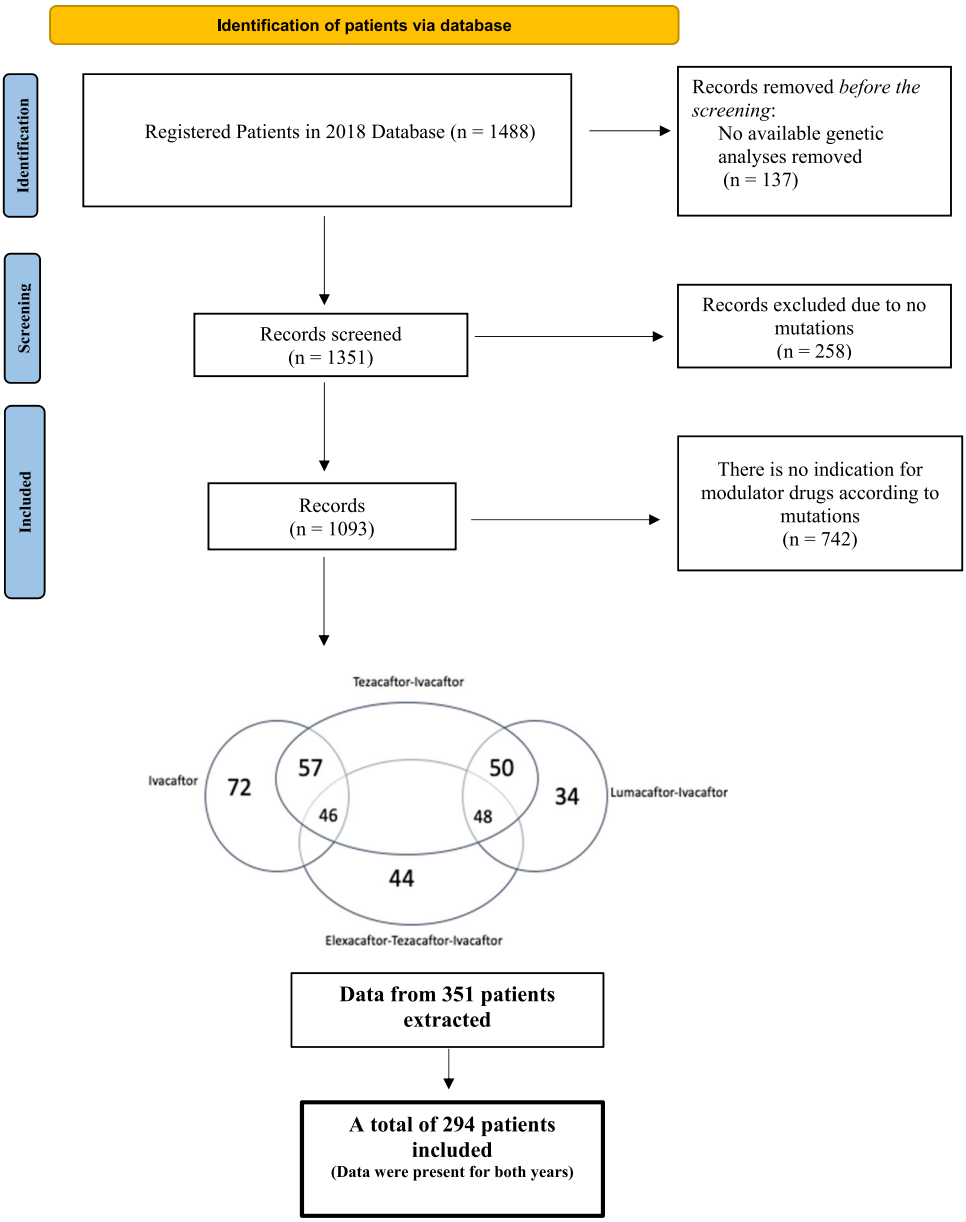

FIGURE 1 Flow chart for including patients.

TABLE 1 BMI and BMI *z*-scores of patients in 2018–2019.

Group	2018 mean ± SD\n (%)	2019 mean ± SD\n (%)	*p*
BMI *z*-scores (*n* = 272)[a]	−0.38 ± 1.52	−0.43 ± 1.52	**0.01**[b]
BMI (kg/m^2) *n*:22[c]	20.68 ± 3.85 (14.3–29.3)	20.42 ± 4.1 (12.8–30.2)	0.5[b]
BMI (kg/m^2) *n*:22[c]			
<18.5	5 (22.7)	8 (36.3)	0.08[d]
18.5–24.9	14 (63.6)	11 (50)	
25–29.9	3 (13.6)	3 (13.6)	

Note: Bold *p*-values indicate statistically significant results at the 5% significance level.

Abbreviations: BMI, body mass index; SD, standard deviation.

[a]BMI *z*-score was calculated for only patients <18 years.

[b]Wilcoxon.

[c]BMI kg/m^2 score was calculated for patients ≥18 years.

[d]Mc Nemar test.

10990496, 2023, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ppul.26535 by Balikesir University, Wiley Online Library on [02/09/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

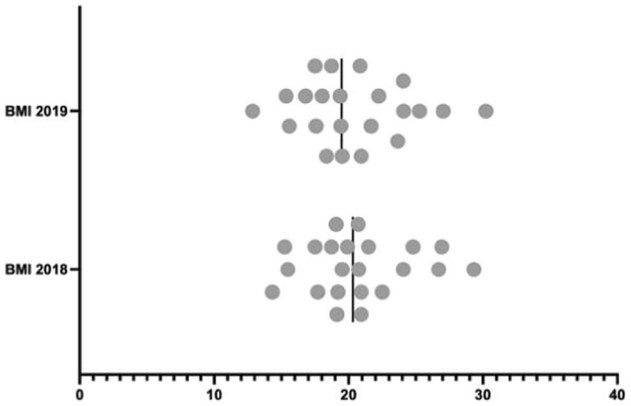

FIGURE 2 Comparison of BMI scores for patients older than 18 years between 2018 and 2019. BMI, body mass index.

TABLE 2 Complications, new support, and treatments of patients with data in both 2018 and 2019.

Variables	2018 (n = 294) n (%)	2019 (n = 294) n (%)	p
Chronic colonization of *Pseudomonas aeruginosa*	82 (28)	77 (26.2)	0.470
Chronic colonization of *Staphylococcus aureus*	96 (32.7)	111 (37.8)	**0.050***
Chronic colonization of *Burkholderia cephacia*	2 (0.7)	3 (1)	1
Using inhaled antipseudomonal antibiotics >3 months	80 (27.2)	92 (31.3)	**0.008***
Inhaled tobramycin	61 (20.8)	73 (24.8)	**0.020***
Inhaled colistin	28 (9.8)	37 (12.5)	0.160
DNase	275 (93.5)	283 (96.3)	**<0.008***
Hypertonic saline ≥%3	30 (10.2)	47 (16)	**<0.001***
Azithromycin	17 (5.8)	27 (9.2)	**<0.040***
Oxygen support	4 (1.4)	13 (4.4)	**0.004***
Noninvasive mechanical ventilation	9 (3.1)	14 (4.8)	0.060
Oral nutritional supplements	169 (57.5)	193 (65.6)	**<0.001***
Allergic bronchopulmonary aspergillosis	9 (3.1)	10 (3.1)	0.500
CFRD	11 (3.7)	13 (4.4)	0.720
Chronic liver diseases	40 (13.6)	44 (15)	0.540
Major hemoptysis over 250 mL	2 (0.7)	2 (0.7)	1
Pneumothorax	1 (0.3)	1 (0.3)	1

Note: * and bold p-values indicate statistically significant results at the 5% significance level.

Abbreviation: CFRD, cystic fibrosis-related diabetes mellitus.

TABLE 3 FEV1 and FEV1 z-scores of patients with data in both 2018 and 2019.

Variable	2018 (n = 160) mean (SD)	2019 (n = 160) mean (SD)	p
FEV1% (years)			
5–12 (n:59)	95.72 (17.73)	96.42 (18.41)	0.730[a]
12–18 (n:73)	84.08 (27.01)	82.94 (30.16)	0.940[a]
>18 (n:28)	66.64 (28.75)	64.5 (28.75)	0.320[a]
FEV1 z-score (years)			
5–12 (n:59)	−0.67 (1.35)	−0.66 (1.5)	0.950[a]
12–18 (n:73)	−1.82 (2.09)	−1.99 (2.23)	0.270[a]
>18 (n:28)	−3.04 (2.22)	−3.04 (2.51)	0.550[a]

Abbreviations: FEV1, forced expiratory volumes; SD, standard deviation.

[a]Wilcoxon test.

TABLE 4 Number of patients with FEV1% <50 and % <30 in 2018 and 2019.

Group	2018 (n = 173) n (%)	2019 (n = 173) n (%)	p
FEV1% < 50	23 (13.3)	29 (16.7)	**0.004**[a]
FEV1% < 30	5 (2.9)	7 (4)	0.250[a]

Note: Bold p-values indicate statistically significant results at the 5% significance level.

Abbreviation: FEV1, forced expiratory volumes.

[a]Mc Nemar test.

BMI is one of the primary outcomes in most CFTR modulator studies.[13] Previous studies consistently show that CFTR modulators result in significant weight and BMI improvements.[14] The 3-year data on IVA collected by Sawicki et al. also revealed an improvement in BMI and weight-for-age z-scores.[15] The United States and United Kingdom registries of IVA follow-up studies revealed a 5-year improvement in BMI from 1.6 to 2.4 kg/m^2 in the United States and from 0.9 to 1.9 kg/m^2 in the United Kingdom.[16] In Liou et al.'s 5-year survivorship study, weight-for-age z-scores had a substantial impact on long-term outcomes.[13] Our findings revealed a significant decrease in the patients' BMI z-scores. Our patients could not receive CFTR modulators during the 1-year follow-up period, and we believe that if they could, their BMI z-scores would not decrease or even increase.

Patients with CF experience frequent acute pulmonary exacerbations, necessitating repeated hospitalizations, and lengthy courses of IV antibiotics that require invasive procedures.[17] Previous studies have suggested that CFTR modulators may improve clinical outcomes by correcting the dysregulated immune functions that characterize CF by enhancing leucocytic antibacterial function and reducing chronic inflammation. One of the earliest studies found that neutrophils from patients with CF taking IVA had increased neutrophil killing of the *P. aeruginosa*.[18] A recent study using UK

10990496, 2023, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ppul.26535 by Balikesir University, Wiley Online Library on [02/09/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

registry data on IVA use in 276 patients found an early and sustained reduction in *P. aeruginosa* infection, a reduction in *Aspergillus* infection, and a minor reduction in *S. aureus* infection, but a nonsignificant change in *Burkhodelpheria Cepacia* complex over 6 years.[19] In addition to the literature, it was shown in our study that the number of patients who needed antipseudomonal inhaled treatment increased, although the number of patients with chronic pseudomonas did not increase.

CF causes pancreatic dysfunction, and cystic fibrosis-related diabetes (CFRD) is typically diagnosed in patients with pancreatic insufficiency.[20,21] After IVA therapy, insulin secretion has been found to improve.[22,23] It was also shown that taking LUM/IVA for a year improved glucose metabolism in patients with either glucose intolerance (78%) or CFRD (22%).[24] The data from patients who were followed prospectively for up to 5 years in the US registry and up to 4 years in the UK registry revealed a reduced prevalence of CFRD in the IVA group (30% vs. 40% in the US registry and 21% vs. 29% in the UK registry).[25] In the current study, two new patients (0.68%) were diagnosed with CFRD during the study period. Because our study shows only 1-year follow-up findings, we could not reach the appropriate conclusion regarding the long-term complications of CF.

FEV1 is the most commonly used measure of respiratory outcome, which can be expressed as a percentage predicted adjusted for age, sex, and height or as an annual percentage decrease. These FEV1 scores are essential predictors of morbidity and life expectancy in patients with CF.[26] In randomized studies, TEZ/IVA and IVA increased FEV1 by 6.8% and reduced acute pulmonary exacerbations by 46% compared to the placebo.[27] In another study, improved lung function and nutritional status were found after 3 months of ELX/TEZ/IVA treatment.[28] The results showed that a trend toward a decrease in FEV1 is in line with the expected annual decrease in CF patients.[29] We believe that if our patients could access the appropriate modulators, their FEV1 values would increase or at least not decrease.

The most common cause of CF-related mortality is pulmonary disease (60%), and lung transplantation is a surgical option that can improve pulmonary complications and quality of life.[10,30] A study on US and UK data demonstrated that IVA use was associated with reduced mortality risk and lung transplantation needs.[25] We assessed lung transplantation needs following the CF Foundation's recommendations,[10] and the number of patients with FEV1% of less than 50% increased significantly during the 1-year follow-up period. We also found that the need for oxygen support increased significantly in 2019. These findings indicated an increase in the number of patients necessitating lung transplantation evaluation within 1 year.

CFTR modulators are inaccessible outside Europe, North America, and Australia. Even within Europe, some regions, such as Eastern Europe and the Baltics, are still inaccessible to the IVA/LUM combination. As of June 2021, CFTR modulators were almost exclusively available in the world's wealthiest countries, with ELX/TEZ/IVA being reimbursed in only 16 countries worldwide. Therefore, it seems it will remain out of reach for patients outside the world's wealthiest countries.[31] The most important reasons why these drugs are not within the scope of reimbursement in our country are the high cost of drugs and the cost-effectiveness of these pharmacotherapies has yet been reported.[32] Generic versions of all CFTR modulator therapies are produced in Argentina, where patent restrictions currently do not apply. Under the Trade-Related Aspects of Intellectual Property Rights agreement, commercial export of generic drugs to a country where such products remain under patent protection is not permitted.[33] Unfortunately, in low-middle-income countries like ours, where the gross national product was $9793 for one person in 2018,[34] most patients could not access these proper treatments due to the exorbitant cost of these drugs. In these conditions, it is impossible to continue the treatment in patients who can reach the treatment individually due to the prohibitive cost.

The excessive cost and lifelong usage of these drugs, combined with prolonged international drug patent laws by international pharma companies and state that international pharma companies have not promoted access to modulator therapy for patients in low-middle-income countries, are significant obstacles that these countries face and need to overcome through awareness of CF in these countries and global advocacy for equal access to affordable CF therapies.[32]

Our findings should be considered in the context of the study's limitations. First, we analyzed an existing data set. Second, the short follow-up duration could limit our findings. Despite these limitations, to the best of our knowledge, this is the first study to examine the clinical data and complications in patients with CF over a 1-year follow-up period in Turkey since the approval of modulator therapy.

5 | CONCLUSION

In conclusion, patients with modulator indications who could not obtain them worsened even after 1 year of follow-up. We hope that this study will raise awareness about the use of modulatory therapies in our country as well as in many other countries worldwide.

AUTHOR CONTRIBUTIONS

Salih Uytun: Conceptualization; investigation; methodology; data curation; writing—review and editing; formal analysis; writing—original draft. **Güzin Cinel**: Methodology; supervision; project administration; investigation; funding acquisition. **Sanem Eryılmaz Polat**: Methodology; investigation. **Satı Ö. Tabakçı**: Methodology; investigation. **Nural Kiper**: Methodology; investigation. **Ebru Yalçın**: Methodology; investigation. **Dilber Ademhan Tural**: Methodology; investigation. **Beste Özsezen**: Methodology; investigation. **Velat Şen**: Methodology; investigation. **Hadice Selimoğlu Şen**: Methodology; investigation. **Derya U. Altıntaş**: Investigation; methodology. **Haluk Çokuğraş**: Methodology; investigation. **Ayşe Ayzıt Kılınç**: Methodology; investigation. **Azer Kılıç Başkan**: Methodology; investigation. **Hakan Yazan**: Investigation; methodology. **Abdulhamit Çollak**: Methodology; investigation. **Selçuk Uzuner**: Investigation; methodology. **Gökçen Ünal**: Methodology; investigation. **Aslı İmran Yılmaz**:

10990496, 2023, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ppul.26535 by Balikesir University, Wiley Online Library on [02/09/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Investigation; methodology. **Hanife Tuğçe Çağlar**: Methodology; investigation. **Ebru Damadoğlu**: Investigation; methodology. **İlim Irmak**: Methodology; investigation. **Esen Demir**: Investigation; methodology. **Gökçen Öztürk**: Methodology; investigation. **Ayşen Bingöl**: Investigation; methodology. **Erdem Başaran**: Methodology; investigation. **Nihat Sapan**: Investigation; methodology. **Yakup Canıtez**: Methodology; investigation. **Ayşe T. Aslan**: Investigation; methodology. **Pelin Asfuroğlu**: Methodology; investigation. **Koray Harmancı**: Investigation; methodology. **Mehmet Köse**: Methodology; investigation. **Melih Hangül**: Investigation; methodology. **Ali Özdemir**: Methodology; investigation. **Nazan Çobanoğlu**: Investigation; methodology. **Gizem Özcan**: Methodology; investigation. **Özlem Keskin**: Investigation; methodology. **Hasan Yüksel**: Methodology; investigation. **Şebnem Özdoğan**: Methodology; investigation. **Erdem Topal**: Investigation; methodology. **Gönül Çaltepe**: Methodology; investigation. **Demet Can**: Methodology; investigation. **Pervin Korkmaz Ekren**: Investigation; methodology. **Mehmet Kılıç**: Methodology; investigation. **Nagehan Emiralioğlu**: Investigation; methodology. **Tuğba Şişmanlar Eyüboğlu**: Methodology; investigation. **Sevgi Pekcan**: Investigation; methodology. **Erkan Çakır**: Methodology; investigation. **Uğur Özçelik**: Investigation; methodology. **Deniz Doğru**: Funding acquisition; investigation; methodology.

AFFILIATIONS

[1]Division of Pediatric Pulmonology, Ankara City Hospital, Ankara, Turkey

[2]Division of Pediatric Pulmonology, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Turkey

[3]Division of Pediatric Pulmonology, Faculty of Medicine, Hacettepe University, Ankara, Turkey

[4]Division of Pediatric Pulmonology, Faculty of Medicine, Dicle University, Diyarbakır, Turkey

[5]Department of Pulmonology, Faculty of Medicine, Dicle University, Diyarbakır, Turkey

[6]Division of Pediatric Allergy and Immunology, Faculty of Medicine, Çukurova University, Adana, Turkey

[7]Division of Pediatric Pulmonology, Cerrahpaşa Faculty of Medicine, İstanbul University-Cerrahpaşa, İstanbul, Turkey

[8]Division of Pediatric Pulmonology, Faculty of Medicine, Bezmialem Vakıf University, İstanbul, Turkey

[9]Division of Pediatric Pulmonology, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey

[10]Department of Pulmonology, Faculty of Medicine, Hacettepe University, Ankara, Turkey

[11]Division of Pediatric Pulmonology, Faculty of Medicine, Ege University, İzmir, Turkey

[12]Division of Pediatric Pulmonology, Faculty of Medicine, Akdeniz University, Antalya, Turkey

[13]Division of Pediatric Allergy and Immunology, Faculty of Medicine, Uludağ University, Bursa, Turkey

[14]Division of Pediatric Pulmonology, Faculty of Medicine, Gazi University, Ankara, Turkey

[15]Division of Pediatric Allergy and Immunology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

[16]Division of Pediatric Pulmonology, Faculty of Medicine, Erciyes University, Kayseri, Turkey

[17]Division of Pediatric Pulmonology, Mersin City Training and Research Hospital, Mersin, Turkey

[18]Division of Pediatric Pulmonology, Faculty of Medicine, Ankara University, Ankara, Turkey

[19]Division of Pediatric Allergy and Immunology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey

[20]Division of Pediatric Pulmonology, Allergy and Immunology, Faculty of Medicine, Celal Bayar University, Manisa, Turkey

[21]Division of Pediatric Pulmonology, Sarıyer Hamidiye Etfal Training and Research Hospital, İstanbul, Turkey

[22]Division of Pediatric Allergy and Immunology, Faculty of Medicine, İnönü University, Malatya, Turkey

[23]Division of Pediatric Gastroenterology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

[24]Division of Pediatric Pulmonology, Faculty of Medicine, Balıkesir University, Balıkesir, Turkey

[25]Department of Pulmonology, Faculty of Medicine, Ege University, İzmir, Turkey

[26]Division of Pediatric Allergy and Immunology, Faculty of Medicine, Fırat University, Elazığ, Turkey

ACKNOWLEDGMENTS

We would like to thank the CFRT for allowing us access to patient data, as well as individual center representatives for allowing us to use the data. We also thank Dr. Merve Cikili-Uytun for her statistical and technical assistance with our research.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Salih Uytun https://orcid.org/0000-0002-7301-3692
Güzin Cinel http://orcid.org/0000-0002-6209-196X
Dilber Ademhan Tural http://orcid.org/0000-0002-0334-6336
Beste Özsezen http://orcid.org/0000-0002-0052-8361
Ayşe Ayzıt Kılınç http://orcid.org/0000-0002-2879-8910
Hakan Yazan http://orcid.org/0000-0002-7680-4000
Aslı İmran Yılmaz http://orcid.org/0000-0003-2689-7904
Gökçen Kartal Öztürk http://orcid.org/0000-0002-0793-9710
Erdem Başaran http://orcid.org/0000-0002-9092-6936
Mehmet Köse http://orcid.org/0000-0002-3003-918X
Melih Hangül http://orcid.org/0000-0001-6226-0340
Ali Özdemir http://orcid.org/0000-0001-7340-0409
Nazan Çobanoğlu http://orcid.org/0000-0002-3686-2927
Gizem Özcan http://orcid.org/0000-0001-9063-4063
Nagehan Emiralioğlu http://orcid.org/0000-0002-1405-8401
Tuğba Şişmanlar Eyüboğlu http://orcid.org/0000-0001-7284-4999
Sevgi Pekcan http://orcid.org/0000-0002-8059-902X
Erkan Çakır http://orcid.org/0000-0002-1438-7854
Deniz Doğru http://orcid.org/0000-0001-9931-9473

10990496, 2023, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ppul.26535 by Balikesir University, Wiley Online Library on [02/09/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

REFERENCES

1. Rey MM, Bonk MP, Hadjiliadis D. Cystic fibrosis: emerging understanding and therapies. *Annu Rev Med*. 2019;70:197-210.
2. Dagenais RVE, Su VCH, Quon BS. Real-world safety of CFTR modulators in the treatment of cystic fibrosis: a systematic review. *J Clin Med*. 2020;10(1):23.
3. Taylor-Cousar JL, Mall MA, Ramsey BW, et al. Clinical development of triple-combination CFTR modulators for cystic fibrosis patients with one or two F508del alleles. *ERJ Open Res*. 2019;5(2):00082-2019.
4. Hubert D, Dehillotte C, Munck A, et al. Retrospective observational study of French patients with cystic fibrosis and a Gly551Asp-CFTR mutation after 1 and 2 years of treatment with ivacaftor in a real-world setting. *J Cyst Fibros*. 2018;17(1):89-95.
5. FDA. FDA expands approved use of Kalydeco to treat additional mutations of cystic fibrosis 2017. 2021. Accessed April 20, 2022. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm559212.htm
6. Guo J, Wang J, Zhang J, Fortunak J, Hill A. Current prices versus minimum costs of production for CFTR modulators. *J Cyst Fibros*. 2022;21:866-872.
7. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respiratory Soc*. 2012;40(6):1324-1343.
8. CFTR2. Clinical and functional translation of CFTR. 2021. Accessed April 26, 2022. https://cftr2.org/
9. Cinel G, Doğru D, Çakır E, et al. CFTR mutations unidentified in CFTR2 database and their phenotypic characteristics: data from cystic fibrosis registry of Turkey. *Eur Respiratory Soc*. 2020;56(sup64):2765.
10. Ramos KJ, Smith PJ, McKone EF, et al. Lung transplant referral for individuals with cystic fibrosis: cystic fibrosis foundation consensus guidelines. *J Cyst Fibros*. 2019;18(3):321-333.
11. Proesmans M, Balinska-Miskiewicz W, Dupont L, et al. Evaluating the "leeds criteria" for *Pseudomonas aeruginosa* infection in a cystic fibrosis centre. *Eur Respir J*. 2006;27(5):937-943.
12. Dogru D, Çakır E, Şişmanlar T, et al. Cystic fibrosis in Turkey: first data from the national registry. *Pediatr Pulmonol*. 2020;55(2):541-548.
13. Liou TG, Adler FR, FitzSimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol*. 2001;153(4):345-352.
14. Rubin JL, O'Callaghan L, Pelligra C, et al. Modeling long-term health outcomes of patients with cystic fibrosis homozygous for F508del-CFTR treated with lumacaftor/ivacaftor. *Therapeutic Adv Resp Dis*. 2019;13:175346661882018.
15. Sawicki GS, McKone EF, Pasta DJ, et al. Sustained benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. *Am J Respir Crit Care Med*. 2015;192(7):836-842.
16. Volkova N, Moy K, Evans J, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: data from national US and UK registries. *J Cyst Fibros*. 2020;19(1):68-79.
17. Agrawal A, Agarwal A, Mehta D, Sikachi RR, Du D, Wang J. Nationwide trends of hospitalizations for cystic fibrosis in the United States from 2003 to 2013. *Intractable Rare Dis Res*. 2017;6(3):191-198.
18. Pohl K, Hayes E, Keenan J, et al. A neutrophil intrinsic impairment affecting Rab27a and degranulation in cystic fibrosis is corrected by CFTR potentiator therapy. *Blood*. 2014;124(7):999-1009.
19. Frost FJ, Nazareth DS, Charman SC, Winstanley C, Walshaw MJ. Ivacaftor is associated with reduced lung infection by key cystic fibrosis pathogens. A cohort study using national registry data. *Ann Am Thorac Soc*. 2019;16(11):1375-1382.
20. Patel S, Sinha IP, Dwan K, Echevarria C, Schechter M, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *Cochrane Database Syst Rev*. 2015;26(3):CD009841.
21. Granados A, Chan CL, Ode KL, Moheet A, Moran A, Holl R. Cystic fibrosis related diabetes: pathophysiology, screening and diagnosis. *J Cyst Fibros*. 2019;18:S3-S9.
22. Tsabari R, Elyashar HI, Cymberknowh MC, et al. CFTR potentiator therapy ameliorates impaired insulin secretion in CF patients with a gating mutation. *J Cyst Fibros*. 2016;15(3):e25-e27.
23. Bellin MD, Laguna T, Leschyshyn J, et al. Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: a small pilot study. *Pediatr Diabetes*. 2013;14(6):417-421.
24. Misgault B, Chatron E, Reynaud Q, et al. Effect of one-year lumacaftor-ivacaftor treatment on glucose tolerance abnormalities in cystic fibrosis patients. *J Cyst Fibros*. 2020;19(5):712-716.
25. Bessonova L, Volkova N, Higgins M, et al. Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. *Thorax*. 2018;73(8):731-740.
26. Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. *J Pediatr*. 1997;131(6):809-814.
27. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor–ivacaftor in residual-function heterozygotes with cystic fibrosis. *N Engl J Med*. 2017;377(21):2024-2035.
28. DiMango E, Overdevest J, Keating C, Francis SF, Dansky D, Gudis D. Effect of highly effective modulator treatment on sinonasal symptoms in cystic fibrosis. *J Cyst Fibros*. 2021;20(3):460-463.
29. Taylor-Robinson D, Whitehead M, Diderichsen F, et al. Understanding the natural progression in% FEV1 decline in patients with cystic fibrosis: a longitudinal study. *Thorax*. 2012;67(10):860-866.
30. Chambers DC, Cherikh WS, Goldfarb SB, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-fifth adult lung and heart-lung transplant report—2018; focus theme: multiorgan transplantation. *J Heart Lung Transplant*. 2018;37(10):1169-1183.
31. Guo J, Garratt A, Hill A. Worldwide rates of diagnosis and effective treatment for cystic fibrosis. *J Cyst Fibros*. 2022;21(3):456-462.
32. Lopes-Pacheco M. CFTR modulators: the changing face of cystic fibrosis in the era of precision medicine. *Front Pharmacol*. 2020;10:1662.
33. GUO J, Wang J, Zhang Z, Fortunak J, Hill A. Current prices versus minimum costs of production for CFTR modulators. *J Cyst Fibros*. 2022;21.5:866-872.
34. Accessed February 22, 2023. https://data.tuik.gov.tr/Bulten/Index?p=Donemsel-Gayrisafi-Yurt-Ici-Hasila-IV.-Ceyrek:-Ekim—Aralik,-2018-30886

How to cite this article: Uytun S, Cinel G, Eryılmaz Polat S, et al. Patients with cystic fibrosis who could not receive the CFTR modulator treatment: what did they lose in 1 year? *Pediatr Pulmonol*. 2023;58:2505-2512. doi:10.1002/ppul.26535

10990496, 2023, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ppul.26535 by Balikesir University, Wiley Online Library on [02/09/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License