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1 **Real-world assessment of LCI following lumacaftor-ivacaftor initiation in adolescents and adults**
2 **with cystic fibrosis**

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40 **Abstract**

41 Lung clearance index (LCI) is a biomarker of ventilation inhomogeneity. Data are scarce on its
42 usefulness in daily practice for monitoring the effects of treatments in older children and adults with
43 CF. In this French observational study of lumacaftor-ivacaftor, 63 of 845 patients (7.5%) had available
44 LCI performed at baseline and at six (M6; n=34) or 12 months (M12; n=46) after lumacaftor-ivacaftor
45 initiation. At inclusion, median [IQR] age was 16 years [13-17], ppFEV₁ was 72.8 [59.6-80.7], and LCI
46 was 12.3 [10.3-15.0]. At both M6 and M12, no statistically significant LCI increases of 0.13 units or
47 1.34% (95% CI: -4.85-7.53) and 0.6 units or 6.66% (95% CI: -0.03-13.5) were observed. Discordant
48 results between LCI and ppFEV₁ were observed in one-third of the patients. In daily practice, LCI
49 monitoring in adolescents and young adults with moderate lung disease gives results that are more
50 heterogenous than those reported in children with milder disease.

51

52 **Keywords:** lumacaftor, CFTR modulators, cystic fibrosis, multiple breath washout

53 **Running title:** LCI in real life

54

55 **Author's contribution.** **Philippe Reix** : conceptualization, data acquisition, test overreading, data
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63 conceptualization, data acquisition, writing review and editing, visualization, project administration

64 **1. Introduction**

65 Multiple breath washout (MBW), which explores ventilation inhomogeneity, has been shown to be a
66 valuable research tool (1). MBW-derived outcomes such as the lung clearance index (LCI) have been
67 used as primary endpoints in phase 3 clinical trials to assess the effects of cystic fibrosis
68 transmembrane conductance regulator (CFTR) modulators in young children who have cystic fibrosis
69 (CF) but preserved lung function (2-4). An absolute decrease in the LCI, corresponding to a reduction
70 in ventilation inhomogeneity, has consistently been reported throughout these trials. Recently, data
71 from an observational cohort study (PROSPECT) conducted in a more diverse population of patients
72 with CF who received follow-up in the year after lumacaftor-ivacaftor initiation have confirmed these
73 findings (5).

74 Several pediatric CF centers in France have deemed it interesting to monitor this biomarker in the CF
75 clinical setting. However, data obtained in clinical trials or in observational studies in experienced
76 centers do not necessarily reflect those obtained in daily practice. In the present study, we took
77 advantage of MBW measurements performed in a large national real-world observational study that
78 followed CF patients aged 12 years or older over the first year after lumacaftor-ivacaftor initiation (6).
79 Our goal was to describe LCI evolution following the initiation of lumacaftor-ivacaftor and to examine
80 its clinical value as compared to ppFEV₁. We hypothesized that LCI may provide clinically-relevant
81 information that may be a useful complement to spirometry.

82 **2. Materials and methods**

83 **2.1 Patients**

84 The study design and organization of the French lumacaftor-ivacaftor observational cohort are
85 described elsewhere (6, 7). That study was registered with (NCT03475391) and approved by the
86 Institutional Review Board of The French Society for Respiratory Medicine (Société de Pneumologie
87 de Langue Française, #2016–004). Patients and parents were informed of the protocol but were not

88 required to provide informed consent as per French law. Being observational by nature, there was no
89 study power calculation.

90 **2.2 MBW measurements and outcomes**

91 All MBW measurements available from the participating CF centers were collected. Patients were
92 considered eligible for this substudy if they had at least one MBW measurement performed at
93 baseline (within 90 days prior to lumacaftor-ivacaftor initiation) and at least one measurement at six
94 (M6) and/or 12 (M12) months after initiation. Six out of 11 pediatric CF centers with a MBW device
95 participated in this sub-study. All were certified by the ECFS-CTN core facility, employed the same
96 device (ExhalyzerD; Ecomedics, Duernten, Switzerland) for the nitrogen washout technique and had
97 high levels of experience with this latter. MBW was performed either before or after a chest
98 physiotherapy course, but always at the same timing throughout the study. MBWs were performed
99 based on the ECFS standard operating procedure, and all traces were reviewed for quality
100 assessment by a single investigator (PR).

101 Lung clearance indices were measured at the fortieth of initial nitrogen concentration (known as
102 $LCI_{2.5}$ but referred to here as LCI) and used as the main MBW outcome. $ppFEV_1$ was used as the main
103 spirometry outcome. Absolute and relative changes were calculated.

104 **2.3 Statistics**

105 Data are presented as numbers and percentages (n, %), means with standard deviations (SD) and
106 confidence intervals (95% CI), or medians with interquartile ranges (IQR) as pertinent. Data obtained
107 for LCI or spirometry at initiation and at M6 and/or M12 were compared using the paired Wilcoxon's
108 test. A P value <0.05 was considered statistically significant. Pearson correlations were used between
109 LCI and $ppFEV_1$. Concordant and discordant results between $ppFEV_1$ and LCI were evaluated using
110 cut-offs of relative changes of 10% and 15% respectively; the former being considered meaningful in
111 clinical practice, the latter based on data published elsewhere (8-10).

112 **3. Results**

113 **3.1 Characteristics of patients**

114 At least one MBW was performed for 77 patients during the study. Six patients were excluded
 115 because they had no LCI at initiation, or no LCI at either M6 or M12. Data from eight patients were
 116 also excluded because their LCIs at initiation were not performed within the 90 days preceding
 117 lumacaftor-ivacaftor administration. There was thus a final dataset of 63 patients including two
 118 adults (Table 1). A total of 144 MBW measurements were collected from them.

119 **Table 1: Characteristics of the 63 CF patients at lumacaftor-ivacaftor initiation**

	Median [IQR]	Min-Max
Age (years)	16 [13-17]	12-20
BMI (Z-score)	-0.81 [-1.09-0.37]	-1.84-4.29
ppFEV ₁	72.8 [59.6-80.7]	33.0-101
ppFEV ₁ <40	0 (0%)	
ppFEV ₁ [40 to 90]	57 (90.5%)	
ppFEV ₁ ≥90	6 (9.5%)	
LCI	12.3 [10.3-15.0]	6.8-23.3
ppFVC	86.5 [75.6-95.2]	50.2-128
Number of IV antibiotic courses* (n = 61)	0 [0-2]	0-4
PI n (%)	62 (98.4%)	
Diabetes	6 (9.6%)	
Liver cirrhosis	1 (1.6%)	

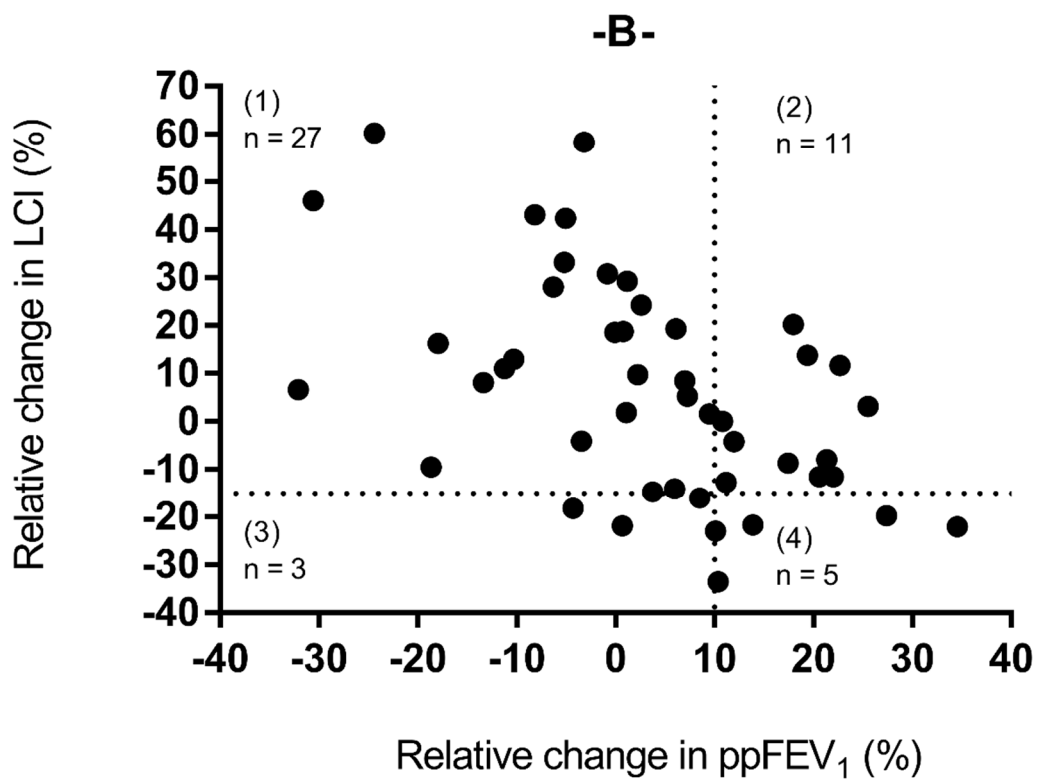
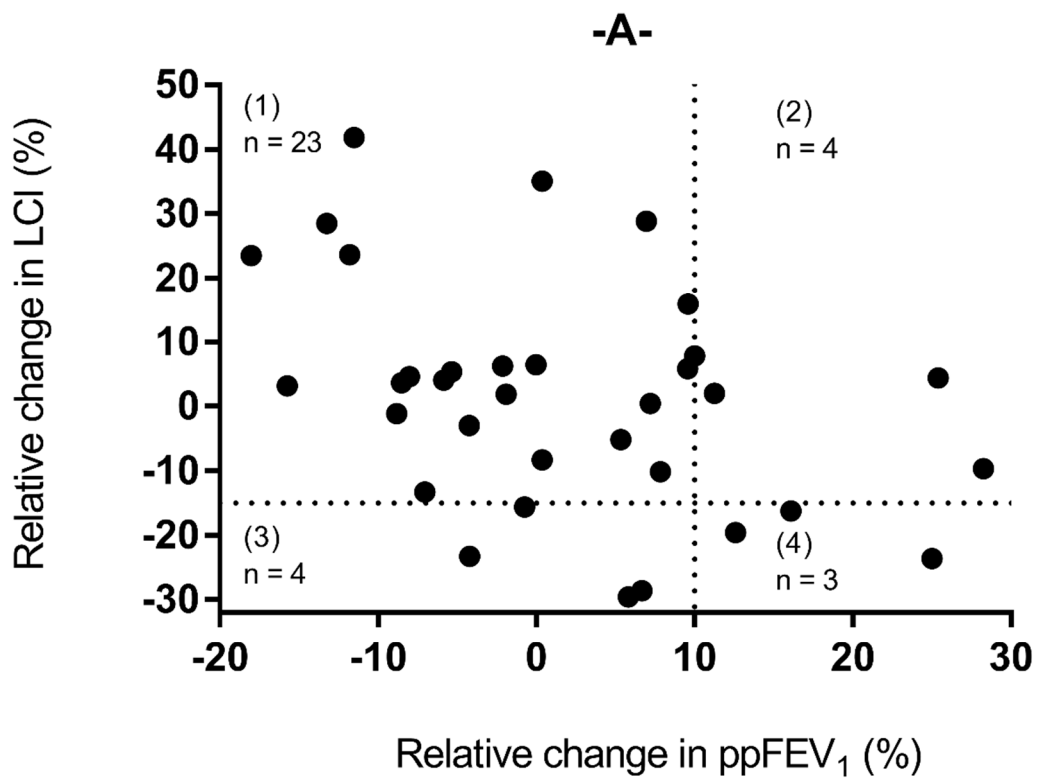
120 *In the preceding year; BMI: body mass index; ppFEV₁: percent predicted forced expiratory volume in
 121 1 second; ppFVC: percent predicted forced vital capacity; LCI: lung clearance index; PI: pancreatic
 122 insufficiency

123 **3.2 LCI variation over time**

124 LCI was measured at initiation and M6 or M12 or at all three time points in 34 (54%), 46 (73%) and 23
 125 (36%) patients respectively (Table 2). At M6, there was a statistically insignificant absolute increase
 126 (worsening) of 0.13±2.34 (95% CI: -0.68-0.95) units and a relative increase of 1.34±17.74% (95% CI: -
 127 4.85-7.53) (p = 0.70). At M12, there was an insignificant mean relative change of 6.7±22.5% (95% CI: -
 128 0.03-13.5) (p = 0.12). Absolute and relative changes of ppFEV₁ were +1.45% (95% CI: -1.4-4.3) and 1.8%
 129 (95% CI: -2.2-5.8) at M6 (p = 0.62), and +2.09% (95% CI: -0.8-4.98) and 3.46% (95% CI: -0.95-7.87) at
 130 M12 (p = 0.08).

131 **3.3 Concordance between LCI and ppFEV₁**

132 A weak correlation was found between ppFEV₁ and LCI at both M6 (R = -0.358; P = 0.0374) and M12
133 (R = -0.486; P=0.0006). As shown in **Figure 1**, relative changes of LCI vs. ppFEV₁ appeared
134 heterogenous at M6 and M12. With a cut-off for relative change of 15% for LCI and 10% for ppFEV₁
135 as indicators of clinically relevant improvement, 76% and 70% of patients had concordant evolution
136 of LCI and ppFEV₁ at M6 and M12 (Table 2). Discordant evolution was found in similar percentages at
137 M6 and M12. For example, at M6, 4 patients (12%) showed improvement for ppFEV₁ but
138 deterioration for LCI.



139

140

141 **Figure 1:** Correlations of relative changes between LCI and ppFEV₁ at M6 (A) or M12 (B). Dashed lines
142 represent cut-off values for relative changes of ppFEV₁ and LCI (respectively set to 10 and 15%)
143 chosen to define clinically relevant improvement. Quadrant (1): LCI stable or increased, ppFEV₁ stable
144 or decreased; Quadrant (2): LCI stable or increased, ppFEV₁ stable or increased; Quadrant (3): LCI
145 stable or decreased, ppFEV₁ stable or decreased, Quadrant (4): LCI stable or decreased, ppFEV₁ stable
146 or increased. LCI increase means ventilation heterogeneity worsening.

147

148

1 **Table 2: LCI: Initial value and changes over time and concordance with ppFEV₁**

LCI initial values and changes					
Initiation vs M6	LCI at initiation	LCI at M6	Absolute change	Relative change	P value
N = 34	12.8±3.5 (95% CI: 11.6-13.9)	12.9±4.0 (95% CI: 11.5-14.3)	0.13±2.34 (95% CI: -0.68-0.95)	1.34±17.74% (95% CI: -4.85-7.53)	0.70
Initiation vs M12	LCI at initiation	LCI at M12	Absolute change	Relative change	P value
N = 46	13.1±3.4 (95% CI: 12.1-14.1)	13.7±3.8 (95% CI: 12.5-14.8)	0.6±2.7 (95% CI: -0.21-1.40)	6.66±22.5% (95% CI: -0.03-13.5)	0.12
LCI and ppFEV ₁ concordance					
At M6	Concordant pairs		Discordant pairs		
	→ or ↘ LCI	→ or ↗ LCI	→ or ↗ LCI	→ or ↘ LCI	
	→ or ↗ ppFEV ₁ *	→ or ↘ ppFEV ₁	→ or ↗ ppFEV ₁	→ or ↘ ppFEV ₁	
N (%)	3 (9%)	23 (67%)	4 (12%)	4 (12%)	
At M12	Concordant pairs		Discordant pairs		
	→ or ↘ LCI	→ or ↗ LCI	→ or ↗ LCI	→ or ↘ LCI	
	→ or ↗ ppFEV ₁ *	→ or ↘ ppFEV ₁	→ or ↗ ppFEV ₁	→ or ↘ ppFEV ₁	
N (%)	5 (11%)	27 (59%)	11 (24%)	3 (6%)	

2 *Cut-offs for relative changes to define clinically relevant improvement were set at ±15% for LCI based on available data on relative changes (8-10) and at
 3 ±10% for ppFEV₁. Symbols: → or ↘ (stable or decreased); → or ↗ (stable or increased) with “stable” meaning a relative change below cut-off values.

1 **4. Discussion**

2 In this real-world observational study of lumacaftor-ivacaftor follow-up with a wide range of
3 pulmonary function, we found no improvement in LCIs during the first year of treatment. We also
4 found that LCI response to lumacaftor-ivacaftor was heterogenous.

5 **4.1 LCI response to lumacaftor/ivacaftor in real life**

6 In the present study, we found no significant changes in LCIs over time. These results do not align
7 with other recently published results. Indeed, in a cohort of 49 patients, Shaw *et al.* reported a
8 median LCI decrease (improvement) of 0.67 units (i.e., relative change of 5.9%) at M6 and 0.55 units
9 (relative change of 4.3%) at M12. In their work, ppFEV₁ did not improve significantly at any time point
10 (5). It is unlikely that the differences between the data of our study and those of Shaw *et al.* are due
11 to the quality of the measurements as all involved centers had trained/qualified personnel for the
12 tests and all traces were reviewed for quality control. The most likely explanation resides more so in
13 marked differences between the study populations; despite similar ages, our patients had more
14 severe disease and lower lung function (medians ppFEV₁ at 72.8% vs 91.3%).

15 **4.2 Concordance between LCI and ppFEV₁**

16 With relative change cut-offs of 15% for LCI and 10% for ppFEV₁, we found that about a third of
17 patients had discordant evolution of both LCI and FEV₁. The relative change cut-off of 15% for LCI was
18 based on previous data obtained in preschool and school-aged children (8-10). Individual correlations
19 of these two outcomes during CFTR modulator administration have never been reported to date, as
20 these data are almost always reported at the group level. This heterogeneity has however been
21 repeatedly reported during pulmonary exacerbation and the resulting data pooled for analysis by
22 Sonneveld *et al.* That team reported an overall decrease in LCI of 0.4 units, but their LCI results were
23 frequently discordant with ppFEV₁ whatever the cut-off used for relative change in LCI and FEV₁ (0, 5,

24 10 or 15%) (11). As a comparison, discordant results using cut-offs similar to ours represent 41.5%,
25 which is higher than in our cases (28% and 30%).

26 **4.3 Implication for using MBW in CF clinics: 1,2, 3...wait**

27 Some authors have raised the question of the use of MBW in clinics (12). Data are accumulating to
28 show that this tool is particularly interesting in young children with milder lung disease. In patients
29 with more severe pulmonary disease, as shown previously, measuring LCI did not bring added value
30 to ppFEV₁ in two thirds of our cases. Because of discordant results in 30% of patients, interpretation
31 will remain problematic for clinicians: Should more weight be put on LCI for decision making when
32 FEV₁ increases and LCI worsens? Should clinicians be reassured by an improvement of LCI when FEV₁
33 deteriorates? Although imaging studies have contributed to a better understanding of LCI
34 heterogeneity, these and other questions do remain (13).

35 **4.4 Limitations**

36 The work we present here does have several limitations. Firstly, only a small percentage (7.5%) of the
37 initial cohort could be enrolled in it. Secondly, only a third of our patients had data for all three of the
38 time points considered in the study. Thirdly, ideally the study would only have included MBW
39 measurements from clinically stable clinic visits. However, it was not possible to retrospectively
40 determine the clinical status of participants and this may have contributed to the observed
41 heterogeneity. Finally, patient's adherence to treatment was not monitored. Lack of the observed
42 treatment effect could also be related to poor adherence even if real life results have shown good
43 adherence to Lumacaftor-Ivacaftor in adolescents 6 and 12 months after initiation (14).

44 **4.5 Conclusion**

45 We found that LCI nor FEV₁ did not decrease after one year of exposure to lumacaftor/ivacaftor in
46 adolescents with CF. Individual LCI and FEV₁ changes at 6 and 12 months showed discordance in

47 around a third of our patients. These results suggest that the MBW test may be a more useful
48 monitoring tool for individuals with early cystic fibrosis lung disease.

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