Real Life Evaluation of the Multi-organ Effects of Lumacaftor/Ivacaftor on F508del Homozygous Cystic Fibrosis Patients

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Research Article

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Abstract

Background: Lumacaftor/Ivacaftor (LUM-IVA), a cystic fibrosis transmembrane conductance regulator (CFTR) protein corrector-potentiator combination, improves lung function and reduces pulmonary exacerbations (PEx) in F508del homozygous CF patients. However, the systemic effects of LUM-IVA outside the respiratory and nutritional domains have not yet been thoroughly investigated.

Methods: A prospective, real-world, one-year study was performed on F508del homozygous adult CF patients who commenced treatment with LUM-IVA. Pancreatic function, bone metabolism, fertility status, nutritional and pulmonary factors were evaluated.

Results: 12 patients with a mean age of 28.3 years (18.6-43.9) were recruited. Following 12 months of treatment, no changes were detected in glucose, insulin, c-peptide or BMI values. A significant relative decrease in mean alkaline-phosphatase levels (122.8 U/L vs 108, p=0.008) and a trend toward an increase in calcium levels (9.5 vs 9.8 mg/dL, p=0.0681) were observed. A non-significant improvement in mean DEXA spine t-score after a year of treatment (-2.1 vs -1.6, n=4, p=0.12) was detected. Sweat chloride concentrations decreased significantly after treatment (-21.4 mEq/L; p=0.003). Pulmonary outcome evaluations revealed improvement in spirometry values during the first three months (FEV1 by 5.7% p=0.019, FEF25-75 by 4.3% p=0.035) with no change in chest CT Bhalla score and CFQR after one year. There was also a shift from IV to oral antibiotics for PEx treatment.

Conclusions: After a year of treatment, a stabilization was observed in the pancreatic indices, nutritional status, structure and function of the lungs, with a beneficial effect on bone mineral metabolism and CFTR function. Additional studies should investigate the effect of CFTR modulators on extra-pulmonary manifestations.

The ClinicalTrials.gov registration number of the study is NCT04623879, registered on 10/11/2020, “retrospectively registered”.

Introduction

Cystic fibrosis (CF) is a genetic multisystem disease that is characterized by chronic airway infection, inflammation associated with loss of lung function, repeated pulmonary exacerbations (PEx), and ultimately, respiratory failure[1]. F508del is the most common mutation that causes CF. In July 2015, the U.S. Food and Drug Administration approved the combination Lumacaftor/Ivacaftor (Orkambi®, Vertex Pharmaceuticals) for use in patients with CF that are homozygous for the F508del mutation[2]. Briefly, this combination of a corrector (Lumacaftor) and potentiator (Ivacaftor) partially restores the activity of the membranous CF transmembrane conductance regulator (CFTR) protein. Lumacaftor improves the processing of F508del CFTR and its transport to the cell surface while Ivacaftor increases the probability for the channel to be open[2]. In clinical trials, treatment with Lumacaftor-Ivacaftor (LUM-IVA) led to increases in lung function and weight, and a significant reduction in the frequency of PEx and CF-related hospitalizations[2–4].

Extra-pulmonary complications are common in CF. Of these, CF-related diabetes (CFRD) is one of the worst prognostic factors[5] as there is a direct correlation between lung function and glycemic control. In people with gating mutations responsive to Ivacaftor, treatment was associated with an improvement in insulin secretion after a glucose challenge[6]. Previous studies reported inconsistent effects of LUM/IVA treatment on glucose metabolism and acute insulin secretion[7–9].

Another important extra-pulmonary complication is CF bone disease (CFBD), characterized by low bone mineral density. Osteopenia and fractures are noted among 50–75% of patients with CF. These effects are attributed to malabsorption of fat-soluble vitamins, sex hormone deficiency, chronic infection and inflammation, and low levels of bone-building exercises resulting from advanced respiratory compromise, as well as primary CFTR dysfunction[10].

Delays in sexual maturity in CF patients secondary to their chronic disease are accompanied by low levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)[11] with an increased risk of subfertility in women.

The current study aimed to evaluate the systemic effects of LUM-IVA treatment on endocrine pancreatic function, bone metabolism, and other extra-pulmonary parameters as well as respiratory changes during and after one year of treatment in adults with CF.

Materials And Methods

Study Design and Participants

The study was a prospective, single center, observational study on F508del homozygous adults with CF who commenced treatment with LUM-IVA and were followed for a year. Pregnant or nursing females, solid organ or hematological transplant recipients, alcohol or drug abusers, patients with an acute upper or lower respiratory infection, and patients with PEx or changes in therapy within 28 days before Day 1 (first dose of LUM-IVA) were excluded.

All subjects received 400 mg Lumacaftor and 250 mg Ivacaftor (LUM-IVA) fixed-dose combination film coated tablets for oral administration every 12 hours. All participants remained on their pre-study stable CF medication regimen throughout the year. They were followed in the CF Center at Carmel Medical Center, Haifa, Israel between November 2016 and June 2019. The institutional board reviewed and approved the study protocol. All patients provided written informed consent. The ClinicalTrials.gov identifier of the study is NCT04623879.

In Israel, F508del allele frequency accounts for only around 23%, and therefore 13 adults with the F508del homozygous genotype attend our center.

Study Period

The screening period started on Day − 28 and ended on Day − 1. The treatment period started on Day 1 and lasted 12 months (± 7 days), with clinic visits scheduled every three months (Day 1 and Weeks 12, 24, 36, and 48 ± 7 days).

Study Assessments

The primary endpoint assessed pancreatic function by the absolute and relative change from baseline in oral glucose tolerance (OGTT) test through 12 months. Secondary endpoints included absolute and relative changes from baseline through 12 months in bone metabolism parameters, nutritional factors, fertility hormones, sweat chloride, pulmonary status, and CFQR score.

Pancreatic function evaluation: At screening visit, 3 months, and 12 months, an OGTT was performed in patients without CF-related diabetes: 75g of glucose were ingested, and glucose, insulin, and c-peptide were examined at three time points: 0, 1 hour, and 2 hours. In addition, HbA1C levels were evaluated in all patients at each study visit.

Bone indices: At screening and at 12 months, bone density was measured, using a dual-energy x-ray absorptiometry (DEXA) scan test. In addition, during every visit, bone metabolism factors, including parathyroid hormone (PTH), alkaline-phosphatase, phosphor, calcium, vitamin D levels, and urine Ca/Cr ratio were assessed.

Nutritional status: Body mass index (BMI) and levels of vitamin A, E (absolute), and albumin were assessed at each visit.

Fertility evaluation: Reproductive hormones including LH, FSH, testosterone, and estradiol were assessed at each visit in individuals of both sexes.

Additional parameters: Vital signs, physical examination, sputum cultures, laboratory tests (e.g. complete blood count [CBC] and chemistry tests including electrolytes, liver and kidney function, and coagulation function) were assessed in every visit.

Pulmonary: Pulmonary and lung morphology evaluations were carried out by

(1) The absolute change from baseline in the percentage of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and forced expiratory flow between 25–75 (FEF25-75), all were assessed every visit. To obtain these parameters, spirometry was performed in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force, using a KoKo® spirometer (n-Spire Healthcare, Inc., Longmont CO, USA)[12]. Absolute values of spirometry were transferred to percent predicted (pp) using Global Lung Function Initiative (GLI) reference data. **(2)** Chest computed tomography (CT) scans were performed at baseline and after one year, scored using the Bhalla scoring method[13] by a radiologist-investigator (the total score ranges from 9 to 25, with a higher score indicating more severe structural lung changes). **(3)** Quality of life was measured using the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score every visit (scores range from 0 to 100,

with higher scores indicating a better quality of life and four points considered to be a minimal clinically important difference)[14]. **(4)** PEx was defined as deteriorations in respiratory symptoms that led to changes in treatment[15]. Each PEx was counted as a separate event, and the number of PEx during one year prior to commencing treatment with LUM-IVA was compared to PEx through the first year of treatment. We documented the number of exacerbations, oral vs. intravenous (IV) antibiotic treatments, hospitalizations, presence of fever > 38°C, laboratory parameters (white blood cells count [WBC], absolute neutrophil count [ANC], and C-reactive protein [CRP] at PEx start in hospitalized patients), sputum culture results, and time to next PEx.

CFTR function: Evaluation was measured through testing the concentration of sweat chloride that was performed at screening and after a year of treatment by Macroduct ® sweat collection system[16].

Statistical Analysis

Statistical analyses were performed using the SAS version 9.4 (SAS Institute, Cary North Carolina, USA). All measured variables and derived parameters were tabulated by descriptive statistics. For categorical variables, summary tables are provided presenting sample size and absolute and relative frequency. For continuous variables, summary tables are provided presenting sample size, arithmetic mean, standard deviation, median, minimum, and maximum for means of variables. A paired t-test for two means (repeated observations) was applied for testing the statistical significance of the change from baseline for each continuous variable. A logistic regression model was applied for testing the statistical significance of the difference in several exacerbation parameters between before and after LUM-IVA treatment. All tests were two-tailed, and a p-value of 5% or less was considered statistically significant.

Results

Baseline Parameters

Out of 13 F508del homozygous adults attending Carmel CF Center who were screened, 12 consented (Fig. 1). 8 males (67%), with a mean age of 28.3 ± 6.9 years and mean BMI 20.5 ± 3.4 Kg/m^2. All patients had pancreatic insufficiency (PI) and 4 patients had CFRD at treatment start. Their baseline parameters are presented in Table 1. The values of pulmonary characteristics (ppFEV1 of 60 ± 16.9 and $ppFEF_{25-75}$ of 30.1 ± 17.4) indicate a relatively progressed stage of CF lung disease at the start of treatment.

Table 1
Baseline characteristics of participants

Before Lumacaftor/Ivacaftor treatment (N = 12)	Mean (SD)
Age in years at start	28.3 (± 6.9)
Male/ Female	8 (67%) / 4 (33%)
CFRD at start	4 (33%)
ppFEV1 %	60 (± 16.9)
ppFVC %	75.5 (± 16.7)
ppFEF25-75 %	30.1 (± 17.4)
BMI Kg/m^2	20.5 (± 3.4)
Sweat chloride mEq/L *	107.7 (± 11.6)
CT Bhalla score **	12.8 (± 2.7)
*N = 11 ** N = 10	

Endocrine Pancreatic Function Assessments

In 8 patients (no CFRD) who underwent OGTT at screening, 3, and 12-month visits, no consistent changes were noticed in glucose, insulin, or c-peptide levels. Following one year of LUM-IVA treatment, the median glucose values at 2 hours of OGTT decreased from 122mmol/L (range 94–159) at screening to 109 mmol/L (range 84–215), without statistical significance [Table 2]. No patient developed CFRD during the first year of LUM-IVA treatment. Also, none of the four CFRD patients were able to reduce the insulin dose under LUM-IVA treatment. The median value of HbA1C for CFRD patients was 9%, and for non-CFRD 5.9%, throughout the study with no detectable change (data not shown).

Table 2
Change in Oral Glucose tolerance test (OGTT) results from baseline

Glucose tolerance test results		N	Mean	Std	Paired T-test P-value of change from baseline
Baseline*	Insulin0	6	13.2	10.3	
	Insulin1	6	81.8	84.5	
	Insulin2	6	102.3	96.9	
	Cpeptide0	6	0.3	0.1	
	Cpeptide1	6	1.1	0.4	
	Cpeptide2	6	1.6	0.5	
	Glucose0	8	93.4	6.5	
	Glucose1	7	151.3	25.3	
	Glucose2	8	125.8	24.7	
3 months after treatment	Insulin0	6	7.1	8.1	0.3738
	Insulin1	5	59	80	0.303
	Insulin2	5	47.7	38	0.2935
	Cpeptide0	7	0.3	0	0.7578
	Cpeptide1	5	1.4	0.4	0.0818
	Cpeptide2	5	1.9	1.2	0.2282
	Glucose0	7	87.1	15.4	0.2512
	Glucose1	7	174.3	52.4	0.1905
	Glucose2	7	133.9	34.6	0.4481
12 months after treatment	Insulin0	8	6.1	9.8	0.3065
	Insulin1	8	35	58.7	0.0853
	Insulin2	8	28	42.8	0.1681
	Cpeptide0	8	134.5	378.8	0.0939
	Cpeptide1	8	164.7	463.2	0.53
	Cpeptide2	7	38.2	98.7	0.5379
	Glucose0	8	98	20.2	0.7552

*Baseline units: Insulin (mIU/L), C-peptide (nmol/L), Glucose (mg/dL).

Glucose tolerance test results		N	Mean	Std	Paired T-test P-value of change from baseline
	Glucose1	8	197.9	47.5	0.065
	Glucose2	8	124.4	41.9	0.1026
*Baseline units: Insulin (mIU/L), C-peptide (nmol/L), Glucose (mg/dL).					

Bone Metabolism Assessments

No deterioration was noted in any of the bone health parameters [Table 3, Fig. 2(A-F)]. A significant relative decrease in the mean alkaline-phosphatase level after 9 months of treatment ($p = 0.008$) and a trend towards increased calcium levels at 6 and 9 months of treatment were observed [Fig. 2(A, B)]. A concomitant increase in urinary excretion of calcium at 6 months was observed as well ($p = 0.0213$) [Fig. 2C]. A trend towards an increase in Vitamin D levels was evident but did not reach statistical significance [Fig. 2D]. There was no change in phosphorus or PTH levels [Fig. 2 (E, F)]. We observed a non-significant improvement in the mean spinal total T-score in DEXA test from − 2.1 to -1.6, $p = 0.12$ in four patients who had DEXA tests at both the screening and 12-month visits.

Table 3
Mean values of bone parameters at baseline and after 3, 6, 9, and 12 months of Lumacaftor/Ivacaftor treatment.

	At Baseline	3 months after start	6 months after start	9 months after start	12 months after start
Vitamin D (SD)	40.9 (± 24.5)	36.6 (± 19.2)	37.6 (± 25.9)	45.8 (± 18.5)	51.9 (± 24.3)
N	8	6	4	4	8
Change from baseline		-2.2	-12.6	3.6	9.2
p-value		0.8682	0.5132	0.7479	0.3948
Phosphorus (SD(	3.7 (± 0.6)	3.8 (± 0.7)	3.6 (± 0.8)	3.5 (± 0.5)	3.3 (± 0.5)
N	11	9	9	11	11
Change from baseline		0.1	-0.1	-0.2	-4.9
p-value		0.5721	0.7797	0.2024	**0.0197**
Calcium) SD(	9.5 (± 0.5)	9.6 (± 0.4)	9.9 (± 0.4)	9.8 (± 0.5)	9.7 (± 0.3)
N	12	12	11	12	12
Change from baseline		0.1	0.3	0.3	0.2
p-value		0.6198	0.0677	0.0681	0.2334
PTH (SD)	40.9 (± 14.4)	38.4(± 10.1)	47.1 (± 14.6)	59.2(± 81.1)	39.7 (± 11.6)
N	8	8	6	6	5
Change from baseline		-2.8	1.2	-2.4	5
p-value		0.5883	0.8139	0.6639	0.1352
Alkaline-phosphatase (SD)	122.8 (± 71)	89.4(± 49.2)	111.3(± 104)	108 (± 99.6)	106.8 (± 78.8)
N	12	10	11	12	12
Change from baseline		-37.5	-13.8	-14.8	-15.9
p-value		**0.0087**	0.1798	0.1431	0.1329

	At Baseline	3 months after start	6 months after start	9 months after start	12 months after start
Relative change (%)		-28.1	-18.9	-18.8	-15.6
p-value		**0.0002**	**0.0065**	**0.008**	0.1055
Urine Ca/Cr (SD)	0.1 (± 0.0)	0.1 (± 0.1)	0.2 (± 0.1)	0.2 (± 0.1)	0.1 (± 0.1)
N	9	8	6	4	7
Change from baseline		0	0.1	0.1	0
p-value		0.8122	**0.0213**	0.2114	0.4711

Nutrition, Vitamins, Liver, and Fertility Status

There was no impact through a year of LUM-IVA treatment on BMI values. However, a significant increase in albumin levels [Table 1 Supplementary] was found at the 6- and 9-month visits (4.4 vs 4.7 mmol/L p = 0.007 and 4.4 vs 4.6 mmol/L, p = 0.03, respectively). No noticeable changes were detected in the levels of liver enzymes (aspartate transaminase, alanine transaminase, and gamma glutamyl transferase), lipid-soluble vitamins (A, E), or fertility hormones (LH, FSH, testosterone, and estradiol) (data not shown).

Cystic Fibrosis Transmembrane Regulator Activity

Sweat chloride test results indicated a decrease in chloride concentration after a year of treatment, at baseline mean 107.7 (± 11.6) vs 86 (± 12) mEq/L, p = 0.003 (change from baseline of -21 (± 15.3) mEq/L, N = 9).

Pulmonary Outcomes

Stable PFT values compared to baseline was observed after a year of treatment (ppFEV1 improved by 0.6% and ppFVC improved by 2.7% at 12 months) [Table 4]. Moreover, at three months, a marked increase was evident (ppFEV1 by 5.7% p = 0.019, ppFEF25-75 by 4.3% p = 0.035) [Table 4]. No change was observed in the chest CT Bhalla total score after a year of treatment (p = 0.43) [Table 4]. No change in quality of life, as evaluated by the CFQR respiratory domain score, was noted (data not shown). 30 PEx events were recorded in the year before starting LUM-IVA treatment as compared to 28 PEx during the study period. The mean PEx rate per patient year was 2.5 before LUM-IVA, and 2.3 during the study. There was no change in the number of hospitalizations nor in the duration of hospitalization per PEx [Table 2 supplementary]. However, fewer PEx were treated with IV antibiotics (28.6% on LUM-IVA vs. 56.7% one year before p = 0.039) [Table 2 supplementary]. No difference was observed between the PEx events before and after LUM-IVA treatment with respect to time of next PEx or complications such as hemoptysis, presence of fever, levels of WBC, ANC, and CRP at PEx start. Bacteriological assessments

showed the presence of *Pseudomonas aeruginosa* (PA) in combination with methicillin susceptible *Staphylococcus Aureus* (MSSA) during PEx in most patients (data not shown).

Table 4
Mean respiratory values after Lumacaftor/Ivacaftor treatment

	3 months after start	**6 months after start**	**9 months after start**	**12 months after start**
	N = 12	**N = 11**	**N = 12**	**N = 12**
FEV1% (SD)	65.7(±16)	61.5(±18.3)	62.6(±17.6)	60.6(±15.8)
Change from baseline	5.7	0.7	2.6	0.6
p-value	**0.0192**	0.8541	0.3275	0.8633
FVC% (SD)	82.8(±18.6)	80.9(±17.7)	77.1(±18.2)	78.2(±17.5)
Change from baseline	7.3	4.6	1.6	2.7
p-value	0.0597	0.3442	0.7392	0.5886
FEF25-75% (SD)	34.5(±17)	31.1(±17.2)	32.6(±17.3)	34(±19.9)
Change from baseline	4.3	0.5	2.5	3.9
p-value	**0.0359**	0.8581	0.2202	0.2653
CT Score (SD)*	-	-	-	12.5(±2.7)
Change from baseline	-	-	-	-0.3
p-value	-	-	-	0.4344
*N = 10				

Discussion

This was a real-life prospective observational study evaluating the systemic effects of LUM-IVA on pancreatic endocrine function, bone metabolism, fertility status, nutritional-state, and pulmonary outcomes in 12 CF patients during a one-year treatment. Our population comprised of adult patients with a long-standing lung disease and a relatively high degree of pulmonary compromise. Left untreated, such patients tend to deteriorate over time, with an estimated annual decline of 1–2% in PFT in CF patients with the same genotype[2].

Pancreatic Function

No consistent changes in levels of glucose, insulin, or c-peptide were detected in this study. We found a trend towards a decrease in the 2-hour glucose value after a year of LUM-IVA treatment, which is the most

important time point for the decision to start insulin treatment. The previously reported findings on the impact of LUM-IVA treatment on the glucose levels are inconsistent, as some found no improvement in the glycemic control[7, 8], while others reported significant reductions in 1- and 2-hour glucose levels[9]. In addition, Kessler and colleagues[17] suggested that the CFTR modulators play a positive role at the very early stage of glucose tolerance abnormalities in CF, which is unfortunately not the case in our adult cohort.

Bone Metabolism

To the best of our knowledge, this is the first study evaluating the effects of LUM-IVA treatment on bone metabolism. We demonstrated decreases in alkaline-phosphatase and increases in calcium levels and urinary excretion of calcium. These changes may indicate improved vitamin D absorption, which mends the grade of osteomalacia and may potentially account for the lower alkaline-phosphatase levels[18]. These findings are in line with a case report[19] describing a 25 year old CF patient with osteomalacia which was improved after a change in vitamin D levels. Similarly, a large CF-registry-data-based observational analysis of patients with a variety of gating mutations showed a lower prevalence and relative risk of CFBD in the Ivacaftor-treated group compared to controls[20]. In a small series by Sermet-Gaudelus and colleagues[21], involving 7 adults with the G551D mutation treated with IVA, a significant improvement in lumbar spine z-scores was observed. In our cohort, the tendency towards improved DEXA test results from after one-year reflect improvement in factors contributing to osteopenia including CFTR dysfunction, malabsorption of fat-soluble vitamin D, and malnutrition[22].

Nutritional Status and Fertility

The mean BMI did not change throughout the study period. This is in accordance with the results presented in real-life studies by Diab-Cáceres *et al*[23] and Hubert, D *et al*[24], but contrary to findings summarized in a systematic review of five randomized controlled trials[25] showing improved BMI, although their power for analysis as limited.

Reduced fertility in CF patients is common not only in men, but also in women, estimated at 35%[26]. We found no change in sex hormones following one year of treatment with LUM-IVA. Jones and colleagues[27], reported a series of female patients who previously required *in vitro* fertilization but were able to become pregnant spontaneously or to have normalized menstrual cycles after IVA treatment. As far as we know, no other studies examined fertility in CF patients treated with LUM-IVA.

CFTR Function

The mean decrease of 21.4 mEq/L in sweat chloride concentration after one year of treatment is numerically similar to those reported in a post-market authorization study by Graeber and colleagues[28] assessing adults and children aged > 12 years. They demonstrated a mean reduction of 17.8 mEq/L in sweat chloride levels after 8–16 weeks of treatment[28].

Pulmonary outcomes

Our pulmonary function results suggest that the treatment prevented deterioration and could potentially, in the long term, delay the need for a lung transplantation. The improvement in ppFEV1 of 5.7% and in ppFEF25-75 of 4.3% at three months of treatment was similar to the modest yet significant results in Phase III studies [2]. Our results were also in line with the PROGRESS study[4] in which there was a 42% slower rate of FEV1% decline over the study period. To the best of our knowledge, this study is the first to evaluate chest CT before and after a year of LUM-IVA treatment. Similar to PFTs, analysis of the CT Bhalla score suggested a lack of deterioration in lung structure. This is contrary to results of the CORK study[29], which evaluated patients with the G551D gating mutation after initiation of Ivacaftor and revealed an improvement in CT imaging scores. In the CORK study, investigators analyzed adult patients with a better baseline ppFEV1 than our cohort, with a relatively milder class 3 CFTR mutation (G511D). The lack of improvement observed in our cohort may be due to the already advanced level of lung morphology damage at baseline.

In our small cohort, no change was detected in quality of life, nor a reduced rate of PEx or hospitalizations, contrary to previously reported studies[2, 3, 25, 30]. This may have resulted from one patient acquiring infection with *M. abscessus* during the study period. We interpret the shift from IV to oral antibiotics in treating PEx as reflecting a milder severity of PEx in our cohort. However, measures of inflammatory response such as CRP, blood leucocytes, and ANC were not affected.

During this study, patients did not experience any adverse events. None of the patients discontinued treatment.

This study had several limitations. First and foremost is the small sample size and that it was conducted within a single center. The design of a real-world study has the inherent problems of data not being consistently available for all patients at all time-points. There was also variability and heterogeneity in clinical response to LUM-IVA treatment due to objective “real-life” reasons such as severe lung disease at baseline with ppFEV1 lower than 40%, new onset *M. abscessus* infection during the study period, and others.

In conclusion, this study on adult patients demonstrates stabilization in the endocrine pancreatic indices, nutritional status, lung morphology and pulmonary function, and suggests a potentially positive impact on bone mineral metabolism and improvement in sweat chloride following a year of LUM-IVA treatment. Further larger studies with heterogeneous patients should continue investigating the effect of CFTR modulators on extra-pulmonary manifestations.

List Of Abbreviations

ANC- Absolute neutrophil count

BMI- Body Mass Index

CF- Cystic fibrosis

CFBD- CF bone disease

CFQR- CF questionnaire-revised

CFRD- CF-related diabetes

CFTR- Cystic fibrosis transmembrane conductance regulator

CRP- C-reactive protein

DEXA- Dual-energy x-ray absorptiometry

FEF25-75- Forced expiratory flow between 25 and 75

FEV1- Forced expiratory volume in 1 second

FVC- Forced vital capacity

FSH- Follicle-stimulating hormone

HbA_1C- Hemoglobin A_1C

LH- Luteinizing hormone

LUM-IVA- Lumacaftor/Ivacaftor

OGTT- Oral glucose tolerance test

PEx- Pulmonary exacerbations

PFT- Pulmonary function tests

PI- Pancreatic insufficient

PP-Percent predicted

PTH- Parathyroid hormone

WBC- White blood cell count

Declarations

Ethics approval and consent to participate:

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The institutional board of Carmel Medical Center reviewed and approved the study protocol.

Informed consent was obtained from all individual participants included in the study.

This article does not contain any studies with animals performed by any of the authors.

Consent for publication:

N/A

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

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Author AI declares that she has no conflict of interest.

Author MK declares that he has no conflict of interest.

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Author Contributions:

KY: Supervision, conception, writing- drafting the initial manuscript. ZS, MK, NS: Acquisition of data. IK: Analysis and interpretation of the endocrinology results. AI: Interpretation of data. A radiologist-investigator who Scored the chest CT. MS: Writing- substantively review of the manuscript. GL: Conceptualization/design, supervision, writing- review and editing of the manuscript. All authors read and approved the final submitted manuscript. All authors have agreed to be personally accountable for the author's own and others contributions.

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Figures

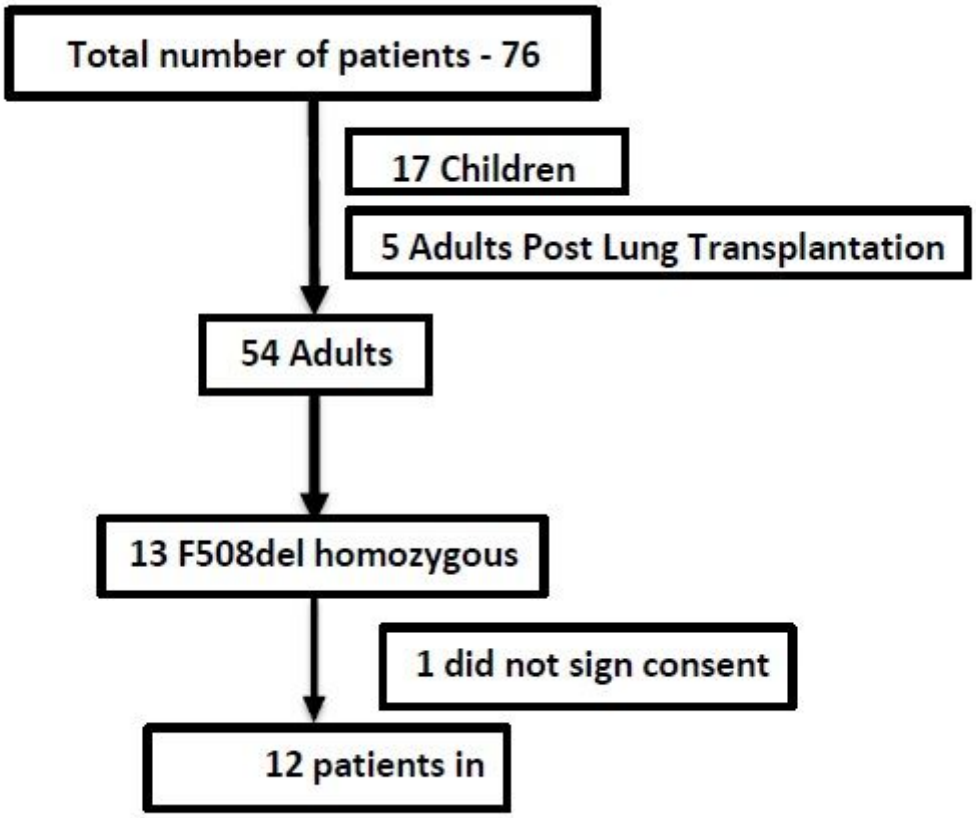

Figure 1

CF patient's flow chart

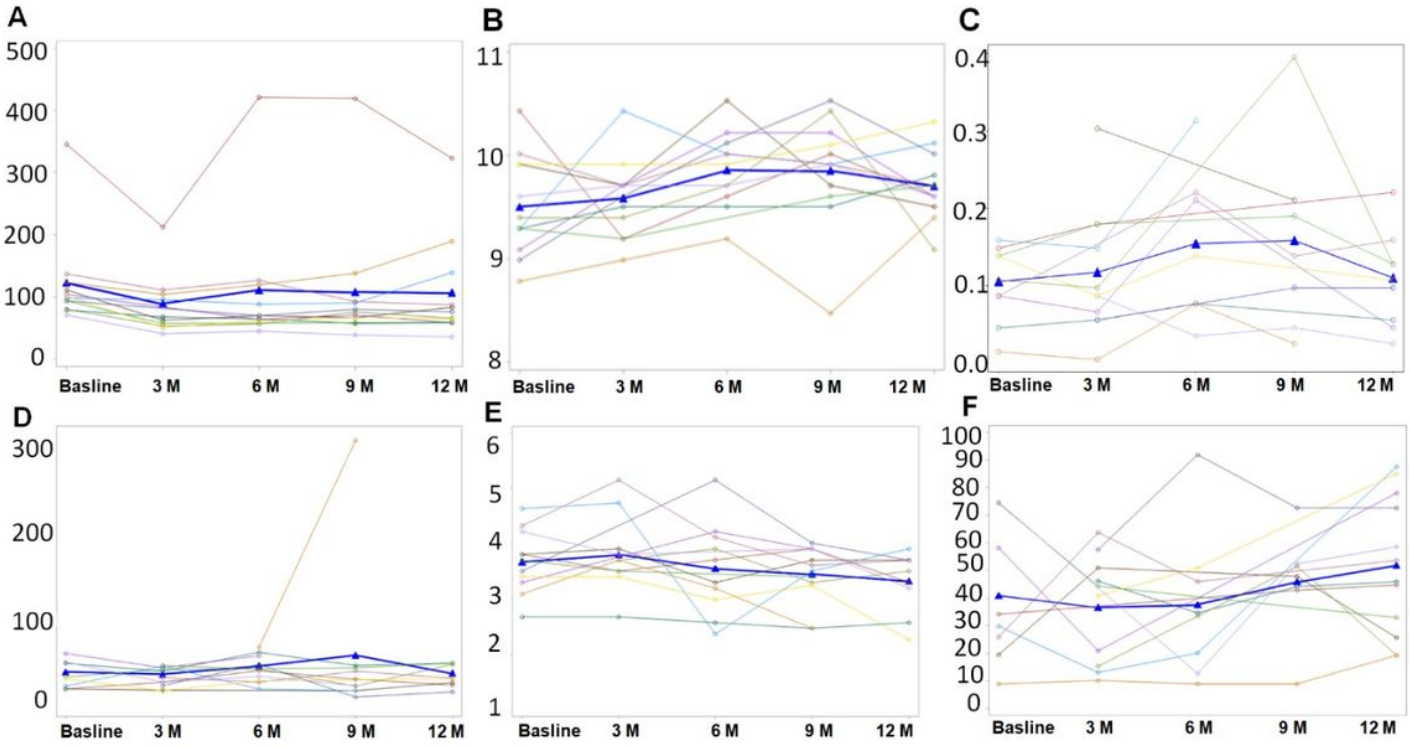

Figure 2

Bone metabolism parameters through 12 months of LUM-IVA treatment Single subject and mean (blue solid) curves are presented for (A) Alkaline-Phosphatase (U/L), (B) Calcium (mg/dL),(C) CA/CR urine,(D) PTH (pg/mL), (E) Phosphor (mg/dL), (F) Vitamin D (nmol/L), X axis represents the study visits in months (M). Y axis represents a scale of the value of each tested parameter.

Supplementary Files

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- Supplementarytables.1.xlsx