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 on the CF lung remain unclear. This study aims to offer novel information on the mode of action of the 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 spirometry, the 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, airway wall volume decreased significantly, 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 the spirometric parameters. Other secondary outcomes showed similar results compared to previous research. Correlations at baseline were found between FRI and clinical parameters, including physical functioning and spirometry.

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 the FRI parameters, reflecting regional and distal lung structures, are more sensitive to changes caused by LUM/IVA than conventional spirometry.

Key words:

Functional respiratory imaging, computational fluid dynamics, cystic fibrosis, CFTR modulator

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations of 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]. *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 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 randomised 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. Additionally, 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 to 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 novel 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]. 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 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 [10–12]. In the CF population, FRI has demonstrated its value by establishing patient-specific airway models to predict the deposition of inhaled antibiotics

[13]. Given these previous findings, we hypothesize that FRI is able to provide valuable insights into the effects of LUM/IVA on lung 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.

2. Methods

2.1. 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 200mg/ivacaftor 125mg) 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 four 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: FRI, nitrogen multiple breath washout (N_2MBW) 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).

2.2. 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 $\geq$ 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 centers: Antwerp University Hospital, GZA hospital campus Sint-Vincentius and Ghent University Hospital.

2.3. Study assessments

2.3.1. Functional Respiratory Imaging

HRCT scans were taken with a GE VCT LightSpeed 64-slice scanner at two breathing levels, total lung capacity (TLC) and functional residual capacity (FRC) monitored with a pneumotachograph. Images were imported into a medical image processing software package, Mimics (Materialise, Leuven, Belgium), for segmentation and 3D reconstruction of the airways and lung lobes. These 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. 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 and simulated using a tidal breathing profile. The particle characteristics of dornase alfa were taken from literature [14]. Details of the analysis can be found in the supplementary material and in a previous publication by De Backer et al [15]. The following FRI parameters were evaluated in this study: air trapping, lobar volume, airway volume, airway wall volume, airway resistance, blood vessel density, ventilation/perfusion matching, internal airflow distribution and aerosol deposition.

2.3.2. Secondary outcomes

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.

2.4. 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 [10].

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 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 determine the association between FRI parameters and secondary endpoints. The distribution of the data was evaluated by QQ plots and the Shapiro-Wilk test. Normally distributed data are represented as mean $\pm$ standard deviation, and non-normal data as median [range]. For all analyses a P value < 0.05 was considered statistically significant.

3. Results

3.1. 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. 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® is not reimbursed in Belgium up to date.

Table 1. Baseline characteristics (n = 12)

Sex (M/F)	11/1
Age (y)	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

Data are presented as mean ± standard deviation or median [range].

3.2. FRI parameters

The FRI analysis showed a decrease in air trapping (16.12 ±19.13% to 13.14 ±17.55%, p<0.001; Figure 1a), lobar volume after normal expiration (0.63 ±0.30 L to 0.57 ±0.27 L, p<0.001; Figure 1b), airway wall volume (22.89 ±16.14 mL/L to 21.32 ±12.51 mL/L, p=0.03; Figure 1c) and blood vessel density (4.75 ±1.79% to 4.19 ±1.32%, p<0.001). Also, a significant improvement of the ventilation/perfusion matching was found (12.92 ±8.65% to 14.66 ±7.43%, p<0.001). 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.

Figure 1. Treatment response in subject 5. Change from baseline in (A) air trapping, (B) lobar volume at FRC, (C) airway wall volume.

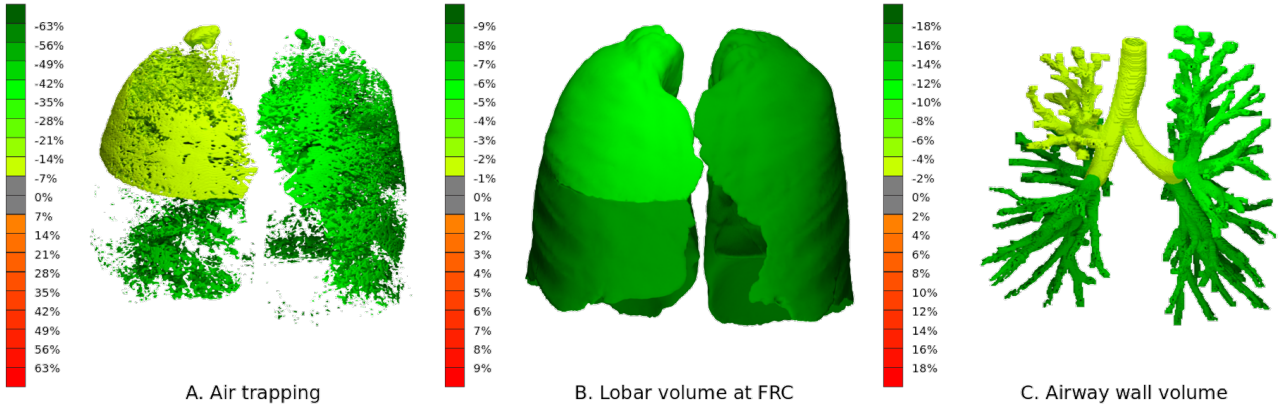

Table 2. Results FRI (n = 11)

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
iVbv at TLC (%)	4.75 ±1.79	4.19 ±1.32	<0.001*
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

Data are presented as mean ± standard deviation. * statistically significant (P < 0.05) Abbreviations: AT, air-trapping; iVlobe, lobar volume; siVaw, specific airway volume; siVaww, specific airway wall volume; siRaw, specific airway resistance; iVbv, blood vessels density; V/Q, ventilation/perfusion; IAD, internal airflow distribution; TLD, total lung deposition; PLD, peripheral lung deposition; C/P ratio, central-to-peripheral deposition.

3.3. Secondary outcomes

ppFEV1 increased by 2.0 ±4.0% (p = 0.3), but this result was not significant (Figure 2). No other significant changes were found in other spirometric parameters. For the N_2MBW, the results of only 5 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 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.

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.

Lastly, 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 3.

Figure 2. Change from baseline in $ppFEV_1$.

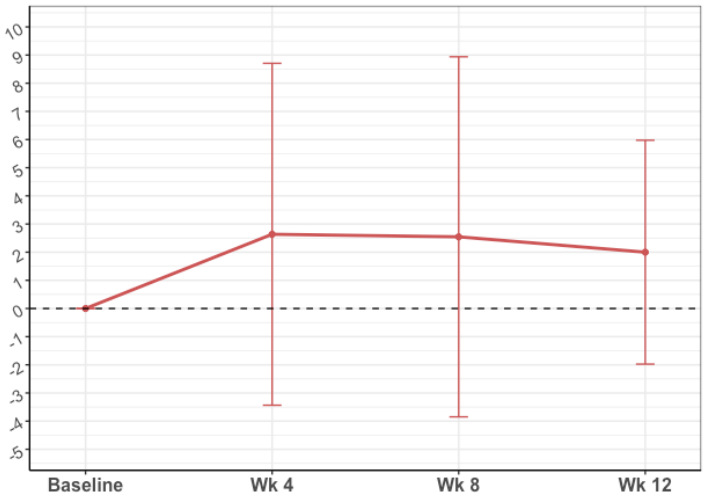

Table 3. Results secondary outcomes (n = 11)

Parameter	Baseline	Week 12	P value
$ppFEV_1$ (%)	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*

Data are presented as mean ± standard deviation or median [range]; * statistically significant ($P < 0.05$).

3.4. 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 ($r = -0.77$, $p = 0.003$); and between lobar volume after normal expiration and $ppFEV_1$ ($r = -0.68$, $p = 0.01$). No associations could be found between the relative change in FRI parameters and secondary outcomes.

Between secondary outcomes, $ppFEV_1$ was correlated with 6MWD ($r = 0.76$, $p = 0.006$) and CFQ-R physical domain ($r = 0.69$, $p = 0.01$) at baseline. In addition, a significant correlation was found between 6MWD and CFQ-R physical domain ($r = 0.86$, $p < 0.001$). When comparing relative changes over time, a change in $ppFEV_1$ was associated with a change in CFQ-R physical domain ($r = 0.78$, $p = 0.005$).

4. 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. In addition, the ventilation/perfusion ratio improved, which can be explained by an improved ventilation following a decreased FRC. Furthermore, airway wall volume and blood vessel density decreased, but the interpretation of these results is less intuitive. We hypothesize that both results 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. Consequently, the calculation of the total airway wall thickness includes mucus adhering to the airway wall. Secondly, mucus plugs obstructing small airways could have been recognized by the applied algorithms as small blood vessels due to the corresponding shape and attenuation values. Although these assumptions could be the effect of improved mucociliary clearance, they cannot be quantified and should therefore be interpreted with caution.

An important finding of this study is that the changes in several FRI parameters were 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 [16]. 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 [17,18]. Over the past decade alternative endpoints for clinical research in CF have been proposed, of which the LCI and CT scores are regarded to be the most promising and feasible [19]. Both the LCI and CT scores 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 [16,20]. The LCI, however, cannot distinguish between regional characteristics as the respiratory system is regarded as a single unit. In addition, the MBW test has a poor reproducibility in patients with more advanced lung disease and mucus plugging, which was a considerable limitation in our study [21]. On the other hand, CT scores provide more regional information in terms of semiquantitative measures per lung lobe, but they are dependent on subjective observations [22]. Although FRI 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 limitations described earlier [10,23]. This method obtains 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 spirometry 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 [24]. In this study, important correlations were found between FRI and clinical parameters, including physical functioning and spirometry. This indicates that improvements in these imaging 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 [25,26]. 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 [27], QoL [6,28] and arterial blood pressure [7].

The study is subject to several limitations. Firstly, the obtained results could not be compared to a control group. No 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.

Secondly, only 12 participants were enrolled instead of the calculated sample size of 14. 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. Nevertheless, significant changes were found in several FRI parameters.

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 [29]. 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.

5. 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. Consistent with findings of previous research, conventional spirometry showed limited changes. Therefore, these results indicate that FRI parameters, reflecting regional and distal lung structures, are more sensitive to changes caused by LUM/IVA. In future research this technology could play an important role in acquiring profound knowledge about the local effects in the respiratory system of new CFTR modulators.

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