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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 (FEV₁) after a unique
4 administration in healthy subjects. The aim of the present study was to assess acute FEV₁
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 FEV₁
7 consistently decreased (-10.4 ±4.6%, range: -1.5; -21.8%). FEV₁ only partially resumed after
8 salbutamol inhalation. Patients with previously known significant reversible airway
9 obstruction and low FEV₁ were more at risk of FEV₁ 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 ≥ 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, FEV₁) 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 FEV₁ of the year preceding LUM/IVA administration (_{best}FEV₁), and maximal level
24 of reversible airway obstruction (RAO) ever measured in the preceding year (improvement of
25 FEV₁ $\geq 12\%$ 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. FEV₁ 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 FEV₁ (_{pre}FEV₁; 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 FEV₁ was measured 4h±15 minutes later (_{postLUM/IVA}FEV₁); 400µg salbutamol was then
18 administered, and 15 minutes thereafter FEV₁ was measured (_{postSABD}FEV₁).

19

20 ***Outcomes***

21 The primary outcome was relative change between _{pre}FEV₁ and _{postLUM/IVA}FEV₁ in
22 ($\Delta\text{FEV}_1 = ((\text{preFEV}_1 - \text{postLUM/IVA FEV}_1) / \text{preFEV}_1)$), because a wide range of _{best}FEV₁ 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 FEV₁ 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 FEV₁ (ΔFEV_1) was -10.4±4.6%
20 (range:-1.5;-21.8%). The absolute change of FEV₁ 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 ΔFEV_1 with other parameters**

2 There was a significant correlation between ΔFEV_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 ΔFEV_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 ***FEV₁ decrease after LUM/IVA administration***

29 FEV₁ decrease (i.e. bronchoconstriction) was consistently observed in the patients
30 investigated here. The mean absolute decrease of FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ were more at risk of a deeper FEV₁ 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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