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

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Abstract

Lung clearance index (LCI) is a biomarker of ventilation inhomogeneity. Data are scarce on its usefulness in daily practice for monitoring the effects of treatments in older children and adults with CF. In this French observational study of lumacaftor-ivacaftor, 63 of 845 patients (7.5%) had available LCI performed at baseline and at six (M6; n=34) or 12 months (M12; n=46) after lumacaftor-ivacaftor initiation. At inclusion, median [IQR] age was 16 years [13-17], $ppFEV_1$ was 72.8 [59.6-80.7], and LCI was 12.3 [10.3-15.0]. At both M6 and M12, no statistically significant LCI increases of 0.13 units or 1.34% (95% CI: -4.85-7.53) and 0.6 units or 6.66% (95% CI: -0.03-13.5) were observed. Discordant results between LCI and $ppFEV_1$ were observed in one-third of the patients. In daily practice, LCI monitoring in adolescents and young adults with moderate lung disease gives results that are more heterogenous than those reported in children with milder disease.

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

Running title: LCI in real life

Author's contribution. Philippe Reix : conceptualization, data acquisition, test overreading, data collection and interpretation, original draft and revision, editing, **Aurélie Tatopoulos:** writing review and editing; **Iulia Ioan:** data acquisition, writing review and editing, **Muriel Le bourgeois:** data acquisition, writing review and editing, **Stéphanie Bui:** writing review and editing**, Marie Luce Choukroun**: data acquisition, writing review and editing, **Katia Bessaci-Kabouya**: writing review and editing, **Michele Gerardin**: data acquisition, writing review and editing, **Plamen Bokov**: data acquisition, writing review and editing, **Jennifer Da Silva**: data base management, writing review and editing, **Jean-Louis Paillasseur**: stastical analysis, writing review and editing, **Pierre Regis Burgel**: conceptualization, data acquisition, writing review and editing, visualization, project administration

1. Introduction

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

Several pediatric CF centers in France have deemed it interesting to monitor this biomarker in the CF clinical setting. However, data obtained in clinical trials or in observational studies in experienced centers do not necessarily reflect those obtained in daily practice. In the present study, we took advantage of MBW measurements performed in a large national real-world observational study that followed CF patients aged 12 years or older over the first year after lumacaftor-ivacaftor initiation (6). Our goal was to describe LCI evolution following the initiation of lumacaftor-ivacaftor and to examine its clinical value as compared to ppFEV$_1$. We hypothesized that LCI may provide clinically-relevant information that may be a useful complement to spirometry.

2. Materials and methods

2.1 Patients

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

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

2.2 MBW measurements and outcomes

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

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

2.3 Statistics

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

3. Results

3.1 Characteristics of patients

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

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 $ppFEV_1$ [40 to 90] $ppFEV_1$ ≥90	0 (0%) 57 (90.5%) 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%)	

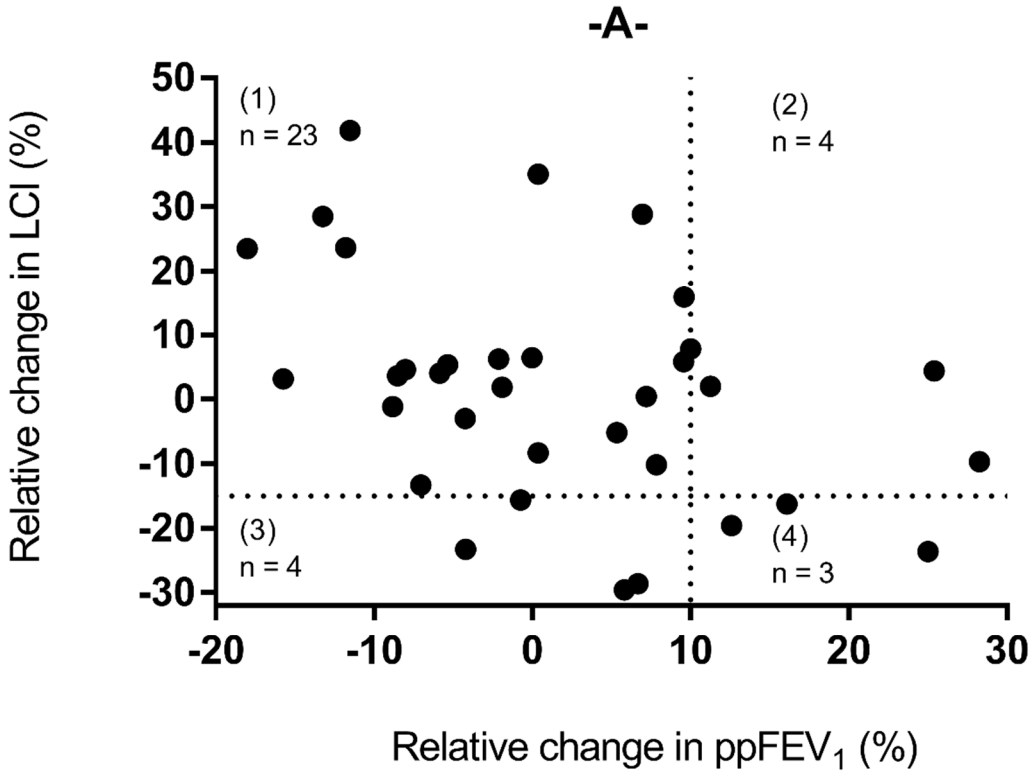
*In the preceding year; BMI: body mass index; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; ppFVC: percent predicted forced vital capacity; LCI: lung clearance index; PI: pancreatic insufficiency

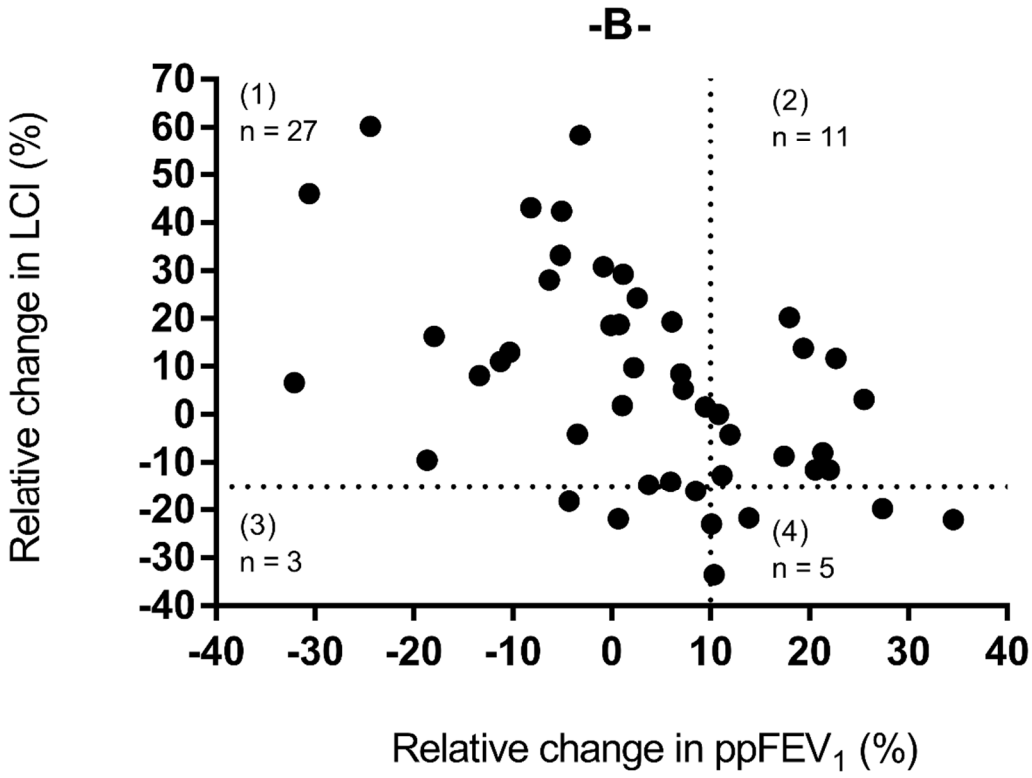
3.2 LCI variation over time

LCI was measured at initiation and M6 or M12 or at all three time points in 34 (54%), 46 (73%) and 23 (36%) patients respectively (Table 2). At M6, there was a statistically insignificant absolute increase (worsening) of 0.13±2.34 (95% CI: -0.68-0.95) units and a relative increase of 1.34±17.74% (95% CI: -4.85-7.53) (p = 0.70). At M12, there was an insignificant mean relative change of 6.7±22.5% (95% CI: -0.03-13.5) (p = 0.12). Absolute and relative changes of $ppFEV_1$ were +1.45% (95% CI: -1.4-4.3) and 1.8% (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 M12 (p = 0.08).

3.3 Concordance between LCI and ppFEV$_1$

A weak correlation was found between ppFEV$_1$ and LCI at both M6 (R = -0.358; P = 0.0374) and M12 (R = -0.486; P=0.0006). As shown in **Figure 1**, relative changes of LCI vs. ppFEV$_1$ appeared heterogenous at M6 and M12. With a cut-off for relative change of 15% for LCI and 10% for ppFEV$_1$ as indicators of clinically relevant improvement, 76% and 70% of patients had concordant evolution of LCI and ppFEV$_1$ at M6 and M12 (Table 2). Discordant evolution was found in similar percentages at M6 and M12. For example, at M6, 4 patients (12%) showed improvement for ppFEV$_1$ but deterioration for LCI.


-A-
(1)
n = 23
(2)
n = 4
(3)
n = 4
(4)
n = 3
Relative change in LCI (%)
Relative change in ppFEV1 (%)
50
40
30
20
10
0
-10
-20
-30
-20
-10
0
10
20
30


-B-
(1)
n = 27
(2)
n = 11
(3)
n = 3
(4)
n = 5
Relative change in LCI (%)
Relative change in ppFEV1 (%)
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-40
-30
-20
-10
0
10
20
30
40

139

140

Figure 1: Correlations of relative changes between LCI and $ppFEV_1$ at M6 (A) or M12 (B). Dashed lines represent cut-off values for relative changes of $ppFEV_1$ and LCI (respectively set to 10 and 15%) chosen to define clinically relevant improvement. Quadrant (1): LCI stable or increased, $ppFEV_1$ stable or decreased; Quadrant (2): LCI stable or increased, $ppFEV_1$ stable or increased; Quadrant (3): LCI stable or decreased, $ppFEV_1$ stable or decreased, Quadrant (4): LCI stable or decreased, $ppFEV_1$ stable or increased. LCI increase means ventilation heterogeneity worsening.

Table 2: LCI: Initial value and changes over time and concordance with $ppFEV_1$

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 ↗$ppFEV_1$*	→ or ↗LCI → or ↘$ppFEV_1$	→ or ↗LCI → or ↗$ppFEV_1$	→ or ↘LCI → or ↘$ppFEV_1$
N (%)	3 (9%)	23 (67%)	4 (12%)	4 (12%)
At M12	**Concordant pairs**		**Discordant pairs**	
	→ or ↘LCI → or ↗$ppFEV_1$*	→ or ↗LCI → or ↘$ppFEV_1$	→ or ↗LCI → or ↗$ppFEV_1$	→ or ↘LCI → or ↘$ppFEV_1$
N (%)	5 (11%)	27 (59%)	11 (24%)	3 (6%)

*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 ±10% for $ppFEV_1$. Symbols: → or ↘ (stable or decreased); → or ↗ (stable or increased) with "stable" meaning a relative change below cut-off values.

4. Discussion

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

4.1 LCI response to lumacaftor/Ivacaftor in real life

In the present study, we found no significant changes in LCIs over time. These results do not align with other recently published results. Indeed, in a cohort of 49 patients, Shaw *et al*. reported a median LCI decrease (improvement) of 0.67 units (i.e., relative change of 5.9%) at M6 and 0.55 units (relative change of 4.3%) at M12. In their work, $ppFEV_1$ did not improve significantly at any time point (5). It is unlikely that the differences between the data of our study and those of Shaw *et al*. are due to the quality of the measurements as all involved centers had trained/qualified personnel for the tests and all traces were reviewed for quality control. The most likely explanation resides more so in marked differences between the study populations; despite similar ages, our patients had more severe disease and lower lung function (medians $ppFEV_1$ at 72.8% vs 91.3%).

4.2 Concordance between LCI and $ppFEV_1$

With relative change cut-offs of 15% for LCI and 10% for $ppFEV_1$, we found that about a third of patients had discordant evolution of both LCI and FEV_1. The relative change cut-off of 15% for LCI was based on previous data obtained in preschool and school-aged children (8-10). Individual correlations of these two outcomes during CFTR modulator administration have never been reported to date, as these data are almost always reported at the group level. This heterogeneity has however been repeatedly reported during pulmonary exacerbation and the resulting data pooled for analysis by Sonneveld *et al*. That team reported an overall decrease in LCI of 0.4 units, but their LCI results were frequently discordant with $ppFEV_1$ whatever the cut-off used for relative change in LCI and FEV_1 (0, 5,

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

4.3 Implication for using MBW in CF clinics: 1,2, 3…wait

Some authors have raised the question of the use of MBW in clinics (12). Data are accumulating to show that this tool is particularly interesting in young children with milder lung disease. In patients with more severe pulmonary disease, as shown previously, measuring LCI did not bring added value to ppFEV_1 in two thirds of our cases. Because of discordant results in 30% of patients, interpretation will remain problematic for clinicians: Should more weight be put on LCI for decision making when FEV_1 increases and LCI worsens? Should clinicians be reassured by an improvement of LCI when FEV_1 deteriorates? Although imaging studies have contributed to a better understanding of LCI heterogeneity, these and other questions do remain (13).

4.4 Limitations

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

4.5 Conclusion

We found that LCI nor FEV_1 did not decrease after one year of exposure to lumacaftor/ivacaftor in adolescents with CF. Individual LCI and FEV_1 changes at 6 and 12 months showed discordance in

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

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