The short-term effects of ORKAMBI (lumacaftor/ivacaftor) on regional and distal lung structures using functional respiratory imaging

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Abstract

Background: Lumacaftor/ivacaftor (LUM/IVA) has shown modest benefits in previous research, but the exact effects in the cystic fibrosis (CF) lung remain unclear. This study aims to offer novel information on the mode of action of the cystic fibrosis transmembrane conductance regulator (CFTR)-modulating drug by assessing lung structure and function using functional respiratory imaging (FRI).

Methods: CF patients aged ⩾12 years homozygous for *F508del* were recruited in an open-label study. Before and after 12 weeks of treatment with LUM/IVA, FRI was used to visualize regional information, such as air trapping, lobar volume and airway wall volume. Secondary outcomes included the CF-CT scoring system, spirometry, the Cystic Fibrosis Questionnaire–Revised (CFQ-R) questionnaire, exercise tolerance and nutritional status.

Results: Of the 12 patients enrolled in the study, 11 completed all study visits. Concerning the FRI parameters, hyperinflation of the lung decreased, indicated by a reduction in air trapping and lobar volume at expiration. Also, a decrease in airway wall volume and a redistribution of pulmonary blood volume were noted, which might be related to a decrease in mucus impaction. Airway resistance, airway volume, internal airflow distribution and aerosol deposition pattern did not show significant changes. No significant improvements were found in any of the CF-CT scores or in the spirometric parameters. Other secondary outcomes showed similar results compared with previous research. Correlations at baseline were found between FRI and conventional outcomes, including physical functioning, spirometry and CF-CT scores.

Conclusions: LUM/IVA decreased lung hyperinflation in combination with a potential decrease in mucus impaction, which can be related to an improved mucociliary transport. These results indicate that several FRI parameters, reflecting regional and distal lung structures, are more sensitive to changes caused by LUM/IVA than conventional respiratory outcomes.

Keywords: CFTR modulator, computational fluid dynamics, cystic fibrosis, functional respiratory imaging

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Introduction

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene.

Deficient or dysfunctional CFTR protein results in a disturbed chloride and bicarbonate transport affecting multiple organs, including the respiratory system, gastrointestinal tract, and exocrine organs.[1]

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F508del is the most prevalent mutation with more than 40% of patients with CF in Europe being homozygous for this allele.[2] This mutation is associated with defective protein folding, which has an impact on the amount of CFTR protein reaching the epithelial membrane.[3] In addition, ion transport is limited due to impaired functionality of the limited quantity of protein that does reach the cell surface.[4] Orkambi® was developed by Vertex Pharmaceuticals (Boston, Massachusetts, USA) as a CFTR-modulating drug for patients homozygous for *F508del* and is composed of two active agents, ivacaftor and lumacaftor. Lumacaftor is a CFTR corrector that improves the processing and the stability of the protein, thus increasing the trafficking of mature protein to the epithelial membrane. The potentiator ivacaftor further increases CFTR-mediated chloride transport by extending the time the ion channels are open.[5] Previous large multi-centre randomized controlled trials have shown modest benefits of lumacaftor-ivacaftor (LUM/IVA). The primary outcome, the percentage of predicted Forced Expiratory Volume in one second (ppFEV$_1$), showed a mean absolute increase of approximately 3% from baseline. In addition, LUM/IVA was associated with clinically meaningful reductions in pulmonary exacerbations.[5,6] In a long-term extension study, a 42% slower rate of ppFEV$_1$ decline was found compared with matched controls.[7] Although these findings are promising, the clinical response is highly variable and the exact effects of LUM/IVA in the CF lung remain unclear.[8]

Functional respiratory imaging (FRI) is a quantifiable method to measure biological responses to therapeutic interventions using high-resolution computed tomography (HRCT) and computational fluid dynamics (CFD). A 3D reconstruction of the respiratory system combined with flow simulations can be used to determine parameters such as patient-specific airflow distribution, airway resistance and volume, lobar volume, and air trapping. This functional and structural evaluation of the lungs allows for an in-depth description of respiratory health and post-treatment effects.[9] Previous studies have demonstrated the validity of the lobar ventilation models and CFD simulations by comparing the results to 3He magnetic resonance imaging (MRI) ventilation measurements and combined single photon emission computed tomography and CT (SPECT/CT) in patients with asthma.[10,11] Besides a detailed report of characteristics on a lobar level, this method has shown to be a more sensitive technique than conventional lung function tests in various obstructive airway diseases. In chronic obstructive pulmonary disease (COPD) and asthma, several studies assessing the effects of bronchodilators and anti-inflammatory compounds showed significant improvements in FRI parameters, while these changes were less pronounced in the results of spirometry and body plethysmography.[12–14] In the CF population, FRI has demonstrated its value by establishing patient-specific airway models to predict the deposition of inhaled antibiotics.[15] Given these previous findings, we hypothesize that FRI parameters related to hyperinflation, airway volume and airway wall thickness could provide valuable insights into the effects of LUM/IVA as imaging biomarkers on lung structure and functionality. This study aims to offer additional and novel information about the mode of action of the CFTR-modulating drug by assessing lung structure and function across multiple FRI parameters.

Methods

Study design

An open-label, single-arm study was conducted to investigate the effects of LUM/IVA over an intervention period of 12 weeks. The investigational product, Orkambi®, was administered as two tablets (lumacaftor 200 mg/ivacaftor 125 mg) twice a day in compliance with the prescribing information and the European Medicines Agency (EMA) approval. Treatment was started after the completion of all baseline measurements. Participants visited the hospital every 4 weeks during the 12-week period at which following study assessments were carried out: physical examination and spirometry. Other assessments were only performed at baseline and at 12 weeks: CT chest imaging, nitrogen multiple breath washout (N$_2$MBW) test, Six-Minute Walk Test (6MWT), sweat chloride test and the Cystic Fibrosis Questionnaire–Revised (CFQ-R). Adverse events and adverse drug reactions were monitored throughout the study. The study was approved by the Ethics committee of the Antwerp University Hospital (EudraCT 2018-001573-24).

Participants

Participants aged 12 years or older were eligible for inclusion if they had a confirmed diagnosis of

CF, homozygous for the *F508del* mutation, a ppFEV1 ⩾50%, and if they were clinically stable. A full description of the eligibility criteria is provided in the Supplementary Material. Patients were recruited from July 2018 to October 2019 through referral from three CF centres: Antwerp University Hospital, GZA hospital campus Sint-Vincentius, and Ghent University Hospital. All study assessments were performed at the Antwerp University Hospital.

Study assessments

Functional respiratory imaging. HRCT scans were taken with a GE VCT LightSpeed 64-slice scanner (GE Healthcare, Chicago, Illinois, USA) at two breathing levels, total lung capacity (TLC) and functional residual capacity (FRC) monitored with a pneumotachograph. A description of specific CT settings can be found in the Supplementary Material. Images were imported into a medical image processing software package, Mimics (Materialize, Leuven, Belgium), for segmentation and 3D reconstruction of the airways and lung lobes. All segmentation and postprocessing steps were automated, except for the identification of the fissures to separate the lung lobes, which were manually adjusted. The computed models were used to determine structural parameters, such as lobar volume, airway volume, and air trapping. After segmentation and postprocessing, the models were used for CFD simulations by solving Reynolds-averaged Navier-Stokes equations, to calculate regional airway resistance and to predict the deposition pattern of inhaled drugs. Pulmonary vasculature was segmented using algorithms based on shape analysis to recognize tubular structures. The cross-sectional area of each identified blood vessel was determined to compute pulmonary blood distribution. Although Orkambi® is not delivered by aerosol, simulations were performed to evaluate whether the treatment would affect the lung deposition of one of the most frequently inhaled drugs by CF patients, dornase alfa. All subjects were coupled with the Pari eFlow Nebulizer (Starnberg, Germany) and simulated using a tidal breathing profile. The particle characteristics of dornase alfa were taken from literature.[16] Details of the analysis can be found in the Supplementary Material and previously published work.[11,17] The following FRI parameters were evaluated in this study: air trapping, lobar volume, airway volume, airway wall volume, airway resistance, pulmonary blood distribution, ventilation/perfusion matching, internal airflow distribution and aerosol deposition.

Secondary outcomes. Structural abnormalities on inspiratory and expiratory chest CTs were visually scored using the CF-CT scoring system, a validated upgraded version of the Brody II score.[18,19] The scans were scored by two independent observers blinded to subject ID and study visit, of whom one experienced chest radiologist and one certified researcher trained in CF-CT scoring. The presence and extent of the following abnormalities were evaluated: bronchiectasis, mucus plugging, parenchymal abnormalities and air trapping. All scores were expressed as a percentage of the maximum score. Data recorded during the monthly physical examination included body weight and length, peripheral oxygen saturation (SpO_2), pulse rate and blood pressure. Pulmonary function was measured by spirometry and N_2MBW. Exercise tolerance was evaluated by the Six-Minute Walk Distance (6MWD). During the exercise test, pulse oximetry was used to monitor SpO_2. Also, the Borg score for dyspnoea and fatigue were questioned before and immediately after the 6MWT. Health-related quality of life (QoL) was evaluated using the CFQ-R. Sweat chloride concentration was measured by pilocarpine iontophoresis. A more detailed description of the study assessments can be found in the Supplementary Material.

Statistical analyses

An initial sample size of 14 subjects was set to reach a power of 80% with a significance level of 0.05. Since no pilot data were available, the calculation was based on the change in airway volume (Cohen's effect size of 0.82) reported in a previous FRI study including patients with COPD.[12]

The analysis of the FRI parameters was based on a linear mixed-effects model, with visit, lobe and their interaction as fixed effects and lung lobe within each subject as a random effect. The heterogeneity across lobes (within subject) was modelled using an unstructured variance-covariance matrix, with independence assumed between subjects. For spirometry, anthropometrics and vital signs a similar approach was taken, excluding the lobar component. Changes in CF-CT scores, exercise tolerance, CFQ-R domain scores, lung clearance index and sweat chloride concentration were explored with the paired samples *t* test or the Wilcoxon signed-rank test, depending on the distribution of the variable. Additional correlation analyses were performed to

Table 1. Baseline characteristics ($n = 12$).

Sex (M/F)	11/1
Age (years)	23.0 [17;46]
BMI (kg/m^2)	22.3 ±3.5
Sweat chloride (mmol/L)	92.5 ±14.1
ppFEV$_1$ (%)	73.3 ±23.0

BMI, body mass index.
Data are presented as mean ± standard deviation or median [range].

determine the association between FRI parameters and secondary endpoints using the Pearson or Spearman correlation, depending on the distribution of the data. The distribution of the data was evaluated by QQ plots and the Shapiro-Wilk test. Normally distributed data are represented as mean ± standard deviation, and non-normal data as median [range]. Intraclass correlation coefficients were calculated using a two-way mixed-effects model for average measures to evaluate the interobserver reliability of the CF-CT score.[20] For all analyses, a p value < 0.05 was considered statistically significant.

Results

Participants
Twelve participants were enrolled in the study, of whom one discontinued treatment after 10 weeks due to respiratory complaints, including cough and increased sputum. Therefore, the latter subject was excluded in further analyses determining the effects of LUM/IVA. Besides the discontinuation of the study at the patient's own initiative, no serious adverse events were reported throughout the study. Baseline characteristics are presented in Table 1. The intended sample size of 14 subjects was not reached, since no other participants could be motivated to enter the trial. The main reason was the relatively short intervention period in combination with the fact that patients were not able to continue taking the drug after the trial, as Orkambi® was not reimbursed in Belgium at that time.

FRI parameters
The FRI analysis showed a decrease in air trapping ($16.12 \pm 19.13\%$ to $13.14 \pm 17.55\%$, $p < 0.001$),

lobar volume after normal expiration (0.63 ± 0.30 L to 0.57 ± 0.27 L, $p < 0.001$) and airway wall volume (22.89 ± 16.14 mL/L to 21.32 ± 12.51 mL/L, $p = 0.03$) per lung lobe. The change in total air trapping, lobar volume at FRC and airway wall volume (i.e. the sum of all five lobes) for each individual have been plotted in Figure 1, and an illustration of the 3D reconstruction of these parameters is shown in Figure 2. Also, a significant improvement of the ventilation/perfusion matching was found ($12.92 \pm 8.65\%$ to $14.66 \pm 7.43\%$, $p < 0.001$). After treatment, a higher proportion of pulmonary blood was found in blood vessels smaller than 5 mm^2 (BV5%) and a lower proportion in vessels larger than 10 mm^2 (BV10%). However, when considering the absolute volumes, no changes were observed in BV5, while the volume of blood vessels between 5 and 10 mm^2 (BV5_10) and BV10 decreased. No significant changes were found for lobar volume after maximal inspiration, airway volume, airway resistance, internal airflow distribution, intrathoracic and peripheral deposition of dornase alpha and the central/peripheral deposition ratio. The results for airway wall volume, airway volume and airway resistance were corrected for lung volume at lobar level. An overview of the results of the FRI analysis can be found in Table 2.

Secondary outcomes
The interobserver variability analysis of the CF-CT scoring method showed a moderate to excellent agreement between the two observers (Table 3). None of the CF-CT components nor the total score changed significantly after treatment.

ppFEV$_1$ increased by $2.0 \pm 4.0\%$ ($p = 0.3$), but this result was not significant. No other significant changes were found in other spirometric parameters. For the N$_2$MBW, the results of only five subjects were retained after evaluating the quality of the tests. The mean LCI$_{2.5}$ did not significantly decrease from 11.98 [9.44; 20.32] to 11.53 [8.54; 15.52] ($p = 0.3$).

The median 6MWD increased from 650 m [512; 790] to 725 m [525; 839] ($p = 0.02$). Although exercise tolerance increased, no significant changes were found in Borg score for dyspnoea and fatigue. The response of oxygen saturation to exercise was also similar between visits.

The CFQ-R questionnaire showed a trend towards an improvement of the physical domain
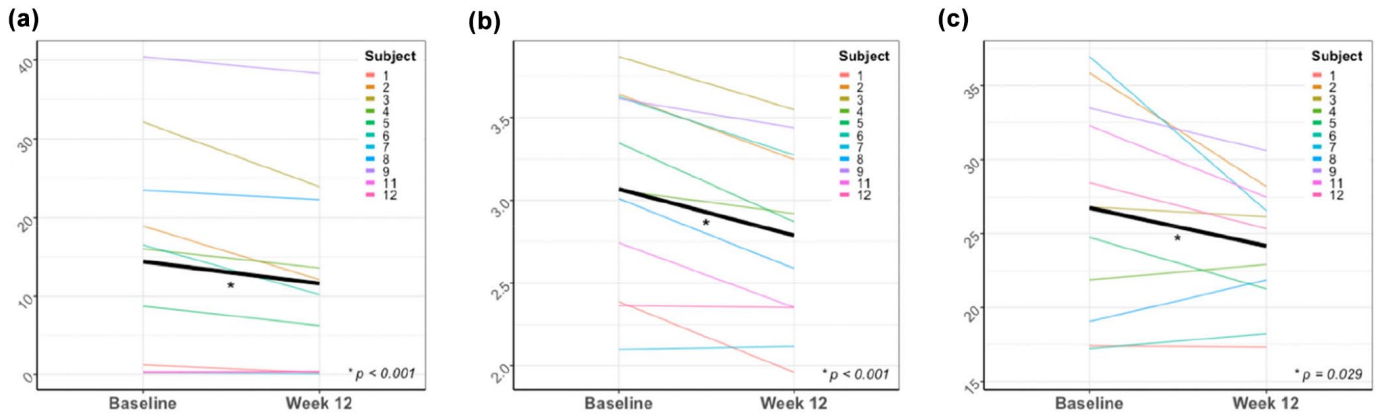
Figure 1. Mean change and individual changes of total (a) air trapping (%), (b) lobar volume at FRC (L), and (c) airway wall volume (mL/L).
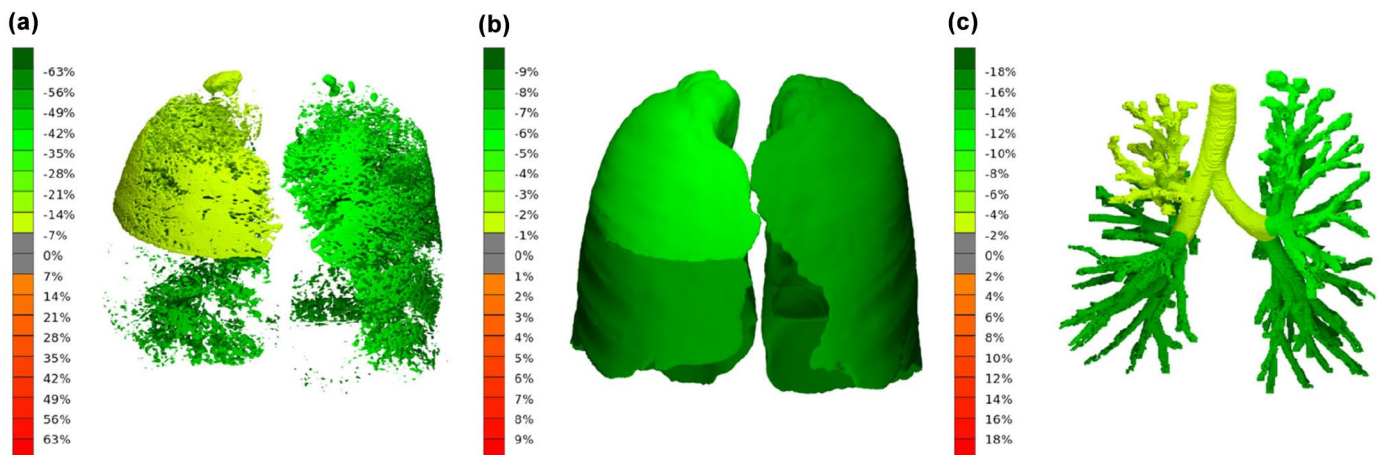
Figure 2. Treatment response in subject 5. The average change per lung lobe from baseline in (a) air trapping, (b) lobar volume at FRC, and (c) airway wall volume.

score as the majority of the patients scored higher after treatment (88% (17; 100) to 88% (58; 100), $p = 0.05$). No other domain scores reached statistical significance.

Body mass index (BMI) increased steadily during 12 weeks of treatment (22.2 ± –3.7 kg/m² to 22.9 ± 4.0 kg/m², $p = 0.04$). Also, systolic (118.5 ± 9.5 mmHg to 129.1 ± 12.8 mmHg, $p = 0.047$) and diastolic blood pressure (69.9 ± 12.1 mmHg to 78.7 ± 6.3 mmHg, $p = 0.04$) increased after treatment. All other vital signs remained stable.

Finally, sweat chloride concentration tended to decrease after 12 weeks (91.6 ± 14.5 mmol/L to 81.6 ± 14.7 mmol/L, $p = 0.07$). A summary of the results of the secondary outcomes can be found in Table 4.

Correlations FRI and secondary outcomes

Significant correlations were found at baseline between air trapping and ppFEV$_1$ ($r = -0.84$, $p < 0.001$), 6MWD ($r = -0.73$, $p = 0.007$) and CFQ-R physical domain ($r = -0.63$, $p = 0.03$); and between lobar volume after normal expiration and ppFEV$_1$ ($r = -0.68$, $p = 0.01$). Multiple correlations were found between FRI parameters and CF-CT scores at baseline. The total CF-CT score correlated with air trapping ($r = 0.79$, $p = 0.004$), lobar volume at FRC ($r = 0.73$, $p = 0.01$), BV10% ($r = 0.72$, $p = 0.01$) and BV5% (-0.69, $p = 0.02$). Interestingly, the CF-CT subscore for mucus plugging correlated with the absolute volumes of BV5_10 ($r = 0.74$, $p = 0.006$) and BV10 ($r = 0.75$, $p = 0.005$). No significant correlations could be found between the relative change in FRI parameters and secondary outcomes. Baseline

Table 2. Results FRI ($n = 11$).

FRI parameter	Baseline	Week 12	*p* value
AT at FRC (%)	16.12 ± 19.13	13.14 ± 17.55	<0.001*
iVlobe at FRC (L)	0.63 ± 0.30	0.57 ± 0.27	<0.001*
iVlobe at TLC (L)	1.22 ± 0.62	1.21 ± 0.59	0.678
siVaw at TLC (mL/L)	6.42 ± 4.87	6.58 ± 4.78	0.173
siVaww at TLC (mL/L)	22.89 ± 16.14	21.32 ± 12.51	0.029*
siRaw at TLC (kPa*s/L)	0.06 ± 0.04	0.06 ± 0.03	0.470
BV5 (mL)	35.13 ± 17.68	34.82 ± 17.22	0.618
BV5%	58.05 ± 9.45	61.04 ± 6.84	0.002*
BV5_10 (mL)	11.14 ± 5.05	10.40 ± 4.70	<0.001*
BV5_10%	19.08 ± 2.61	18.85 ± 2.60	0.254
BV10 (mL)	12.80 ± 6.49	11.08 ± 5.83	0.002*
BV10%	22.86 ± 8.09	20.11 ± 5.62	0.002*
V/Q matching	12.92 ± 8.65	14.66 ± 7.43	<0.001*
IAD to upper lobes (%)	11.19 ± 6.43	11.36 ± 6.15	0.946
TLD (% delivered dose)	35.06 ± 13.93	35.01 ± 11.58	0.992
PLD (% delivered dose)	18.34 ± 6.37	19.21 ± 6.17	0.748
C/P ratio	0.90 ± 0.29	0.84 ± 0.26	0.595

AT, air trapping; BV5, blood volume of vessels smaller than 5 mm²; BV5%, BV5 in relation to total blood volume; BV5_10, blood volume of vessels between 5 and 10 mm²; BV5_10%, BV5_10 in relation to total blood volume; BV10, blood volume of vessels larger than 10 mm²; BV10%, BV10 in relation to total blood volume; C/P ratio, central-to-peripheral deposition; FRI, functional respiratory imaging; IAD, internal airflow distribution; iVlobe, lobar volume; PLD, peripheral lung deposition; siRaw, specific airway resistance; siVaw, specific airway volume; siVaww, specific airway wall volume; TLD, total lung deposition; V/Q, ventilation/perfusion.
Data are presented as mean ± standard deviation.
*Statistically significant ($P < 0.05$).

Table 3. Interobserver variability of the CF-CT scoring method presented as ICC [95% CI].

Total score	0.84 [0.62; 0.93]
Bronchiectasis	0.86 [0.68; 0.94]
Mucus plugging	0.81 [0.56; 0.92]
Bronchial wall thickening	0.48 [−0.20; 0.78]
Parenchyma	0.93 [0.83; 0.97]
Air trapping	0.67 [0.23; 0.86]

CF, cystic fibrosis; CI, confidence interval; CT, computed tomography; ICC, intraclass correlation coefficient.

correlations between air trapping measured by FRI and secondary outcomes are shown in Figure 3.

Between secondary outcomes, ppFEV$_1$ was correlated with CF-CT total score ($r = -0.82$, $p = 0.002$), 6MWD ($r = 0.76$, $p = 0.007$) and CFQ-R physical domain ($r = 0.66$, $p = 0.02$) at baseline. In addition, significant correlations were found between 6MWD and CF-CT total score ($r = -0.71$, $p = 0.01$) and CFQ-R physical domain ($r = 0.86$, $p < 0.001$). When comparing relative changes over time, only a change in ppFEV$_1$ was associated with a change in CFQ-R physical domain ($r = 0.78$, $p = 0.005$).

Table 4. Results secondary outcomes (n = 11).

| Parameter	Baseline	Week 12	p value
CF-CT Total score (%)	23.71 [12.81; 34.10]	23.46 [7.46; 36.68]	0.4648
CF-CT Bronchiectasis (%)	27.43 [14.76; 37.50]	24.31 [3.65; 43.23]	0.9658
CF-CT Mucus (%)	30.56 [8.33; 55.56]	30.56 [1.39; 43.06]	0.1139
CF-CT Bronchial wall thickening (%)	29.17 [20.37; 47.45]	30.56 [15.74; 40.97]	0.5935
CF-CT Parenchyma (%)	9.26 [0.00; 21.30]	6.48 [0.00; 25.93]	0.3411
CF-CT Air trapping (%)	33.33 [22.22; 67.59]	31.48 [3.70; 64.82]	0.6835
$ppFEV_1$ (%)	74.64 ± 23.56	76.64 ± 23.56	0.278
ppFVC (%)	86.09 ± 15.34	86.82 ± 14.82	0.361
$ppMEF_{25}$ (%)	62.55 ± 69.53	64.82 ± 78.04	0.238
$ppMEF_{25-75}$ (%)	56.91 ± 42.22	62.09 ± 49.32	0.201
$LCI_{2.5}$ (n = 5)	11.98 [9.34; 20.32]	11.53 [8.54; 15.52]	0.313
Sweat chloride (mmol/L)	91.64 ± 14.45	81.64 ± 14.67	0.070
BMI (kg/m^2)	22.22 ± 3.67	22.87 ± 4.01	0.044*
CFQ-R physical (%)	88 [17; 100]	88 [58; 100]	0.052
CFQ-R respiratory (%)	78 [44; 89]	83 [61; 94]	0.139
6MWD (m)	650 [512; 790]	725 [525; 839]	0.021*

BMI, body mass index; CF, cystic fibrosis; CFQ-R, Cystic Fibrosis Questionnaire–Revised; CT, computed tomography; 6MWD, Six-Minute Walk Distance.
Data are presented as mean ± standard deviation or median [range].
*Statistically significant ($p < 0.05$).

Discussion

This study aimed to gain more insight into the short-term effects of LUM/IVA by evaluating the patient's lung structure and function across multiple FRI parameters. The results showed a decrease in lung hyperinflation indicated by a significant decrease in air trapping and in lobar volume after normal expiration. Furthermore, airway wall volume decreased and the proportion of pulmonary blood volume shifted from larger to smaller blood vessels. The larger proportion of blood in smaller blood vessels would indicate an average decrease in pulmonary vascular resistance downstream that resulted from an improved regional ventilation. The absolute volume of BV5, however, did not significantly change. We hypothesize that both the redistribution of pulmonary blood and the decrease in airway wall volume could be related to a reduction in mucus impaction, due to the similar attenuation properties of mucus, airway walls and blood vessels in the CT images causing bias. Consequently, the calculation of the total airway wall thickness includes mucus adhering to the airway wall. Second, mucus plugs obstructing small airways could have been recognized by the applied algorithms as larger blood vessels due to the corresponding shape and attenuation values. This could explain the significant correlation between the CF-CT subscore for mucus plugging and the absolute values of BV5_10 and BV10 at baseline. Although these assumptions indicate improved mucociliary clearance, the CF-CT score for mucus plugging did not show any differences after treatment. This could be related to the insensitivity of the CF-CT score to detect subtle changes, as the smallest increment of the score represents an increase in the extent of one-third of a lobe.[21] The same reasoning can be applied to
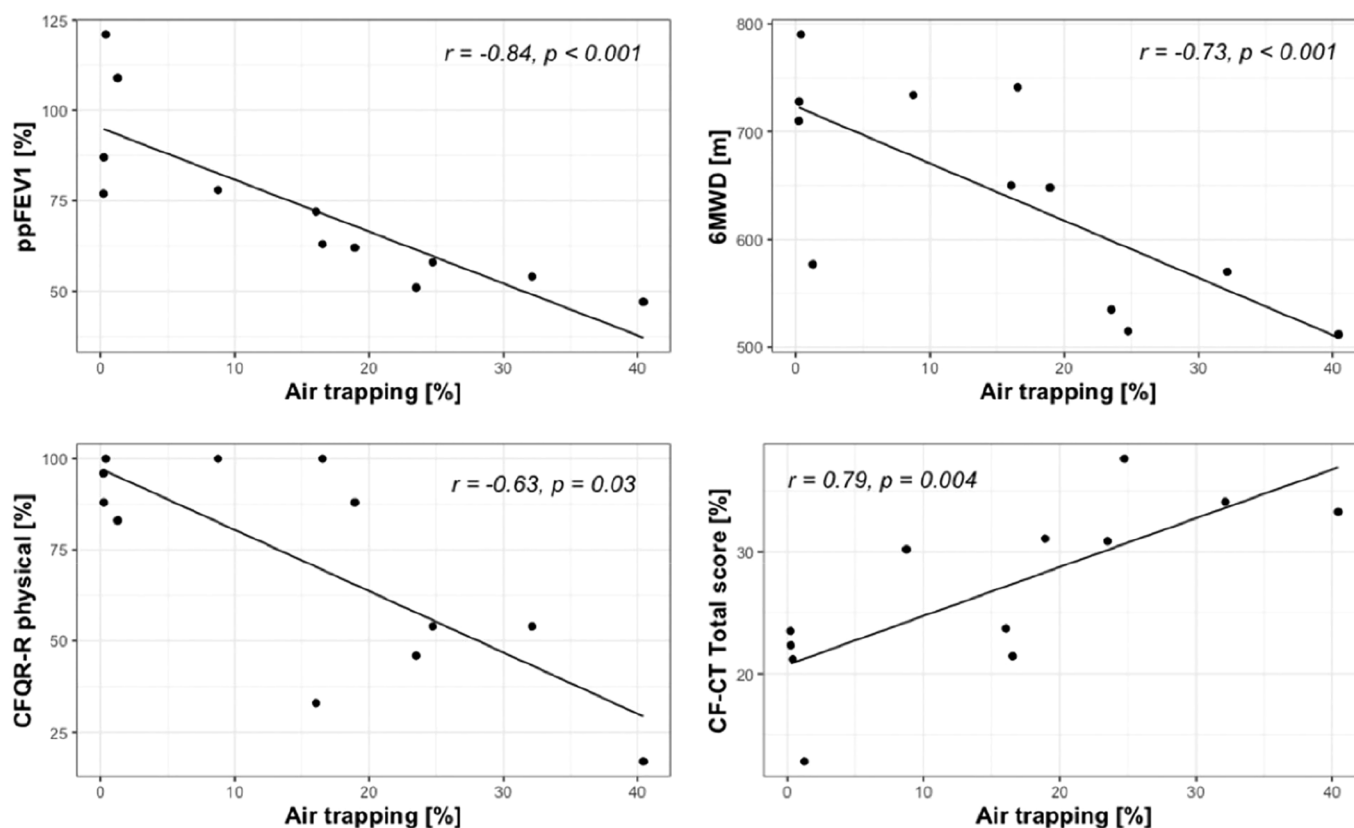
Figure 3. Baseline correlations between air trapping measured by FRI and ppFEV1, 6MWD, CFQ-R physical and CF-CT total score.

explain the lack of change in other CF-CT scores. More particularly, differences in air trapping and airway wall volume determined by FRI were not reflected in CF-CT scores for air trapping and bronchial wall thickening, respectively. In contrast to our study, a recent retrospective study evaluating structural changes using the modified Brody score after the initiation of LUM/IVA therapy showed a significant improvement in the CT total score, which was mostly related to a decrease in mucus plugging.[22] The higher number of participants and longer treatment period compared with our study could explain these significant differences. In addition, Sheikh *et al.*[23] reported significant improvements on HRCT imaging using the Brody scoring system after 1 year of ivacaftor treatment in patients with a *G551D* mutation. Similar to the retrospective study by Arnaud *et al.*, these significant results could be related to a longer treatment period, but more importantly, ivacaftor has been associated with a much higher effectiveness in patients with a *G551D* mutation compared with LUM/IVA in patients homozygous for *F508del*.[24]

Another important finding of this study is that the changes in several FRI parameters were also not reflected in any of the spirometric parameters in this small group of patients. The limitations of spirometry to measure therapeutic responses have been widely recognized: they are considered too insensitive to detect treatment effects and the heterogeneity of the pathology cannot be captured.[25] Nevertheless, FEV_1 is still considered one of the most important primary endpoints by the EMA for research in CF, since FEV_1 is an established marker for disease progression and a strong predictor of survival.[26,27] Over the past decade, alternative endpoints for clinical research in CF have been proposed, of which the LCI, CT scores and magnetic resonance imaging (MRI) are regarded to be the most promising.[28,29] LCI, CT scores as well as MRI outcomes have shown to be more sensitive to detect early lung disease, which is an important advantage since the progression of CF lung disease is slowing down and the FEV_1 remains within the normal range at older age.[25,30,31] Two previous observational studies showed that LUM/IVA therapy

was associated with a decrease in LCI, while no significant changes were observed in ppFEV$_1$.[32,33] Unfortunately, a recent real-world study by Reix *et al.*[34] could not confirm these results in a heterogenous group of patients monitored during the first year of LUM/IVA treatment. LCI nor FEV$_1$ changed significantly, and discordant results between FEV$_1$ and LCI were observed on an individual level. While LCI monitoring has shown to be valuable for the follow-up of patients with mild lung disease, the authors indicate that the application of this biomarker in a clinical setting remains less clear in patients with moderate to severe lung disease. The MBW has previously been associated with poor reproducibility in patients with more advanced lung disease and mucus plugging, which has shown to be a considerable limitation in our study.[35] Another disadvantage of the LCI is that this measure cannot distinguish between regional characteristics, as the respiratory system is regarded as a single unit.[35] On the other hand, CT scores, such as the CF-CT scoring system, provide more regional information in terms of semiquantitative measures per lung lobe, but they are dependent on subjective observations.[36] The role of CT scores in previous CFTR modulator studies have been discussed earlier. A more objective CT measure is the airway-artery ratio for the quantification of bronchiectasis,[37] but to our knowledge this method has not been used to assess the effects of CFTR modulator therapy to date. Finally, MRI is increasingly used in CF to evaluate structural as well as functional characteristics of the respiratory system.[29] Graeber *et al.*[32] recently showed that the MRI morphology score and perfusion score significantly improved after 8 to 16 weeks of LUM/IVA therapy in a comparable patient cohort. The MRI score is a visual semiquantitative scoring method using conventional proton MRI combined with contrast-enhanced perfusion MRI.[38] Similar to our findings, they reported that LUM/IVA may result in improved ventilation and in a decrease in mucus impaction in the small airways as indicated by a decrease in perfusion deficits reflecting hypoxic pulmonary vasoconstriction. Other more sophisticated MRI techniques are emerging as well, such as hyperpolarized gas MRI, which can directly visualize ventilation defects, but these techniques require expensive specialized equipment available in only a few centres worldwide.[29] Their role in the assessment of CFTR modulator therapy is yet to be determined.

Although FRI as described in this study is a new tool in the field of CF research, previous studies in other obstructive lung diseases, such as COPD and asthma, have shown that FRI is able to overcome several of the shortcomings or challenges associated with other methods as described earlier.[12,39] Although FRI is based on CT imaging, this imaging modality currently remains the gold standard to evaluate structural abnormalities of the respiratory system, due to its higher spatial resolution compared with MRI. FRI biomarkers obtain regional information of both structural and functional characteristics using objective image processing techniques. Therefore, FRI has the potential to provide valuable contributions to future interventional studies targeting CF lung disease. Similar to studies in COPD and asthma patients, our results confirm that FRI is more sensitive than conventional outcomes, such as spirometry and CF-CT scores, to pick up local changes in the respiratory system. Consequently, a smaller sample size is required and the intervention period of a clinical trial can be reduced. This is an important benefit since disease progression in CF is slowing down as mentioned earlier, which would imply larger clinical studies of a longer duration to demonstrate significant changes in conventional outcomes.[40]

In this study, important correlations were found between FRI and other respiratory outcomes, including physical functioning, spirometry, and structural abnormalities on chest CT. This indicates that improvements in specific FRI parameters could be related to an improved clinical outcome in the long term. Correlations between CT findings and lung function in CF have been reported in previous research, showing a higher correlation between LCI and CT than FEV$_1$ and CT.[41,42] Therefore, it would have been interesting to compare the LCI with FRI parameters, but unfortunately the number of successful MBW tests was insufficient to perform such analysis.

Although the result of ppFEV$_1$ in this study was not significant, the mean change from baseline was comparable to the findings of the pivotal clinical trials.[6] Changes in most secondary outcomes were also similar to those reported in previous research, including nutritional status,[7] exercise tolerance,[43] QoL[6,44] and arterial blood pressure.[7]

The study is subject to several limitations. First, the obtained results could not be compared to a control group. A high variability was found between subjects across several FRI parameters as well as secondary outcomes, which can be related to the varying levels of disease severity and wide age range representing a heterogeneous group of patients. No previous FRI studies have been performed in the CF population to determine which changes can be expected over time and what treatment effects can be considered clinically important.

Second, only 12 participants were enrolled instead of the calculated sample size of 14. Although this is relatively small sample size, it should be stressed that all FRI parameters were evaluated at a lobar level, which implies five data points per subject. This partially explains why significant results could be detected by FRI in contrast to secondary outcomes. In retrospect, it would have been more appropriate for a study including CF patients to perform the sample size calculation using an FRI parameter other than airway volume, such as air trapping. Due to the presence of structural airway damage, in particular bronchiectasis, LUM/IVA is not expected to affect airway volume considerably during a short intervention period. The choice of airway volume to estimate the effect size was based on a previous study including COPD patients, since no other FRI studies with CF patients have been performed to date.

Over the past few years, new CFTR modulators have been proposed for the treatment of CF patients homozygous for *F508del*. The most recent triple combination therapy, elexacaftor plus tezacaftor plus ivacaftor, has shown substantially larger effects on lung function, sweat chloride concentration, QoL and pulmonary exacerbations than those of LUM/IVA.[45–47] Therefore, it is expected that LUM/IVA will become less relevant in future CF management, since this treatment provides only modest health benefits and is associated with a very high cost.[5] Nonetheless, this study demonstrated the added value of FRI analysis to assess the effectiveness of CFTR modulators. This method revealed a more detailed outline of the mode of action of the drug, allowing a better understanding of post-treatment effects. With that in mind, it would be highly interesting to conduct similar future studies to assess the effects of new CFTR modulator therapies in CF patients.

Conclusion

This study is the first to perform FRI to evaluate the effects of CFTR-modulating drugs on lung functionality. The analysis showed that LUM/IVA decreased lung hyperinflation in combination with a potential decrease in mucus impaction, which can be related to an improved mucociliary transport. These FRI parameters, reflecting regional and distal lung structures, appear to be more sensitive to changes caused by LUM/IVA than conventional outcomes, such as spirometry and subjective CT scores. The objective and quantitative FRI methodology could play an important role in acquiring profound knowledge about the local effects in the respiratory system of new CFTR modulators in future research.

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Supplemental material

Supplemental material for this article is available online.

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