

## Lung clearance index response in patients with CF with class III CFTR mutations

### BACKGROUND

Ivacaftor (KALYDECO) is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator that increases transmembrane chloride flux in vitro and leads to significant benefits in patients with cystic fibrosis (CF) with class III gating mutations.<sup>1–5</sup> Ivacaftor is associated with sustained improvement in FEV<sub>1</sub> and weight as well as reduced time to next pulmonary exacerbation.<sup>5–7</sup> It has also been shown that 4 weeks of ivacaftor improves the lung clearance index (LCI) in patients with CF with preserved lung function.<sup>8</sup>

It is presently unclear whether LCI, a measure of ventilation inhomogeneity, provides additional information among patients with more impaired lung function as well as whether the sustained effectiveness of ivacaftor as demonstrated by improvements in the previously mentioned outcomes is also evident in the LCI response. The aim of this observational study was to assess the LCI before and after initiation of ivacaftor treatment over 6 months in patients with CF with a wider range of lung disease severity using a nitrogen tracer gas multiple breath washout (MBW) system (MBW<sub>N2</sub>).

### METHODS

Ten patients with CF and a class III CFTR gating mutation (p.G551D, p.G178R) on at least one allele were included in this study. MBW<sub>N2</sub> (Exhalyzer D, EcoMedics, Switzerland) and spirometry were performed at baseline and 1 month, 3 months and 6 months after the start of treatment with 150 mg ivacaftor tablets twice daily. The primary outcome measure for this intention-to-treat analysis was the change in LCI at 2.5% of the starting concentration from baseline. Secondary outcome measures included FEV<sub>1</sub> and other MBW parameters. The rate of change of LCI was estimated using a linear regression generalised estimating equation model with a first-order autoregressive correlation structure to account for repeated measures within each subject. Inclusion and exclusion criteria, MBW<sub>N2</sub> and spirometry details and additional methodological details can be found in the online supplementary material.

### RESULTS

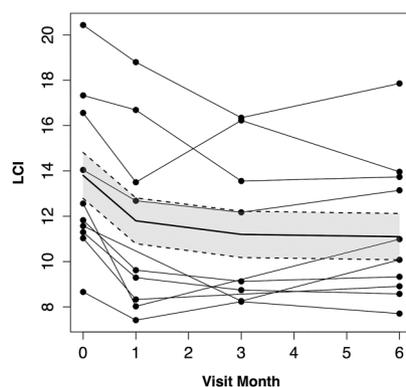
At baseline, patients were on average 28.3 years old (SD 13.7) and had an

average per cent-predicted FEV<sub>1</sub> of 70% (range 38% to 122%). LCI was abnormal in all 10 participants at baseline (average 13.5, range 8.7–20.4), where the upper limit of normal was derived from a healthy population measured at the same centre using the same equipment and protocol.<sup>9</sup> There was a significant improvement in LCI from baseline to 1 month (mean change  $-2.2$  (95% CI  $-3.0$  to  $-1.3$ ,  $p < 0.001$ )), and this effect was sustained at 6 months (mean change from baseline  $-2.1$  (95% CI  $-2.7$  to  $-1.5$ ,  $p < 0.001$ )). The mean absolute improvement in per cent-predicted FEV<sub>1</sub> from baseline to 1 month was 11% (95% CI 2% to 20%,  $p = 0.02$ ). LCI improved from baseline in all patients at 1 month, whereas two patients experienced negative changes in FEV<sub>1</sub> at the 1-month time point. There was no correlation between the change in LCI and the change in FEV<sub>1</sub> ( $r = -0.37$ ,  $p = 0.32$ ). LCI at a 5% cut-off of the washout (LCI<sub>5</sub>) also improved at 1 month (mean change  $-0.9$  (95% CI  $-1.5$  to  $-0.3$ ,  $p = 0.008$ )).

The rate of improvement in LCI (figure 1) and FEV<sub>1</sub> was not linear; the greatest improvements were observed at 1 month and were sustained thereafter. In addition, the rate of improvement in LCI was attenuated by baseline LCI and age (see online supplementary table S1). A similar response was observed for all secondary outcomes, and the complete analysis is described in online supplementary table S1.

### CONCLUSIONS

The short-term effectiveness of ivacaftor as measured by LCI in patients with CF with a wide range of disease severity was



**Figure 1** Changes in the lung clearance index (LCI) over the 6-month study period associated with ivacaftor treatment. Closed circles connected by lines represent each patient; the average response and 95% CIs from the unadjusted generalised estimating equation model are shown by the solid line and grey area, respectively.

similar to that previously observed in patients with mild lung disease. While the overall response was similar for FEV<sub>1</sub> and LCI, the response for LCI was consistent for all patients. Although the minimal clinically important difference (MCID) for LCI has yet to be defined and the generalisability of these findings are limited due to small sample size in this single centre observational study, our findings suggest that the LCI is more sensitive compared with FEV<sub>1</sub> for detecting treatment response, which may be particularly relevant in patients in which lung function abnormalities are influenced by changes in peripheral airways.

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