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Short Communication

Real-life acute lung function changes after lumacaftor/ivacaftor first administration in pediatric patients with cystic fibrosis

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Abstract

The combination of lumacaftor and ivacaftor (LUM/IVA) has been reported to induce a mean acute absolute drop of −4.1% predicted forced expiratory volume in 1 s (FEV_1) after a unique administration in healthy subjects. The aim of the present study was to assess acute FEV_1 changes after the first dose of LUM/IVA in CF patients. A total of 32 pediatric patients were included. Respiratory manifestations occurred in only 3 patients (9.4%), but FEV_1 consistently decreased (−10.4 ± 4.6%, range: −1.5; −21.8%). FEV_1 only partially resumed after salbutamol inhalation. Patients with previously known significant reversible airway obstruction and low FEV_1 were more at risk of FEV_1 decrease.
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1. Introduction

The lumacaftor/ivacaftor (LUM/IVA) combination is the first Cystic Fibrosis conductance Transmembrane Regulator (CFTR) protein modulator to be approved for CF patients aged ≥12 years and bearing two F508del mutations. The TRAFFIC and TRANSPORT trials reported 7.7–9.9% of patients experiencing "abnormal respiration" such as chest tightness or dyspnea after LUM/IVA administration [1]. Recently, in healthy volunteers (HV) a mean 4.1% drop of (forced expiratory volume in 1 s, FEV_1) was observed after first LUM/IVA administration, that almost completely resolved with short-acting bronchodilator (SABD); two subjects had respiratory manifestations [2]. We were therefore interested to assess acute changes of spirometry after the first LUM/IVA administration in CF patients.

2. Material and methods

2.1. Patients

Data from 32 patients from our pediatric CF center eligible for LUM/IVA initiation (i.e. clinically stable, defined as no pulmonary exacerbation or acute upper/lower respiratory illness other than CF within 28 days) were studied from March–December 2016. Data collected at time of LUM/IVA first administration included age, sex, weight, height, and BMI (expressed as Z-scores); history of allergic bronchopulmonary aspergillosis (ABPA), *Pseudomonas aeruginosa* (PA) colonization, use of SABD and inhaled corticosteroids (ICS) alone or associated with a long-acting bronchodilator (ICS-LABD), and the number of oral/intravenous antibiotic courses in the preceding year. Personal/familial atopy was documented by a compatible clinical history as well as by total IgE and eosinophil (Eos) levels. Best FEV_1 of the year preceding LUM/IVA administration ($_{best}FEV_1$), and maximal level of reversible airway obstruction (RAO) ever measured in the

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preceding year (improvement of $FEV_1 \geq 12\%$ considered as significant RAO [3]) were also collected from previous pulmonary function tests.

Patients and parents were informed of the study and provided with an information letter. As LUM/IVA is currently available for patients, we asked and obtained from our local Institutional Review Board (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Lyon) the authorization to collect data obtained during routine clinical practice; written informed consent was not required in accordance with legislation in place at the time of the study.

2.2. Study protocol

The first LUM/IVA (400 mg/250 mg) administration was organized at the hospital. Patients were asked not to take SABD for 6 h and/or LABD (including ICS-LABD) for 12 h before their visit. FEV_1 was the outcome measure, expressed as percent of predicted value [4] and Z-score using the Global Lungs Initiative 2012 software (http://www.spirxpert.com). A physical exam was performed and FEV_1 ($_{pre}FEV_1$; MasterScreen, PFT System, Jaeger, Germany) measured immediately before LUM/IVA administration. After administration, patients were asked to report any respiratory-related symptoms (cough, chest tightness, wheezing, breathlessness) experienced. A second physical exam was performed immediately before FEV_1 was measured 4 h ± 15 min later ($_{postLUM/IVA}FEV_1$); 400 μg salbutamol was then administered, and 15 min thereafter FEV_1 was measured ($_{postSABD}FEV_1$).

2.3. Outcomes

The primary outcome was relative change between $_{pre}FEV_1$ and $_{postLUM/IVA}FEV_1$ in ($\Delta FEV_1 = ((_{pre}FEV_1 - _{postLUM/IVA}FEV_1) / _{pre}FEV_1)$), because a wide range of $_{best}FEV_1$ values among patients was expected. Secondary outcomes included absolute changes between $_{pre}FEV_1/_{postLUMIVA}FEV_1$ and $_{postLUM/IVA}FEV_1/_{postSABD}FEV_1$.

2.4. Statistics

Descriptive data are reported as mean ± standard deviation (SD). Normality was assessed using Q-Q plots. When distribution was normal, paired Student T-tests were used; in case of non-normality, Wilcoxon signed-rank test was used. Two-way ANOVA was used for comparison of means for repeated measurements. Pearson's correlation coefficient (r) was used to assess relationships between 2 variables. Statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA) or GraphPad Prism V6.00 (GraphPad Software, La Jolla, CA, USA). Significance level was set at 0.05.

3. Results

3.1. Characteristics

Data from 32 clinically stable pediatric patients (18 male) of mean ± SD age 15.5 ± 1.6 years were collected (Table 1).

3.2. Primary outcome

A drop of FEV_1 was observed in all 32 patients following first LUM/IVA administration (Fig. 1A). After 4 h, three patients (9.4%) spontaneously reported wheezing spells of mild severity (no oxygen desaturation at second physical exam) that resolved after SABD administration (as defined in the protocol). For these patients $_{pre}FEV_1$ was 57%, 70%, and 81%.

The mean ± SD $_{pre}FEV_1$ was 87.0 ± 16.7%. The relative change of FEV_1 (ΔFEV_1) was −10.4 ± 4.6% (range: −1.5; −21.8%). The absolute change of FEV_1 was −9.4 ± 3.6% (range: −1; −17%). The $_{postLUM/IVA}FEV_1$ was 77.6 ± 16.7%; it partially recovered after salbutamol administration ($_{postSABD}FEV_1$: 82.6 ± 17.0). The absolute difference between $_{pre}FEV_1$ and $_{postLUM/IVA}FEV_1$ was significantly different ($p < 0.001$), as it was between $_{pre}FEV_1$ and $_{postSABD}FEV_1$ ($p < 0.001$; Fig. 1B).

Table 1
Patient characteristics.

	Total population, n = 32
Age, years (mean ± SD)	15.5 ± 1.6
Male, n (%)	18 (56)
$_{best}FEV_1$ (% pred)	90.0 ± 15.2
$_{best}FEV_1$ (Z-score)	−1.9 ± 1.2
$_{best}FEF25–75$ (% pred)	57.5 ± 35.6
$_{best}$ FEF25–75 (Z-score)	−2.4 ± 1.4
Patients with significant RAO [a], n (%)	15 (46.8)
RAO level (mean ± SD)	11.8 ± 6.8
PE insufficiency n (%)	32 (100)
Z-score weight (mean ± SD)	−0.9 ± 1.4
Z-score height in cm (mean ± SD)	−0.7 ± 1.2
Z-score BMI in kg/m^2 (mean ± SD)	−0.7 ± 0.9
Atopy personal, n (%)	12 (37.5)
Atopy familial, n (%)	16 (50)
Chronic PA, n (%)	11 (34.4)
Bronchopulmonary aspergillosis, n (%)	8 (25)
SABD, n (%)	16 (50)
ICS alone, n (%)	8 (25)
ICS-LABD, n (%)	10 (31.2)
Number of oral ATB (mean ± SD) [b]	5.7 ± 1.8
Number of IV ATB (mean ± SD)	3.9 ± 1.3

Abbreviations. RAO: reversible airway obstruction as defined by the level of FEV_1 improvement after 400 μg of salbutamol inhalation, PE: pancreatic exocrine, SABD: short acting bronchodilator, ICS: inhaled corticosteroids, LABD: long acting bronchodilator, ATB: antibiotic therapy.

[a] Improvement of $FEV_1 \geq 12\%$ after short acting bronchodilator inhalation (salbutamol 400 μg).

[b] Number of oral or IV antibiotic received in the year preceding LUM/IVA initiation.

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