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

3

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1 **Abstract**

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

10

## 1           **1. Introduction**

2   The lumacaftor/ivacaftor (LUM/IVA) combination is the first Cystic Fibrosis conductance  
3   Transmembrane Regulator (CFTR) protein modulator to be approved for CF patients aged  
4    $\geq 12$  years and bearing two F508del mutations. The TRAFFIC and TRANSPORT trials  
5   reported 7.7-9.9% of patients experiencing “abnormal respiration” such as chest tightness or  
6   dyspnea after LUM/IVA administration (1). Recently, in healthy volunteers (HV) a mean 4.1%  
7   drop of (forced expiratory volume in one second, FEV<sub>1</sub>) was observed after first LUM/IVA  
8   administration, that almost completely resolved with short-acting bronchodilator (SABD); two  
9   subjects had respiratory manifestations (2). We were therefore interested to assess acute  
10  changes of spirometry after the first LUM/IVA administration in CF patients.

## 12           **2. Material and methods**

### 13    ***Patients***

14  Data from 32 patients from our pediatric CF center eligible for LUM/IVA initiation (i.e.  
15  clinically stable, defined as no pulmonary exacerbation or acute upper/lower respiratory  
16  illness other than CF within 28 days) were studied from March-December 2016. Data  
17  collected at time of LUM/IVA first administration included age, sex, weight, height, and BMI  
18  (expressed as Z-scores); history of allergic bronchopulmonary aspergillosis (ABPA),  
19  *Pseudomonas aeruginosa* (PA) colonization, use of SABD and inhaled corticosteroids (ICS)  
20  alone or associated with a long-acting bronchodilator (ICS-LABD), and the number of  
21  oral/intravenous antibiotic courses in the preceding year. Personal/familial atopy was  
22  documented by a compatible clinical history as well as by total IgE and eosinophil (Eos)  
23  levels. Best FEV<sub>1</sub> of the year preceding LUM/IVA administration (<sub>best</sub>FEV<sub>1</sub>), and maximal level  
24  of reversible airway obstruction (RAO) ever measured in the preceding year (improvement of  
25  FEV<sub>1</sub> $\geq 12\%$  considered as significant RAO (3)) were also collected from previous pulmonary  
26  function tests.

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

7

### 8 ***Study protocol***

9 The first LUM/IVA (400mg/250mg) administration was organized at the hospital. Patients  
10 were asked not to take SABD for 6h and/or LABD (including ICS-LABD) for 12h before their  
11 visit. FEV<sub>1</sub> was the outcome measure, expressed as percent of predicted value (4) and Z-  
12 score using the Global Lungs Initiative 2012 software (<http://www.spirxpert.com>). A physical  
13 exam was performed and FEV<sub>1</sub> (<sub>pre</sub>FEV<sub>1</sub>; MasterScreen, PFT System, Jaeger, Germany)  
14 measured immediately before LUM/IVA administration. After administration, patients were  
15 asked to report any respiratory-related symptoms (cough, chest tightness, wheezing,  
16 breathlessness) experienced. A second physical exam was performed immediately before  
17 FEV<sub>1</sub> was measured 4h±15 minutes later (<sub>postLUM/IVA</sub>FEV<sub>1</sub>); 400µg salbutamol was then  
18 administered, and 15 minutes thereafter FEV<sub>1</sub> was measured (<sub>postSABD</sub>FEV<sub>1</sub>).

19

### 20 ***Outcomes***

21 The primary outcome was relative change between <sub>pre</sub>FEV<sub>1</sub> and <sub>postLUM/IVA</sub>FEV<sub>1</sub> in  
22 ( $\Delta\text{FEV}_1 = ((\text{preFEV}_1 - \text{postLUM/IVA FEV}_1) / \text{preFEV}_1)$ ), because a wide range of <sub>best</sub>FEV<sub>1</sub> values among  
23 patients was expected. Secondary outcomes included absolute changes between  
24  $\text{preFEV}_1 / \text{postLUM/IVA FEV}_1$  and  $\text{postLUM/IVA FEV}_1 / \text{postSABD FEV}_1$ .

25

## 1 **Statistics**

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

9

## 10 **3. Results**

### 11 **Characteristics**

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

### 14 **Primary outcome**

15 A drop of FEV<sub>1</sub> was observed in all 32 patients following first LUM/IVA administration (Figure  
16 1A). After 4h, three patients (9.4%) spontaneously reported wheezing spells of mild severity  
17 (no oxygen desaturation at second physical exam) that resolved after SABD administration  
18 (as defined in the protocol). For these patients  $_{pre}FEV_1$  was 57%, 70%, and 81%.

19 The mean±SD  $_{pre}FEV_1$  was 87.0±16.7%. The relative change of FEV<sub>1</sub> ( $\Delta FEV_1$ ) was -10.4±4.6%  
20 (range:-1.5;-21.8%). The absolute change of FEV<sub>1</sub> was -9.4±3.6% (range:-1;-17%). The  
21  $_{postLUM/IVA}FEV_1$  was 77.6±16.7%; it partially recovered after salbutamol administration  
22 ( $_{postSABD}FEV_1$ :82.6±17.0). The absolute difference between  $_{pre}FEV_1$  and  $_{postLUM/IVA}FEV_1$  was  
23 significantly different (p<0.001), as it was between  $_{pre}FEV_1$  and  $_{postSABD}FEV_1$  (p<0.001; Figure  
24 1B).

## 1 **Correlation of $\Delta FEV_1$ with other parameters**

2 There was a significant correlation between  $\Delta FEV_1$  and  $_{best}FEV_1$  ( $r=-0.49$ ; 95%CI $[-0.72;-0.16]$ ,  
3  $p=0.0040$ ; Figure 1C), as well as RAO ( $r=-0.39$ ; 95%CI $[-0.66;-0.048]$ ,  $p=0.0236$ ; Figure 1D).  
4 There was no correlation with total IgE ( $r=-0.27$ ; 95%CI $[-0.59;0.11]$ ,  $p=0.1462$ ) or Eos levels  
5 ( $r=-0.12$ ; 95%CI $[-0.46;0.24]$ ,  $p=0.5017$ ). There was a significant correlation with the number  
6 of intravenous antibiotic treatments ( $r=-0.51$ ; 95%CI $[-0.74;-0.20]$ ,  $p=0.0025$ ), but not with the  
7 number of oral antibiotics ( $r=-0.20$ ; 95%CI $[-0.52;0.17]$ ,  $p=0.2684$ ).

## 8 **Sub groups**

9 Personal/familial atopy, PA colonization, history of ABPA, ICS/ICS-LABD treatment were not  
10 associated with a greater drop of  $FEV_1$ ; the small number of patients in each subgroup  
11 precluded further statistical analysis. When categorizing patients by level of RAO (RAO $<12\%$ ,  
12  $n=17$  and RAO $\geq 12\%$ ,  $n=15$ ), we found that there was a deeper drop of  $\Delta FEV_1$  in patients with  
13 RAO level  $\geq 12\%$  ( $-12,7\pm 1,3$ ) than in patients with RAO $<12\%$  ( $-9,4\pm 0,9$ ) ( $p=0.0499$ ).

## 14 **4. Discussion**

15 LUM/IVA consistently induced a decrease of  $FEV_1$  after first administration in pediatric CF  
16 patients, but was responsible for wheezing in less than 10% of participants. It was also found  
17 that SABD only partially restored  $_{pre}FEV_1$ , and that the decrease of  $FEV_1$  was correlated with  
18  $_{best}FEV_1$  and level of RAO. Of note, our study only addresses short term effects and the  
19 durability of these changes are not assessed in this data set.

## 20 **CFTR modulators and acute respiratory manifestations**

21 The first CFTR modulator to be tested in class-III mutations was IVA. In the trial, patients  
22 receiving ivacaftor 150mg/12h had no adverse events such as “abnormal respiration” (5).  
23 When IVA (250mg/12h) was combined with LUM (400mg/12h) “abnormal respiration”  
24 occurred in 7.7 to 9.9% of patients respectively included in the TRAFFIC and TRANSPORT  
25 trials; reaching 14.5% with LUM 600mg/12h (1). Similar proportions have also been recently

26 reported in HV (2). In this study, the proportion experiencing wheezing spells is coherent with  
27 previous reports.

### 28 ***FEV<sub>1</sub> decrease after LUM/IVA administration***

29 FEV<sub>1</sub> decrease (i.e. bronchoconstriction) was consistently observed in the patients  
30 investigated here. The mean absolute decrease of FEV<sub>1</sub> was around 10%, which is greater  
31 than that reported in HV (-4.1±5.6%)(2). We found that SABD only partially reversed  
32 bronchoconstriction (+5% absolute), while HV fully recovered. Incomplete recovery may be  
33 related to the lower dose of salbutamol used (400µg through spacer vs. 2.5mg  
34 albuterol/0.5mg ipratropium nebulized)(2), and/or incomplete reversibility due to other  
35 mechanisms involved in LUM/IVA-induced obstruction (mucociliary clearance restoration and  
36 mucus blowing or persistence of increased airway collapsibility). As the administration of  
37 LABD 12h prior to first LUM/IVA administration attenuates FEV<sub>1</sub> decrease in HV(2), we  
38 speculate that it should be the same in CF patients.

### 39 ***Airway smooth muscle (ASM) and CFTR function restoration***

40 In human ASM cells, it was shown that the absence of functional CFTR was responsible for  
41 altered intracytoplasmic calcium homeostasis (6). In the newborn CF pig, loss of CFTR  
42 causes a primary defect in ASM function which increases ASM tone. CFTR was shown to be  
43 expressed in the sarcoplasmic reticulum of ASM, which drives calcium re-uptake. In this  
44 model, restoring CFTR activity with IVA decreased ASM tone (7). This was also observed in  
45 a recent study conducted in 12 adults with CF with the *G551D-CFTR* mutation. IVA  
46 administration shown indirect evidences of an acute ASM relaxation and airway dilatation (8).  
47 Paradoxically, our data indicate that acute CFTR restoration with LUM/IVA induced airway  
48 narrowing mainly through bronchoconstriction and ASM contraction. Although yet unproven  
49 *in vitro*, this suggests a direct action of LUM or the combination LUM/IVA on ASM contraction  
50 pathways, which is likely to be independent of basal CFTR activity as it was also observed in



51 healthy subjects (2). The more pronounced drop of FEV<sub>1</sub> in the most severe patients may be  
52 related to the inflammation-mediated increase ASM contractibility (review in (9)).  
53 In conclusion, the study found that LUM/IVA consistently induced a bronchoconstriction that  
54 was associated with clinical symptoms in around 10%. Patients with a known significant RAO  
55 level (ie ≥12%) and/or low baseline FEV<sub>1</sub> were more at risk of a deeper FEV<sub>1</sub> drop and  
56 should be more closely monitor in clinics in the following hours after their first LUM/IVA  
57 administration.

## 58 **5. Acknowledgements**

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