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Assessment of Physical Condition in Cystic Fibrosis Patients during 12-month Treatment with Cystic Fibrosis Transmembrane Conductance Regulator Modulators

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Abstract

Objective – To investigate the effect of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy on physical condition in children with cystic fibrosis (CF) during a 12month period. **Materials and Methods** – This is a retrospective cohort study including children aged ≥5 years treated with Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA) or Lumacaftor/Ivacaftor (LUM/IVA). A six-minute walk test (6MWT) was performed at baseline and at the 3-month follow-ups. Changes in spirometry and sweat chlorides, and body mass index (BMI) were also observed. Collected data were analysed for changes in 6MWT results in correlation with other parameters. The 6MWT results were compared to those predicted for healthy peers. Missing values were replaced using imputation. **Results** – Study includes 34 patients (median age 14 years); 28 received ELX/TEZ/IVA, and 6 LUM/IVA. The average 6MWT walking distance (6MWD) increased from 519.3±107.7 m at baseline to 620.0±99.5 m after 12 months (P<0.0001). The 12 month 6MWD values matched those expected for healthy peers. The increase in BMI z-score (P=0.019) and ppFEV1 (P<0.0001) visible at the 3-month followup was sustained throughout the rest of the year. Sweat chloride concentration decreased (P< 0.0001); after 12 months 13/34 subjects had values below 60 mmol/L. No correlation between 6MWD and other parameters was observed. **Conclusion** – Significant improvement in 6MWT results was already visible at three months following the initiation of CFTR modulator treatment. After 12 months patients performed 6MWT at a level indistinguishable from that expected of healthy peers.

Key Words: Cystic Fibrosis ▪ Elexacaftor/tezacaftor/ivacaftor ▪ Lumacaftor/ivacaftor ▪ Six-minute Walk Test.

Introduction

Cystic Fibrosis (CF) is an autosomal recessive monogenic disorder caused by a mutation in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene which encodes for a protein acting as an epithelial ion channel that primarily regulates transport of chloride and hydrogen carbonate ions, and plays an important role in fluid and electrolyte homeostasis on the apical surface of epithelial cells of the affected organs (1). Dysfunction in the CFTR protein typically presents as a multisystem disorder, characterized by chronic lung disease and recurrent respiratory infections, malabsorption, pancreatic insufficiency, and electrolyte imbalance marked by increased sweat chloride levels. Impaired physical condition is also often found in patients with CF, and is considered a consequence of pulmonary dysfunction, malnutrition, but also deconditioning due to a lack of physical activity (1, 2).

Until the development of CFTR modulators, patients with CF were treated solely symptomatically, with the primary aim of slowing the progression of lung dysfunction, maintaining normal

growth and adequate nutrition, as well as preventing or delaying and treating comorbidities (3). CFTR modulators are small molecules that offer a completely new approach to treating CF. They target the root cause of the disease, either by increasing the function of CFTR channels on the cell surface (CFTR potentiators) or by improving the production, folding and transport of mutated CFTR proteins to the cell membrane (CFTR correctors). Several combinations of potentiators and correctors have been approved by the European Medical Agency (EMA), including Lumacaftor/Ivacaftor (LUM/IVA) indicated for treatment of Phe508del homozygotes and Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA) that is effective in both Phe508del homozygotes and heterozygotes, making it applicable for use in up to 90% of all CF patients.

These CFTR modulators have brought about a significant improvement in lung function, and a decrease in the number of pulmonary exacerbations, as well as improvement in nutritional status and overall quality of life (3). CFTR modulators have also been linked with improvement in physical condition (4). Several studies have reported sustained improvement in the six-minute walk test (6MWT) used for assessment of physical condition in adult patients treated with both LUM/IVA and ELX/TEZ/IVA.

The Agency for Medicinal Products and Medical Devices of Croatia (HALMED) made LUM/IVA available for treatment of Phe508del homozygotes for patients aged 2 years and above, and ELX/TEZ/IVA for treatment of patients, either Phe508del homozygotes or heterozygotes, with a minimal function mutation on the second allele, aged 12 years and over, starting on November 15th, 2021. By the end of 2022, 89 children and adults with CF had commenced treatment with CFTR modulators at the Paediatric and Adult Cystic Fibrosis Centre at the University Hospital Centre in Zagreb, Croatia.

In contrast to the majority of previous studies exploring the connection between treatment with CFTR modulators and physical condition, that included adult patients, our aim was to investigate the response to CFTR modulator therapy during a 12-month period in only young patients. Changes in physical status assessed by the 6MWT, lung function assessed by spirometry, nutritional status, and sweat chloride concentration were analysed.

Patients and Methods

Patients

This was a retrospective analysis based on data collected from the medical documentation of 34 children treated at the Paediatric and Adult Cystic Fibrosis Centre at the University Hospital Centre, Zagreb, who were on CFTR modulator treatment (either LUM/IVA or ELX/TEZ/IVA) for at least 12 months in the period between November 2021 and June 2023. The study was limited to patients aged 5 to 18 years, as spirometry and 6MWT could not be reliably performed in younger patients. The study was approved by the Ethics Committee of the University Hospital Centre, Zagreb.

Methods

We analysed data collected during regular visits according to the standard CFTR modulator therapy care protocol: the percentage of predicted FEV_1 ($ppFEV_1$), 6MWT results, and BMI zscore on the day of initiating CFTR modulator treatment, and at follow-ups after 3, 6, 9, and 12 months. The sweat test was performed at baseline and after 6 and 12 months of treatment.

Spirometry was performed using a Ganshor/Schiller SpiroScout spirometer. BMI z-scores were calculated using the WHO Anthro and Anthroplus software (https://www.who.int/tools/). The sweat test was performed following the Gibson and Cooke procedure (pilocarpine iontophoresis, manual mercurymetric titration, the Shales and Shales method) (5). The 6MWT protocol was performed according to the American Thoracic Society guidelines (2002) (6). Heart rate (HR) and arterial blood oxygen saturation (SpO_2) were monitored by pulse oximetry during the test, and their values were noted at the beginning and after every 60 seconds of the test.

For each patient, expected 6MWD values for a healthy individual of the same sex, age, weight, and height were calculated at each follow-up, using the formulas derived by Ulrich et al., who collected the 6MWD values of healthy Swiss children and adolescents (7). One subject, aged 18 years, was excluded from this analysis as the formulas were devised to be used for children aged 5 to 17 years.

The following formulas were used: (age in years, weight in kg, height in m) (7)

male patients:

$13.40 \cdot y - 2.16 \cdot kg + 196.53 \cdot m + 276.92$

female patients:

$372.3 \cdot m - 2.635 \cdot kg + 172.05$

Statistical Analysis

Statistical analysis was performed in R v4.2.2. Some patients did not perform the 6MWT at every follow-up for one of the following reasons: 6MWT was only introduced to the protocol in February 2022, occasionally it could not be performed successfully in younger children, the results were not valid due to an unrelated injury or disease, etc. Missing data were replaced using the "Last Observation Carried Forward" (LOCF) and/or "Next Observation Carried Backwards" (NOCB) imputation methods during statistical analysis. The following number of patients were missing 6MWT results at each follow-up: 17 at treatment initiation, 5 after 3 months, 6 after 6 months, 7 after 9 months, and 10 after 12 months of treatment. In a few patients the sweat chloride test results were not valid due to inadequate sample volume. In such cases the same imputation methods were used to replace the missing values: two patients were missing sweat chloride values at treatment initiation, one patient after 6 months, and 3 patients after 12 months of treatment. The normality of distribution was tested with the Shapiro-Wilks test. Numerical variables are reported as means and standard deviations, or as medians with minimum and maximum values. For continuous, normally distributed variables, the Paired Samples Student's T-test, and one-way and two-way ANOVA were used to compare differences. Pearson's Correlation was used to assess correlations between variables. A P-value of less than 0.05 was considered statistically significant.

Results

A total of 49 pediatric patients commenced treatment with either ELX/TEZ/IVA or LUM/IVA before June 2023. Of those, thirty-four participants were included in the study on the basis of the predefined inclusive criteria. Their baseline characteristics are presented in Table 1.

The study results are presented in Table 2.

The median age at treatment initiation was 14 years. Out of the 34 patients, 28 patients were aged 12 years and over, and commenced treatment with ELX/TEZ/IVA, while 6 patients, who were under the age of 12, commenced treatment with LUM/IVA. In the middle of treatment, HALMED lowered the age requirement for ELX/TEZ/IVA prescription from 12 to 6 years, so following this change 4/6 patients who had been treated with LUM/IVA were switched to ELX/TEZ/IVA. 21/34 patients were homozygous for Phe508del mutation while 13/34 patients had a single Phe508del allele and another minimal-function mutation.

Table 1. Baseline Characteristics of Subjects (N=34)

Gender (M/F)	19/15
Age (years)	14 (5;18)
CFTR mutation	
Phe508del homozygotes	21
Phe508del heterozygotes	13
Baseline values	
6-minute walk test	
6MWD*, m	519.3±107.7
ΔSpO2†, %	-2±2.1
ΔHR‡, min^{-1}	41.2±31.7
BMI z-score§	-0.49±0.98
ppFEV1II, %	68.1±23.6
Sweat chloride, mmol/L	114.3±25.9

*Six-minute walk distance; †Blood oxygen arterial saturation maximal decrease; ‡Heart rate max increase; § Body mass index; II percent-predicted forced expiratory volume in 1 second. Data are presented as mean ± standard deviation or median (range).

Table 2. Parameters of the 6-minute Walk Test, BMI z-score, ppFEV1, and Sweat Chloride Concentration during the 12-month Follow-up Period (N=34)

Outcome	Baseline	Month 3	Month 6	Month 9	Month 12	Change at month 12 from baseline	P-value
	6-minute walk test						
6MWD* (m)	519.3± 107.7	552.1± 92.0	592.8± 107.9	597.8± 85.4	620± 99.5	+100.7	<0.0001
ΔSpO2† (%)	-2±2.1	-1.9± 2.1	-1.4± 1.7	-2.6± 2.4	-2.5± 2.4	-0.5	>0.05
ΔHR‡ (min^{-1})	41.2± 31.7	38.7± 30.5	34.4± 30.0	49.6± 1.3	52.5± 27.7	+11.3	=0.043
BMI z-score§	-0.49± 0.98	-0.16± 0.99	-0.16± 1.10	-0.08± 1.08	-0.02± 0.99	+0.47	<0.0001
ppFEV1 ǁ (%)	68.1± 23.6	81.5± 21.3	82.3± 22.7	79.9± 22.7	81.9± 21.2	+13.80	<0.0001
Sweat chloride, (mmol/L)	114.3± 25.9	-	68.8± 37.2	-	79.2± 42.8	-35.1	<0.0001

* Six-minute walk distance; †Blood oxygen arterial saturation max decrease; ‡Heart rate max increase; § Body mass index; ǁPercent-predicted forced expiratory volume in 1 second. Data are presented as mean ± standard deviation. Analysis was done using one-way ANOVA.

The Six-Minute Walk Test

The mean baseline of the 6MWD was 519.3±107.8 m (Table 1). A significant improvement in the 6MWD was already visible at the first follow-up after three months of treatment (P=0.035); a mean increase of 6.3% was observed. Improvement in the 6MWD compared to the values at baseline and after 3 months persisted after 6, 9 and 12 months of treatment (P<0.0001) (Fig. 1). After 12 months, the mean 6MWD was 620.0±99.5 m; a total mean increase of 22.2% was observed (Table 2). The maximum drop in saturation (ΔSpO_2) during the 6MWT did not change significantly with the duration of treatment; a mean drop of around 2% was observed at baseline and all follow-ups. A borderline significant difference (P=0.043) in maximum increase of heart rate (ΔHR) with the duration of treatment was observed.

A significant difference was observed between the actual 6MWD values at baseline and those expected for healthy peers (P<0.0001); the average actual/expected 6MWD ratio was 79.9%. The difference steadily decreased after 3, 6 and 9 months of treatment, but remained significant (P<0.05) (Fig. 2). However, no significant difference was present after 12 months of treatment; the average actual/expected 6MWD ratio was 96.5%.

Body Mass Index

The mean baseline BMI z-score was -0.49±0.98 (Table 1). Prior to treatment initiation, 10/34 participants (29.41%) had a favorable z-score value (≥0). A significant improvement in BMI was visible after 3 months of treatment (P=0.019); with a mean absolute increase of +0.34±0.59. Improvement in BMI zscore compared to the baseline persisted after 6, 9, and 12 months of treatment (P<0.0001) (Fig. 1). After 12 months a mean value of -0.02±0.99 was observed; the mean absolute increase in BMI z-score in the 12month period was +0.48±0.55 (Table 2). A total of 16 subjects had a satisfactory BMI z-score (≥0) after 12 months of treatment; in 7/24 patients who were suboptimally nourished (BMI z-score <0) prior to treatment initiation, an increase in BMI z-score above 0 was observed, while in 1/10 patients who had optimal BMI, the BMI z-score decreased to below 0. One patient (1/34) had a BMI z-score ≥2 (obesity) at the end of monitoring, and the BMI did not improve of 1/2 patients who were severely malnourished (BMI z-score <-2) at the beginning of treatment,.

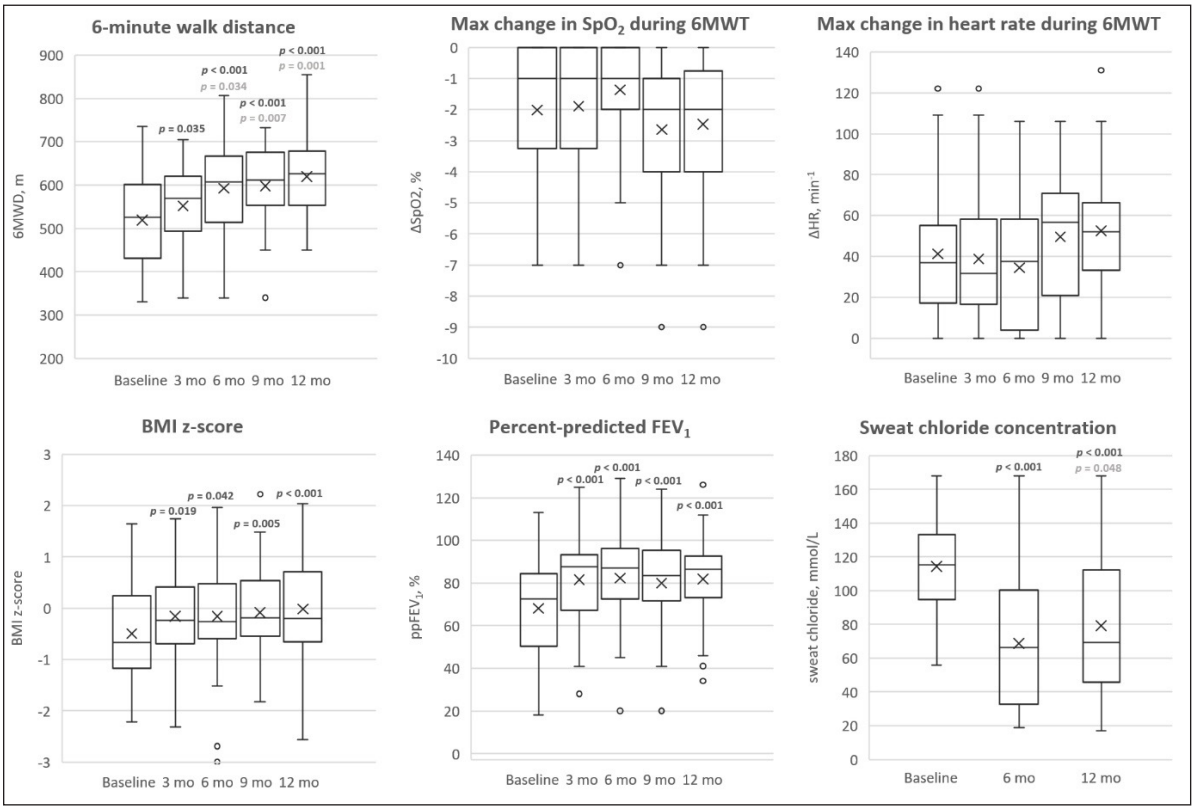

Fig. 1. *Data on the 6MWT results, BMI z-score, ppFEV1 and sweat chloride relating to 34 subjects over 12 months. The median and interquartile range, as well as mean values and individual extreme data points are represented. The analysis was conducted using the paired samples T-test. The P-values of groups different from the baseline (P<0.05) are represented for each parameter. Additionally, 6MWD P-values in light gray represent a significant difference from the 3 month value. For sweat chloride concentration, a Pvalue in light gray represents a significant difference between 6 and 12 month values. Abbreviations: 6MWT – six-minute walk test; BMI – body mass index; FEV1 – forced expiratory volume in one second; SpO2 – blood oxygen arterial saturation*

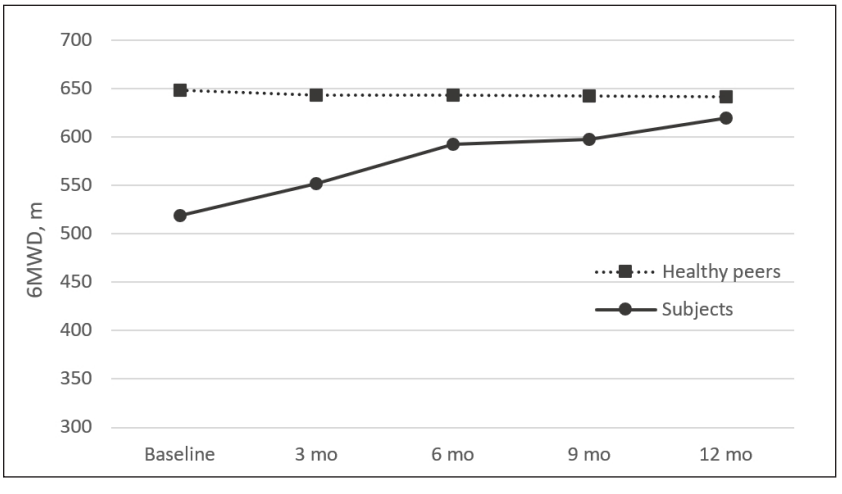

Fig. 2. *6-minute walk distance values observed compared to expected distances for healthy individuals of the same age, sex, weight and height (N=33). After 12 months of treatment no statistically significant difference was present between the expected and the actual 6MWD values. Abbreviations: 6MWD – six-minute walking distance. Predicted distances were calculated using formulas by Ulrich et al.(19).*

Spirometry and Percent Predicted FEV_1

The mean baseline $ppFEV_1$ was 68.1±23.6%; 14/34 subjects (41.2%) had optimal lung function with $ppFEV_1 \geq 80\%$ prior to treatment initiation (Table 1). A significant improvement in $ppFEV_1$ was visible after 3 months of treatment (P<0.0001); a mean absolute increase of 13.4±12.8% was observed. Improvement in $ppFEV_1$ compared to the baseline persisted after 6, 9, and 12 months of treatment (P<0.0001) (Fig. 1). After 12 months of treatment the mean $ppFEV_1$ was 81.88±21.19%; and the average absolute increase in $ppFEV_1$ was +13.8±13.9% (Table 2). The majority of subjects (22/34 or 64.71%) had optimal lung function at the end of the monitoring period.

Sweat Chloride Concentration

The mean baseline sweat chloride concentration was 114.27±25.92 mmol/L; in only 1/34 subjects was baseline sweat chloride <60 mmol/L (Table 1). A significant decrease in sweat chloride was visible after 6 months of treatment (P<0.0001); the average concentration was 68.77±37.25 mmol/L (Fig. 1). At that point, 9/34 participants had intermediate sweat chloride concentration (30-59 mmol/L), and 4/34 <30 mmol/L. A decrease from baseline was also observed after 12 months (P<0.0001), however, the average concentration was 79.21±42.84 mmol/L. 10/34 patients had intermediate sweat chloride concentrations, and 3/34 <30 mmol/L. The difference in sweat chloride concentration between the 6 month and 12 month follow-ups was only borderline significant ($p = 0.048$).

Changes in sweat chloride concentrations were compared between homozygous and heterozygous subjects for the Phe508del mutation and no difference was observed.

Correlation Between Parameters

Potential correlations between 6MWT results, BMI z-score, $ppFEV_1$, and sweat chloride were explored but none were significant. Patients who had good lung function at baseline ($ppFEV_1 \geq 80\%$) continued to achieve better spirometry results at the 3 month to 12 month follow-ups compared to patients with $ppFEV_1 < 80\%$ at baseline (P<0.001). When compared on the basis of baseline nutritional status, patients with a favorable BMI z-score (≥0) and those with a suboptimal BMI z-score (<0) at baseline showed no significant difference in BMI at follow-ups.

Discussion

In this study, starting ELX/TEZ/IVA or LUM/IVA CFTR modulator therapy led to a significant increase in the 6MWD that was already visible at the first follow-up after 3 months of treatment, peaked at 6 months, and was maintained after a full year of treatment. The observed total average increase of +100.7 m or +22.2% in this study is comparable to the results of previous studies done on adult patients. Wark et al. reported a total increase of +118.1 m or +22.2% after 12 months of treatment with LUM/IVA (8). Giallongo et al. reported an increase of +138 m or +28.6% in adults treated with ELX/TEZ/IVA (4). An analysis of various studies using the 6MWT in patients with different cardiorespiratory diseases showed that an increase of 14 to 30.5 m in the 6MWD between two assessments can be considered clinically significant (9). Comparison of the observed 6MWD values and expected 6MWD values for matched healthy individuals showed a significant difference between the expected and the actual values at baseline (7). The difference persisted but decreased after 3, 6, and 9 months of therapy. After 12 months, the difference between the two was no longer statistically significant; the average observed 6MWD was only 21.9 m shorter than that predicted for a healthy individual. This should be considered an additional indicator that one year of CFTR modulator treatment can bring CF patients close to completely normal everyday functioning comparable to that of their peers.

No significant change in SpO_2 decrease during the 6MWT was observed in the followup period. This result is consistent with previous studies

which have shown that SpO_2 does not change significantly during the 6MWT in either healthy individuals or patients with CF (10, 11). This is unsurprising as the 6MWT is a submaximal exercise test, in which patients self-determine the pace and intensity of physical exertion (10). The 6MWT has also been found to cause less stress to cardiorespiratory parameters compared to similar submaximal tests, such as the three-minute step test (12). A borderline significant change in heart rate increase during the 6MWT was observed: a higher increase in heart rate was visible after 12 months of treatment compared to the baseline. This can be explained by the increased oxygen demands of the muscle tissue, as improvement in physical condition enabled patients to perform the 6MWT with increased intensity, and cover more distance in the same time frame.

Improvements in BMI and $ppFEV_1$ with CFTR modulator therapy were consistent with results from previous studies (13-18). The BMI zscore increased on average by 0.33 after 6 months of treatment. After 12 months of treatment, the median BMI z-score was -0.2 and the total number of patients with a BMI z score ≥ 0 had risen from 10/34 at baseline to 16/34, with only one patient gaining too much weight, resulting in obesity. Percent-predicted FEV_1 increased on average by 14.2% after 6 months of treatment. This is comparable to results from Middleton et al. who reported an increase of 13.9% after 6 months of treatment with ELX/TEZ/IVA, although our study included a few patients treated with LUM/IVA (13). LUM/IVA has been previously found to have a smaller effect on lung function compared to ELX/TEZ/IVA, with a reported improvement of 3% after a 6-month period (18). It should be noted that any improvement in $ppFEV_1$, even stagnation, should be considered clinically significant, as without CFTR modulator treatment, pulmonary exacerbations and the overall progression of chronic lung disease leads to an annual decline in $ppFEV_1$ of 1% to 3% (19). After 12 months of treatment, the median $ppFEV_1$ was 86.5% and the total number of patients with ppFEV1 ≥80% had risen from 14/34 at baseline to 22/34. The positive impact on both $ppFEV_1$ and BMI z-score was already visible at the first follow-up after 3 months of treatment, and was maintained with no further significant improvements throughout the rest of the year, which is in line with results from previous studies (22). The 6MWD values reached a plateau at the 6 month follow-up, but remained lower than the expected values for healthy peers until the 12-month follow-up. This was the result of weight having a negative effect on the estimated 6MWD in formulas used for its calculation, so the expected 6MWD slightly decreased with treatment duration due to the increase in body weight.

No correlation was found between improvement in nutritional status or lung function and physical condition, which is consistent with the results of the majority of the previous studies comparing BMI, $ppFEV_1$, and 6MWT results in CF patients (12, 23-26). However, a few studies have demonstrated a correlation between BMI z-score and 6MWD z-score, as well as $ppFEV_1$ and 6MWD in a subgroup of patients with severe lung disease, and it has been suggested that the 6MWT could be used as a predictor marker for lung disease in such patients (12, 27).

Changes in sweat chloride concentration are a direct indicator of the systemic effect of CFTR modulators (28). A significant decrease in sweat chloride concentration was present after 6 months, and was maintained after 12 months of treatment. 10/34 patients had a reduction in sweat chloride to <60 mmol/L which is considered an intermediate concentration, and 3/34 patients to <30 mmol/L which is a level below the diagnostic value for CF (29). According to previous reports, children who are homozygous for Phe508del are expected to experience a greater reduction in sweat chloride concentration than children with a single Phe508del allele. This was explained by the increased quantity of Phe508delCFTR protein that could be achieved by modulators in homozygous patients (30). However, no such difference was observed in our study. We also could not establish any correlation between a sweat chloride decrease and the

improvements in lung function, nutritional status, or physical condition.

This study has several limitations. First, it is a combined analysis of patients treated with ELX/TEZ/IVA and those treated with LUM/IVA, as the sample size was too small for separate analysis, as well as the fact that some patients who started treatment with LUM/IVA were switched to ELX/TEZ/IVA following the change in the age requirement. Another limitation was the use of imputation methods to replace missing 6MWT values. We believe that the use of LOCF/NOCB imputation methods does not invalidate our findings, but may in fact underestimate the actual increase in the 6MWD. The benefits of this study are a longer follow-up period of 12 months compared to most previous studies exploring the connection between CFTR modulator treatment and physical condition, as well as the inclusion of solely pediatric patients as subjects. Previous studies on the topic were mostly conducted on adult or mixed adult and adolescent subjects. Another benefit is the longitudinal follow-up of treatment every 3 months, which allowed us to judge the rate of change in 6MWT performance. This study also provides a comparison of 6MWT results in patients with CF and their healthy peers, although equations by Ulrich et al. were used to estimate 6MWD in healthy individuals instead of using a matched control group.

Conclusions

This study demonstrated an improvement in physical condition assessed by the 6MWT in children with CF aged 5 to 18 years, treated with CFTR modulators, either LUM/IVA or ELX/TEZ/IVA, over a period of one year. A statistically significant improvement was already present at the 3 month follow-up, with an additional improvement observed after 6 months of treatment. After one year of treatment, children with CF had a significant improvement in the 6MWD compared to their baseline, and performed the 6MWT at a rate statistically indistinguishable from the one expected in healthy individuals of the same sex, age, weight, and height.

Conflict of Interest: The authors declare that they have no conflict of interest.

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