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Evidence of Small Airways Disease and the Immediate Effects of Lumacaftor/Ivacaftor in Children with Cystic Fibrosis

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Abstract

Aim

The aim of this study was to explore risk factors for acute changes in lung function following initiation of lumacaftor/ivacaftor (LUM/IVA) in children with cystic fibrosis.

Methods

Retrospective review of all children commenced on LUM/IVA treatment over a one-year period. CT Thorax images were reviewed for evidence of air trapping using the Brody score.

Results

Data was collected from 15 children. A transient decline in $ppFEV_1$ was observed after initiation of LUM/IVA in 93% (n=14) of patients with an absolute mean decline of -10.8%. There was a statistically significant inverse relationship between ΔFEV_1 and baseline $ppFEV_1$. There was no relationship between air trapping score and ΔFEV_1 (p=0.41).

Conclusion

Pre-existing small airways disease is not a risk factor for acute changes in lung function following initiation of LUM/IVA. Our results suggest that a LUM/IVA-related decline in lung function is more significant in CF children with higher baseline FEV_1.

Introduction

Cystic Fibrosis conductance Transmembrane Regulator (CFTR) modulators represent a major breakthrough in the pharmacological management of Cystic Fibrosis (CF). Clinical trials have shown significant improvements in lung function, nutritional status and rates of pulmonary exacerbations[1,2]. Subsequent studies, however, reported acute lung function changes following administration of LUM/IVA. This phenomonen was not documented in initial trials assessing the effects of LUM/IVA in CF patients (F508del/F508del)[1] but in a later trial examining the efficacy and safety of LUM/IVA in ≥6-11year olds which demonstrated an abrupt decline in $ppFEV_1$ within 4 hours of treatment[2]. Similar findings were noted in a study performed with healthy adult volunteers, revealing that administration of LUM/IVA resulted in a transient decline in $ppFEV_1$ with a mean decrease of 4.1%[3]. Furthermore, a paediatric study observed a consistent reduction in $ppFEV_1$(-10.4 ± 4.6%), with only partial recovery following short acting $beta_2$ agonist (SABA) inhalation[4].

Pulmonary function is strongly associated with CF mortality and is a valid surrogate measure of lung health, with an acute decrease in FEV_1 of 10-15% determined to be the most significant predictor of pulmonary exacerbation in patients 6 years and older[5]. The benefits of LUM/IVA have been well established and initiation is generally well tolerated, however the mechanism of drug-induced decline in $ppFEV_1$ following initiation is not known and caution may be required, particularly in patients with end-stage lung disease. Identifying risk factors for this decline could improve individual patient management during initiation and help understand the mechanisms involved.

The small airways are not felt to contribute significantly to the total airway resistance in healthy lungs; it is estimated that approximately 75% of the small airways would have to be obstructed to cause a decrease in FEV_1[6–8]. However, significant small airway disease is commonly present in patients with CF[9]. Evidence of small airway inflammation and obstruction can be demonstrated using high resolution computed tomography (HRCT)[10]. In CF this takes the form of heterogeneous areas of radiolucency secondary to air trapping and a 'tree-in-bud'-like pattern which implies impaction of mucus and inflammatory exudate within the bronchioles[11]. Increased mucus production is a commonly reported adverse effect of LUM/IVA initiation[12] therefore we questioned if the transient decline in $ppFEV_1$ is more severe in children with HRCT evidence of small airways disease.

In this study we sought to confirm the immediate effects of LUM/IVA initiation on lung function in a cohort of paediatric CF patients and explore links between changes in $ppFEV_1$ and CT imaging evidence of small airways disease along with other potentially influencing factors.

Methods

We performed a retrospective study of all children who were commenced on LUM/IVA between September 2016-August 2017 in our institution. Data collected prior to initiation of treatment included gender, weight, age, antimicrobial colonisation in the previous six months, spirometry (including any previous bronchodilator response test (BDR)) and antimicrobial treatment history.

In 2004 Brody et al described a scoring system to convert the CT thorax findings in a patient with CF into numerical data[13]. For this study, the CT images were reviewed by two paediatric radiologists (SR and AS). Using Brody's method, the amount of air trapping was graded. All HRCT was performed prior to commencing therapy.

All children were administered a nebulised SABA (salbutamol) fifteen minutes prior to treatment initiation. Patients were commenced on a starting dose of LUM/IVA 200mg/125mg twice daily with a fat-containing snack. Patients were observed for 4 hours following drug administration. Spirometry was repeated at 4 hours post dose, 24 hours, 1 week, 2 weeks, 1 month and 3 monthly thereafter. Patients were asked to report any respiratory-related symptoms. After one week of treatment, the dose was increased to LUM/IVA 400mg/250mg twice daily as tolerated.

Statistical analyses were performed using IBM SPSS Statistics. Descriptive data were reported as mean and standard deviation (SD) for parametric data, and median and range for non-parametric data. A number of statistical tests were carried out to assess whether a relationship existed between absolute change in ppFEV1 ($\Delta ppFEV_1$) with demographic and patient variables. Significance was defined as $p \leq 0.05$.

Ethics approval was not required.

Reimbursement for LUM/IVA has since been granted for patients aged 2 years and older. Our treatment approach was similar for 6-11 year olds based on observed tolerability in the 12+ age group. The granule preparation does not allow for half dosing therefore children aged 2-5 years are initiated on full dose as per manufacturer licence.

Results

Characteristics

Data was collected from 15 children initiated on LUM/IVA. Table 1 shows baseline characteristics of our cohort. Baseline spirometry reported a mean $ppFEV_1$ of 77%±21.6%. One child in our cohort had a baseline $ppFEV_1$ of <40%. BDR had been tested in 12 of 15 patients (80%) and none were positive using ATS/ERS criteria[14]. The majority of children were colonised with more than 2 different organisms, the most common organisms being *Staphylococcus aureus*(86%) and *Pseudomonas aeruginosa*(46%).

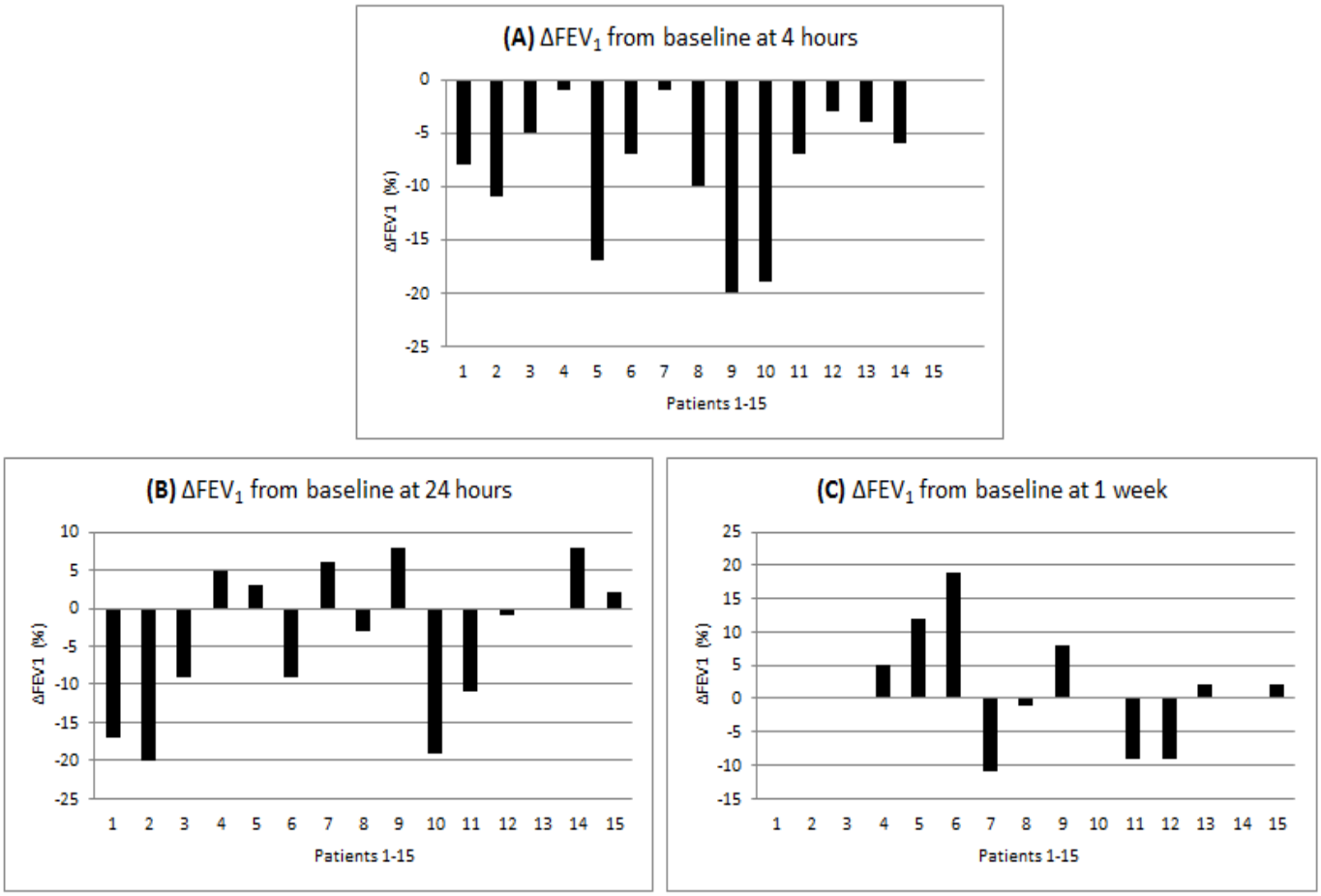
Table 1: Baseline characteristics

	Mean	Standard Deviation (SD)
Age (years)	14	1.72
Weight (kg)	47.3	8.97
Baseline ppFEV$_1$ (%)	77	21.6
	Median	**Range**
Brody score (number)	2.5	0-13
Time since most recent antimicrobial treatment (days)	35	0-90

Acute change in lung function

We observed a transient decline in ppFEV$_1$ in 93% (n=14) of patients at 4 hours post first dose in each case. Some patients experienced a further decline in ppFEV$_1$ at a later stage. The absolute change in ppFEV$_1$ at different time intervals are shown in Figure 1. The mean absolute (±SD) decline in ppFEV$_1$ was -10.87%±6.57%, with a maximum absolute decline in ppFEV$_1$ of -20%. Spirometry returned to baseline in all children on LUM/IVA treatment. The median time for ppFEV$_1$ to return to baseline was 7 days, ranging from 0 to 90 days.

Fig. 1: Absolute change in FEV$_1$ (ΔFEV$_1$) post treatment from baseline ppFEV$_1$ at (A) 4 hours, (B)24 hours and (C)1 week



Adverse drug reactions (ADR) - Three out of fifteen CF children (20%) reported mild transient respiratory side effects within the first 24 hours, including increased sputum production(n=2) and chest tightness(n=2). There were no reported episodes of cough, wheeze or dyspnoea. No treatments were disrupted as a result of ADRs.

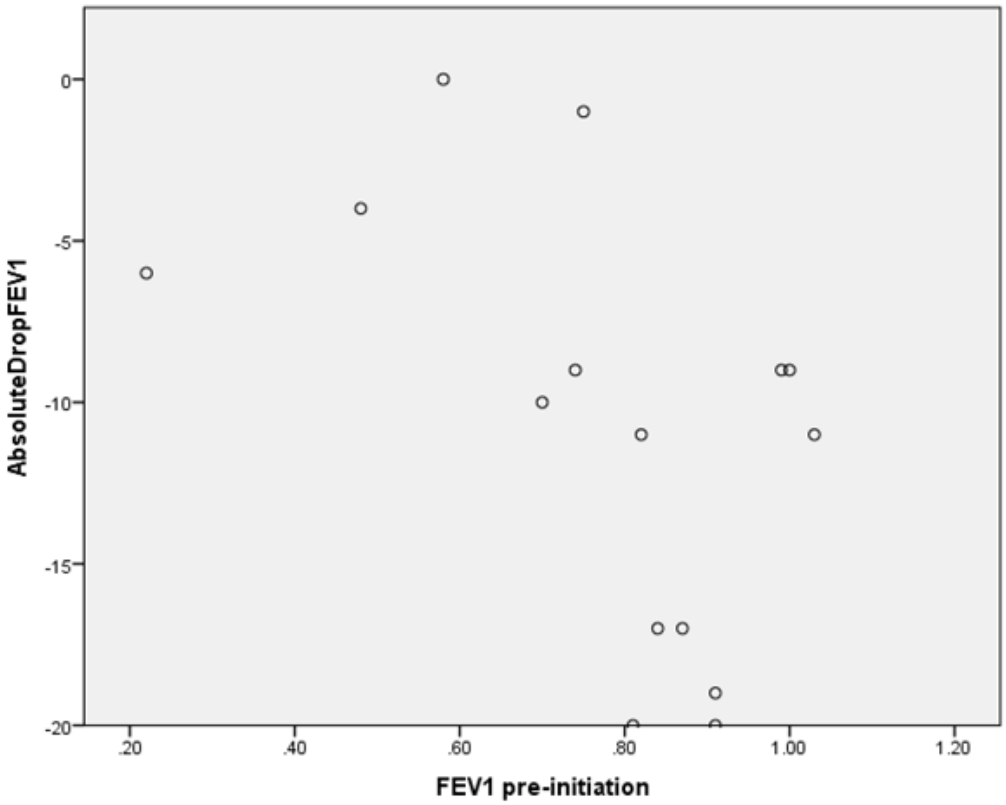
Evaluation of air trapping

CT Thorax images were available in 14 children. 10/14 cases included expiratory phase images. Brody scores ranged from 0 to 13 (median 2.5). We report no relationship between air trapping score and ΔFEV_1 (p=0.41) using Mann-Whitney-U test.

Relationships between ΔFEV_1 and patient variables

There is a statistically significant inverse relationship between ΔFEV_1 and baseline $ppFEV_1$ (r = 0.50; 95%CI[-31.09; 0.35], p=0.05) as illustrated in the scatter box (Figure 2). This indicates that children with higher baseline $ppFEV_1$ experienced a greater decline in $ppFEV_1$ compared to children with a lower baseline $ppFEV_1$.

Fig. 2: Relationship between absolute change in FEV_1(%) and baseline $ppFEV_1$(%)



We report no relationship between weight and ΔFEV_1 using linear regression method(p=0.66), between gender and ΔFEV_1 using independent t-test(p=0.53) or between recent antibiotic treatment and ΔFEV_1 using Mann-Whitney-U test(p=0.14).

Table 2: Relationship between $ppFEV_1$ and time from most recent antimicrobial treatment

		Median No. Days	Range
Change Category: 0-9%	(n=7)	63	158
Change Category: 10-20%	(n=8)	24.5	87
P-value:	0.142		

Discussion

Clinical trials have demonstrated that treatment with LUM/IVA improves lung function, nutritional status and pulmonary exacerbation rates in children with CF[1]. Our results confirm an acute, transient decline in $ppFEV_1$ post initiation of LUM/IVA (-10.87%±6.57%) in keeping with previously published data. Although initial RCTs reported absolute change from baseline $ppFEV_1$ at week 24, they did not report changes prior to day 15[1]. A study of CF patients (ΔF508/ΔF508) aged 6-11, showed a transient decline in $ppFEV_1$ that was most profound at 4-6 hours post drug administration (-7.7%±7.3%)[2]. This decline is similar in magnitude to that observed in our study (-7.93±6.41%). This phenomenon has also been observed and documented in other real life studies[3,4,15].

Acute decline in $ppFEV_1$ after initiation has been attributed to bronchoconstriction. CF patients with previously recognised significant reversible airway obstruction were noted to have a higher risk of FEV_1 decrease[4,15]. Furthermore, acute change in $ppFEV_1$ of healthy individuals was rapidly reversed following administration of a SABA, suggesting that bronchoconstriction is a potential off-target effect of lumacaftor[3]. It remains questionable, however, if bronchoconstriction alone provides an explanation for early FEV_1 deterioration. Unlike in healthy volunteers, administration of SABA to patients with CF did not fully alleviate the acute decline in $ppFEV_1$. Labaste et al. found that the initial decrease in $ppFEV_1$ was only partially corrected with salbutamol inhalation[4]. Further, the incidence of symptoms of bronchoconstriction on initiation of LUM/IVA is low. In our study, only 2 out of 15 patients reported chest tightness within the first 24 hours; with no reported episodes of cough, wheeze or dyspnoea. It could be argued that this reflected the comparatively short duration of this study but the study length reflected the period of time necessary for $ppFEV_1$ to return to baseline. In our patient group, 80% had been tested previously for BDR and were all negative. The validity of the recognised threshold of 12% and 200 mL or greater change in FEV_1 from baseline has been questioned in the paediatric population[16,17], and it is recognised that a negative BDR test does not rule out a clinical response to bronchodilator therapy. Therefore in order to pre-empt bronchoconstriction, a SABA was pre-administered to all patients. Despite this, we identified similar declines in lung function following initiation to those previously published. Although we did not assess the effect of post-treatment bronchodilators on lung function, this raises further doubt about bronchoconstriction as a mechanism for the transient deterioration of $ppFEV_1$. Finally, there is no explanation as to the mechanism of LUM/IVA induced bronchoconstriction. We looked for underlying risk factors for an acute decline in $ppFEV_1$ beyond bronchoconstriction; postulating that children with more severe underlying small airways disease would experience a greater decrease in $ppFEV_1$ after initiation.

Brody's scoring system is a systematic method that evaluates each lobe of a HRCT for severity and extent of CF lung disease[13]. It describes a number of morphologic changes[18]. The score of air trapping ranges from 0 to 27 for the total lung. We used this scoring system to specifically evaluate for evidence of air trapping as a potential risk factor for acute changes in lung function. However, no relationship was found between absolute changes in $ppFEV_1$ and air trapping score($p=0.41$). The small airways express CFTR and may be an area of so-called off target effects of LUM/IVA but CT thorax findings are, unfortunately, not predictive of the severity of acute decline in $ppFEV_1$ on initiation of LUM/IVA.

We found a statistically significant inverse relationship between $\Delta ppFEV_1$ and baseline $ppFEV_1$. Patients with higher baseline $ppFEV_1$ experienced a greater acute transient decline in lung function post initiation of treatment ($p=0.05$). This is a new finding that has not been reported previously. Labaste et al. found that patients with a low baseline FEV_1 were at greater risk of experiencing a more profound decline and they recommended close monitoring during this period[4]. Our study had only one patient with a pre-initiation $ppFEV_1$ of <40%, so it may be that the greater transient declines of $ppFEV_1$ occur at both extremes of patient lung function. Reassuringly, we also report full recovery in $ppFEV_1$ was made in all patients without any serious adverse effects.

This study of 15 patients represents all of the children in our CF unit who were commenced on LUM/IVA during the study time-period. The relatively small sample size may have influenced the statistical strength of the relationships between absolute change in lung function and patient variables, however we have shown that evidence of pre-existing small airways disease on HRCT is not a risk factor for increased acute loss of FEV_1. We confirm significant acute declines in $ppFEV_1$ as great as -20% from baseline at 4 hours or more post initiation of LUM/IVA and report the new finding of a statistically significant inverse relationship between ΔFEV_1 and baseline $ppFEV_1$. Although clinicians must be considerate of this potential decline in $ppFEV_1$ when initiating LUM/IVA in patients, this offers reassurance when initiating LUM/IVA as the patients who experience significant declines in lung function have a greater respiratory reserve with which to support this reduction. No subsequent changes have been made to dosing recommendations for LUM/IVA as a result of our findings.

Declaration of Conflicts of Interest:
No conflicts of Interest to disclose

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References:

1. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. N Engl J Med [Internet]. 2015 Jul 16 [cited 2017 Jun 20];373(3):220–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25981758
2. Ratjen F, Hug C, Marigowda G, Tian S, Huang X, Stanojevic S, et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. Lancet Respir Med. 2017 Jul;5(7):557–67.
3. Marigowda G, Liu F, Waltz D. Effect of bronchodilators in healthy individuals receiving lumacaftor/ivacaftor combination therapy. J Cyst Fibros. 2017 Mar;16(2):246–9.
4. Labaste A, Ohlmann C, Mainguy C, Jubin V, Perceval M, Coutier L, et al. Real-life acute lung function changes after lumacaftor/ivacaftor first administration in pediatric patients with cystic fibrosis. J Cyst Fibros. 2017 Nov;16(6):709–12.
5. Rabin HR, Butler SM, Wohl MEB, Geller DE, Colin AA, Schidlow D V, et al. Pulmonary exacerbations in cystic fibrosis. Pediatr Pulmonol. 2004 May;37(5):400–6.
6. Burgel P-R, de Blic J, Chanez P, Delacourt C, Devillier P, Didier A, et al. Update on the roles of distal airways in asthma. Eur Respir Rev [Internet]. 2009 Jun 1;18(112):80 LP-95. Available from: http://err.ersjournals.com/content/18/112/80.abstract
7. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet (London, England). 2004 Aug;364(9435):709–21.
8. Cosio M, Ghezzo H, Hogg JC, Corbin R, Loveland M, Dosman J, et al. The relations between structural changes in small airways and pulmonary-function tests. N Engl J Med. 1978 Jun;298(23):1277–81.
9. Jaffe A, Balfour-Lynn IM. Treatment of severe small airways disease in children with cystic fibrosis: alternatives to corticosteroids. Paediatr Drugs. 2002;4(6):381–9.
10. Hansell DM, Rubens MB, Padley SP, Wells AU. Obliterative bronchiolitis: individual CT signs of small airways disease and functional correlation. Radiology. 1997 Jun;203(3):721–6.
11. Helbich TH, Heinz-Peer G, Fleischmann D, Wojnarowski C, Wunderbaldinger P, Huber S, et al. Evolution of CT findings in patients with cystic fibrosis. Am J Roentgenol [Internet]. 1999 Jul 1;173(1):81–8. Available from: https://doi.org/10.2214/ajr.173.1.10397104
12. Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. Lancet Respir Med. 2017 Feb;5(2):107–18.
13. Brody AS, Klein JS, Molina PL, Quan J, Bean JA, Wilmott RW. High-resolution computed tomography in young patients with cystic fibrosis: distribution of abnormalities and correlation with pulmonary function tests. J Pediatr. 2004 Jul;145(1):32–8.
14. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005 Nov;26(5):948–68.
15. Popowicz N, Wood J, Tai A, Morey S, Mulrennan S. Immediate effects of lumacaftor/ivacaftor administration on lung function in patients with severe cystic fibrosis lung disease. J Cyst Fibros. 2017 May;16(3):392–4.

16. Galant SP, Morphew T, Amaro S, Liao O. Value of the bronchodilator response in assessing controller naive asthmatic children. J Pediatr. 2007 Nov;151(5):457–62, 462.e1.
17. Dundas I, Chan EY, Bridge PD, McKenzie SA. Diagnostic accuracy of bronchodilator responsiveness in wheezy children. Thorax. 2005 Jan;60(1):13–6.
18. Brody AS, Kosorok MR, Li Z, Broderick LS, Foster JL, Laxova A, et al. Reproducibility of a scoring system for computed tomography scanning in cystic fibrosis. J Thorac Imaging. 2006 Mar;21(1):14–21.