An 8 week open-label interventional multicenter study to evaluate the lung clearance index as endpoint for clinical trials in cystic fibrosis patients ≥ 6 years of age, chronically infected with *Pseudomonas aeruginosa*

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Abstract

Background Forced expiratory volume in 1 second (FEV₁) is the only parameter currently recognized as a surrogate endpoint in cystic fibrosis (CF) trials. However, FEV₁ is relatively insensitive to changes in the small airways of patients with milder lung disease. This pilot study aimed to evaluate the lung clearance index (LCI) as a marker for use in efficacy trials with inhaled antibiotics in CF.

Methods This open-label, single-arm study enrolled CF patients with *Pseudomonas aeruginosa* infection, who were treated with tobramycin (28-day on/off regime). FEV₁, LCI and bacterial load in sputum (CFU) were assessed at baseline, after 1, 4 and 8 weeks of treatment.

Results All patients (n=17) showed elevated LCI of >11 despite 3 patients having normal FEV₁ (>90% predicted) at baseline. Overall, LCI improved in 8 (47%) patients and FEV₁ in 9 (53%) patients. At week 4, LCI decreased by 0.88, FEV₁ increased by 0.52%, and *P. aeruginosa* reduced by 30481.3 CFU/mL. These changes were however statistically non-significant. Six adverse events occurred in 5/17 (29.4%) patients, most of which were mild-to-moderate in severity.

Conclusions Due to the low evaluable sample size, no specific trend was observed related to the changes between LCI, FEV₁ and CFU. Based on the individual data from this study and from recently published literature, LCI has been shown to be a more sensitive parameter than FEV₁ for lung function. However, LCI alone does not seem to be the ideal clinical endpoint for efficacy studies with antibiotic treatment in small groups of CF patients.

Trial registration : The study is registered with ClinicalTrials.gov, identifier: NCT02248922

Background

Cystic fibrosis (CF) is a life-limiting, autosomal recessive genetic disease [1], characterized by a reduced quantity and/or function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, leading to an impaired mucociliary clearance of the airways, followed by chronic inflammation, infection and thus progressive and irreversible loss of lung function [2]. The main driver of lung function decline beyond infancy in people with CF is the chronic infection with *Pseudomonas aeruginosa* [3]. Although it is a complex multiorgan and multifactorial disease, the chronic lung infection by *P. aeruginosa* is the primary cause of morbidity. Therefore, an antibiotic maintenance therapy is the preferred standard treatment in these patients. [2]. Inhaled tobramycin typically given in 28 day cycles of one month on and one month off periods, is recommended for treating individuals with CF aged ≥ 6 years, who have mild to moderate lung disease with persistent *P. aeruginosa* infection [4].

Currently, forced expiratory volume in one second (FEV₁) and rate of FEV₁ decline are the only accepted surrogate markers for assessing lung function decline [5]. However, with significant advances in the care of patients with CF, such as the newly introduced CFTR-targeted therapies and considerable improvement in survival rates, the rate of decline in FEV₁ has slowed [6, 7], leading to a preservation of spirometric lung

function within the normal range into young adulthood [8, 9]. Moreover, FEV₁ is insensitive during early stages of lung disease resulting in normal spirometry findings, despite the progression of structural damage in lungs, for example in bronchiectasis. Therefore, the reliability on FEV₁ as an indicator of disease progression especially in the early stages of lung disease has become questionable [9, 10]. Increasing evidence suggest that in patients with CF, pulmonary deterioration starts early in life and can occur in the absence of respiratory symptoms at normal lung function in terms of FEV₁ [11]. Thus, there is a need for early intervention before onset of irreversible lung damage based on alternative clinically sensitive surrogate markers for detection of early CF lung disease [12].

A multiple breath washout (MBW) test assessing ventilation inhomogeneity has been shown to be a sensitive lung function test to detect early pathology in patients with CF [12]. The most commonly reported MBW outcome is the lung clearance index (LCI), which is a robust, noninvasive technique to detect early lung disease changes across all age groups [13, 14]. Consequently, LCI has been evaluated as a new sensitive surrogate endpoint for measuring trial outcomes focusing on the early stages of disease [13]. LCI was used for the first time as the primary study endpoint in a pivotal trial in children (6–11 years) with CF treated with an oral combination of CFTR modulators, lumacaftor (LUM) and ivacaftor (IVA). Treatment with LUM/IVA, demonstrated a statistically significant improvement in lung function, as measured by LCI_{2.5} and percent predicted FEV₁ (ppFEV₁), versus placebo in children with CF homozygous for F508del-CFTR [15]. However, there is still very limited data available on the use of LCI as a clinical endpoint for CF patients treated with inhaled antibiotics.

The aim of the present study was to examine the clinical utility of LCI for assessing short-term clinical response to inhaled tobramycin antibiotic therapy in patients with CF positive for *P. aeruginosa*, aged 6 years and older with mild to moderate lung disease.

Methods

Study design and patients

This was an open-label, single arm study in CF patients with *P. aeruginosa* infection. The study consisted of screening period (5 to 26 days) to test the presence of *P. aeruginosa* (Visit 1), a baseline visit (Visit 2), a visit one week after baseline visit (Visit 3), followed by a visit after 28 days on-treatment period (Visit 4) and subsequently a visit after 28 days off-treatment period (Visit 5, end of study). All patients were treated with tobramycin monotherapy, either as an inhalation solution (TIS) 300 mg twice daily (BID) or as an inhalation powder (TIP) 128 mg BID. FEV₁, LCI and bacterial load in sputum (colony forming units [CFU]) were assessed at baseline, after 1, 4 and 8 weeks of treatment. Spirometric and LCI assessments were conducted before or at least one hour after the inhalation of the drug. MBW measurements to assess the LCI were performed with the ExhalyzerD (Eco Physics GmbH, Munich, Germany). The study design was approved by the independent ethics committee and institutional review boards; and was in accordance with the Declaration of Helsinki.

The study enrolled patients diagnosed with CF aged 6 to 50 years, with a pulmonary infection of *P. aeruginosa* within the last 12 months and at screening. Patients with an elevated LCI of ≥ 7.5 and FEV₁ of $\geq 50\%$ at screening, and those receiving inhaled tobramycin monotherapy in 28 days on/off regime in the past 3 month before screening were included. Informed consent was obtained from patients for having their data collected. Patients receiving more than one class of inhaled antipseudomonal antibiotic during the study or in the past 56 days prior to the baseline visit, or who used oral or intravenous antipseudomonal antibiotics within 28 days prior to the on-phase of the study drug or loop diuretics within 7 days prior to the first study medication administration, were excluded.

Study assessments

The primary endpoint was change in LCI after 4 weeks of treatment versus baseline. Secondary endpoints included change in FEV₁ and CFU after week 4 following treatment; change of LCI after week 1 following treatment; change of LCI, FEV₁ and CFU between week 4 (end of the study drug inhalation in the current treatment cycle) and week 8 (prior to the start of the study drug inhalation in the following treatment cycle); and correlation between the changes of LCI, FEV₁ and CFU after weeks 1, 4 and 8 versus baseline, respectively.

For LCI assessment, the multiple breath washout device Exhalyzer D (Ecomedics, Zurich, Switzerland) was used, with Nitrogen as the tracer gas. All equipment and the device software were identical throughout the sites. LCI was determined according to the Exhalyzer D SOP of the manufacturer and all study sites have been provided with a device specific training before start of the study. For the measurements used to calculate the mean value, a quality control was done by a central assessor (MBW specialist).

Statistical analysis

Assuming a change of 5% in FEV₁ with an intraindividual standard deviation of 9% between the on- and off-treatment cycles, 28 patients would provide 80% power on a 2-sided 5% significance level to detect this change. To compensate for protocol deviations and dropouts, 35 patients were planned to be recruited into this trial. All variables were summarized using descriptive statistics. Analyses were performed by using SAS Version 9.4.

Changes in LCI from baseline were analyzed using an analysis of variance (ANOVA) model. Estimates over time were presented as least squares (LS)-means, pairwise LS-mean differences along with 95% confidence intervals (CI) and 2-sided p-values for the pairwise differences between visits. If the baseline value was missing, then change was calculated from the data recorded at the screening. The primary analysis included patients with a valid observation at the baseline and post-baseline visits.

Results

In total, 17 patients (5 patients treated with TIS and 12 patients with TIP) were enrolled and completed the study. The majority of the patients (14 patients, 82.4%) were aged > 17 years, with an overall mean age of 26.4 ± 9.99 years and body mass index (BMI) of 21.1 ± 2.46 kg/m². The study had a higher proportion of men (64.7%) versus women (35.3%). At baseline, mean LCI was 17.99 ± 4.73 (95% CI: 11.16–29.14) and FEV₁ was $76.96 \pm 18.60\%$ predicted (95% CI: 44.66–115.5) (Fig. 1a). All patients demonstrated considerably elevated LCI of > 11 (normal range 6.5–7.5) despite 3 patients having a normal lung function (FEV₁ > 90% predicted) at baseline. The demographics and characteristics of patients at the baseline are presented in Table 1.

Age, years	26.4 (9.99)
Men, n (%)	11 (64.7)
Height, cm	171.12 (12.8)
Weight, kg	62.6 (12.9)
Waist circumference, cm	85.1 (22.6)
BMI, kg/m ²	21.1 (2.5)
LCI	17.99 (4.7)
FEV ₁ (%)	76.96 (18.6)

Data are expressed as mean (SD) unless indicated otherwise.

BMI, body mass index; FEV₁, forced expiratory volume in one second; LCI, lung clearance index; SD, standard deviation

Table 1. Patient demographics and baseline characteristics (N=17)

The mean LCI decreased slightly over time from baseline. At week 4, LCI decreased by 0.88 (17.10 ± 0.84 ; 95% CI: 15.31–18.88) from baseline, which was statistically non-significant ($p = 0.41$). Overall, 8 (47%) patients showed an improved LCI at week 4 from baseline. At least 3 patients showed worsening of LCI despite improvement in FEV₁ (Table 2).

Table 2
Lung function parameters after visit 4 versus baseline

Patient #	Age	FEV ₁ at baseline (% predicted)	dLCI in % of baseline	dFEV ₁ in % of baseline	dCFU [/g]
1	17	82.6	29.8%	11.0%	-17,120
2	17	84.7	3.8%	10.6%	-
3	37	71.5	-42.4%	7.2%	-224,700
4	19	68.2	-24.6%	7.0%	-
5	19	115.5	-19.8%	4.4%	-
6	24	109.9	10.5%	2.7%	-12,200
7	35	77.8	-3.0%	2.1%	-12,640
8	37	79.5	6.7%	0.9%	-40
9	22	44.7	-24.1%	0.6%	20,800
10	18	65.9	-4.8%	0.0%	-225,600
11	41	61.9	-4.6%	0.0%	-8,800
12	30	51.5	-15.6%	-1.0%	100
13	8	88.9	-6.9%	-2.2%	732
14	43	101.1%	8.7%	-5.1%	14,000
15	34	67.9%	17.1%	-6.9%	-10,040
16	23	75.3%	4.8%	-12.5%	29,600
17	24	68.6%	36.2%	-13.0%	-
CFU, colony forming units; d, difference at week 4 versus baseline; FEV ₁ , forced expiratory volume in one second; LCI, lung clearance index.					

The mean FEV₁ increased by 0.52% (77.48 ± 20.56; 95% CI: 66.91–88.05) at week 4 from baseline, which was not statistically significant (p = 0.70). At week 4, 9 patients (53%) showed an improved FEV₁ and *P. aeruginosa* reduced by 30481.3 CFU/mL (26113.0 CFU/mL; 95% CI: (– 32035.02–84261.05) as compared to baseline (56594.3). However, the change in CFU was not statistically significant (p = 0.35). The mean LCI decreased slightly (– 0.479) after 1 week of drug inhalation (p = 0.59). The changes in LCI (p = 0.42), FEV₁ (p = 0.39), and CFU (p = 0.35) from week 4 to week 8 were statistically non-significant (Fig. 1b-d). A statistically significant positive correlation was observed between LCI and CFU at week 1 (r = 0.59, p =

0.0321) and week 4 ($r = 0.79$, $p = 0.0046$) from baseline. A negative correlation ($r = -0.64$) was seen between FEV₁ and CFU at week 4 from baseline, which was statistically significant ($p = 0.0462$).

Overall, 6 adverse events (AEs) occurred in 5/17 patients (29.4%) (3 patients on TIP and 2 patients on TIS), most of which were related to respiratory, thoracic and mediastinal disorders ($n = 3$, 17.6%). Most of these were mild or moderate in severity (Table 3).

Table 3
Adverse event

System organ class	TIS (N = 5) n (%)	TIP (N = 12) n (%)	Overall (N = 17) n (%)
Any MedDRA system organ class	2 (40.0)	3 (25.0)	5 (29.4)
Injury, poisoning and procedural complications	1 (20.0)	0 (0.0)	1 (5.9)
Sunburn	1 (20.0)	0 (0.0)	1 (5.9)
Investigations	1 (8.3)	0 (0.0)	1 (5.9)
Forced expiratory volume decreased	1 (8.3)	0 (0.0)	1 (5.9)
Respiratory, thoracic and mediastinal disorders	2 (16.7)	1 (20.0)	3 (17.6)
Cough	1 (8.3)	0 (0.0)	1 (5.9)
Haemoptysis	0 (0.0)	1 (20.0)	1 (5.9)
Obstructive airways disorder	1 (8.3)	0 (0.0)	1 (5.9)
TIS, Tobramycin inhalation solution; TIP, Tobramycin inhalation powder. Percentages are based on N of each group in safety set. A patient with multiple occurrences of an AE is counted only once in the AE category. A patient with multiple adverse events within a primary system organ class is counted only once in each system organ class total row. MedDRA version 20.0 has been used for coding of adverse events.			

Discussion

It has been shown that lung damage induced by inflammation precedes FEV₁ decline [10]. LCI derived from MBW not only reflects ventilation defects in the respiratory tract, but also helps identify early dysfunction in small airways that are not easily identified with traditional spirometry methods [13]. Therefore, the present study assessed the clinical utility of LCI for assessing the response to inhaled tobramycin antibiotic therapy in patients with CF positive for *P. aeruginosa*. In the present study, three patients had a significantly elevated LCI despite having a normal FEV₁ % at baseline. In addition, the single normalized differences in LCI at week 4 versus baseline for individual patients were higher than the respective normalized FEV₁ differences (Table 2 and Fig. 2), indicating a higher sensitivity of lung function assessment with MBW compared to classical spirometry. Similar findings from previously

published data also showed that LCI provides a more sensitive overall estimate of ventilation inhomogeneity compared to FEV_1 , at least in patients with mild lung disease [16].

There is increasing evidence on the clinical utility of LCI. In addition to LCI being used as a clinical endpoint [5, 15], it has also been used to assess mucociliary clearance in young children [17] treated with CFTR-modulators [15] and to monitor disease progression [18], or both [19]. However, this study with inhaled tobramycin demonstrated that changes in LCI, FEV_1 and CFU at week 1, 4 and 8 were not statistically significant. There was no specific trend observed with respect to correlation between the changes of LCI, FEV_1 and CFU after week 1, 4 and 8 versus baseline. This may be attributed to the heterogeneity in LCI response to antibiotic treatment seen in the individual data for MBW and spirometry shown in Fig. 2. These results are in line with previously published studies [20, 21] and pooled analyses [22]. Despite the use of a more efficient therapy (inhaled formulation) in terms of an increased bioavailability of tobramycin in sputum we observed heterogeneity in the present study which is comparable to the findings seen with intravenous antibiotic treatment in children with CF [20]. In contrast to the outcome from the present study, a short-term study (one month) with 32 CF children on intravenous antibiotic treatment showed a significant improvement in LCI compared with FEV_1 [23]. However, data about LCI as outcome measure for short-term efficacy of antibiotics in CF remains very limited.

The observed heterogeneity in lung function response to therapy can partly be attributed to the non-responders, which could be due to a few patients becoming refractory to inhaled antibiotics [24]. Further, there were single cases of negative, or positive change in CFU in some patients however, such findings are not conclusive, also because not all patients were able to expectorate sputum and thus, CFU data was missing for some patients. In addition, CFU assessment in general is characterized by huge intraindividual variation and therefore, any non-significant findings have to be evaluated with caution. Based on this data, one may speculate that therapy response in these patients with mild to moderate lung disease, chronically treated with inhaled tobramycin was weak and/or heterogeneous. At least 3 patients showed worsening of LCI despite an improvement in FEV_1 , which could be due to increased ventilation inhomogeneity in newly ventilated lung regions following inhaled antibiotic therapy (eg. by reduced air-trapping) [21, 25].

In addition, chest physiotherapy to remove sticky mucus from the airways, prior to lung function testing may also lead to heterogeneity in LCI response. The inherent ventilation inhomogeneity combined with the clearance of mucus plugged airways (after chest physiotherapy) which were previously poorly ventilated (at baseline) leads to an increased LCI [26]. Indeed, a mean reduction of 0.2 in LCI response 30 min after physiotherapy was observed in CF patients with lung disease of varying severity, suggesting unpredictability of short-term physiotherapy on LCI responses [27]. Similar to previously reported studies, the standard physiotherapy performed in the present study is strongly dependent on the therapist's discretion as well as on the daily performance and adherence of the individual CF patient. Although chest physiotherapy is typically performed before inhalation and is done at least 1 h prior to MBW, there is no guidance on the timing for the physiotherapy at each visit. Hence, chest physiotherapy could have

affected the outcome of lung function testing in this study to a certain degree. A detailed documentation of the timing and type of physiotherapy relative to MBW lung function testing in future clinical trials using LCI as a study endpoint is therefore recommended [26].

Based on the results from the present study as well as from available literature, it can be hypothesized that LCI can be an appropriate endpoint for efficacy trials in CF patients if the heterogeneity in lung function is limited by enrolling only drug naïve patients. Furthermore, including younger patients with milder lung disease and specifically defined time points for chest physiotherapy; while excluding false negative changes in lung function outcomes resulting from physiotherapy is recommended.

Overall, treatment with tobramycin showed a favorable safety profile. During the study period six AEs were reported, all of which were mild and moderate in severity, which is in line with previously published phase III data [28, 29].

A major limitation of the present study is the small sample size because of difficulties with patient enrollment and recruitment. The standard of care changed during the setup of the study, i.e., the majority of *P. aeruginosa* positive CF patients were to be treated with continuous inhaled sequential antibiotic combinations [30]. Hence, enrollment of patients on monotherapy was a challenge and thus, the study could include only 17 patients versus 35 patients that were planned to be enrolled.

Conclusions

In summary, the changes in LCI, FEV₁ and CFU were statistically non-significant at week 1, 4 and 8 when compared with baseline which may be due to the heterogeneity in LCI response to antibiotic treatment and the low evaluable sample size.

Even if LCI is not identified as the ideal clinical efficacy endpoint for studies with antibiotic treatment (either intravenous or inhaled), it does not jeopardize the overall value of LCI as a more sensitive lung function parameter for CF patients with mild to moderate lung disease. Considering previously published data, LCI seems to be a suitable endpoint for drugs affecting the mucociliary clearance and to assess disease progression in cystic fibrosis. However, LCI alone does not seem to be the ideal clinical endpoint for efficacy studies with antibiotic treatment (either intravenous or inhaled) in small groups of CF patients.

Abbreviations

AE	Adverse events
ANOVA	Analysis of variance
BID	Twice daily
BMI	Body mass index
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CFU	Colony forming units
CI	Confidence intervals
d	Difference
FEV1	Forced expiratory volume in one second
IVA	Ivacaftor
LCI	Lung clearance index
LS	Least squares
LUM	Lumacaftor
MBW	Multiple breath washout
P. aeruginosa	Pseudomonas aeruginosa
ppFEV1	Percent predicted FEV ₁
SD	Standard deviation
TIP	Tobramycin inhalation powder
TIS	Tobramycin inhalation solution

Declarations

Ethics approval and consent to participate: The study design was approved by the independent ethics committee and institutional review boards (Supplementary material); and was in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient (or from parents for children <16 years of age) in writing before randomization.

Consent for publication: Not applicable.

Competing interests: SS has served as an investigator in clinical trials for Galapagos, Proteostasis, Celtaxsys, Flatley, Novartis Pharma GmbH and Vertex Pharmaceuticals Incorporated and has consulted

for Teva GmbH, Novartis Pharma GmbH, Chiesi GmbH and Vertex Pharmaceuticals Incorporated. SN and UM have nothing to disclose. CS and JZ are employees of Novartis Pharma GmbH.

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Author contributions: All authors assume responsibility for the accuracy of the data interpretation and approved the manuscript for publication. UM, CS, and JZ contributed to study conception, protocol development, data analysis and interpretation of data. SN and UM contributed on the interpretation of data and critical review of the study, SS and JZ drafted the first version of the manuscript. All authors helped with the review and finalization of the manuscript.

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Availability of data and materials: The data generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Figures

Figure 1: Lung function parameters (LCI and FEV₁) and CFU at baseline and over time

Figure 1

Lung function parameters (LCI and FEV₁) and CFU at baseline and over time. CFU, colony forming units; FEV₁, forced expiratory volume in one second; LCI, lung clearance index; SD, standard deviation

Figure 2: Matched pairs of relative changes in LCI and FEV₁ at week 4 from baseline

Figure 2

Matched pairs of relative changes in LCI and FEV1 at week 4 from baseline. d, difference; FEV1, forced expiratory volume in one second; LCI, lung clearance index

Supplementary Files

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