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.[1–5] Ivacaftor is associated with sustained improvement in FEV_1 and weight as well as reduced time to next pulmonary exacerbation.[5–7] It has also been shown that 4 weeks of ivacaftor improves the lung clearance index (LCI) in patients with CF with preserved lung function.[8]

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_{N2}).

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_{N2} (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_1 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_{N2} 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_1 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.[9] 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_1 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_1 at the 1-month time point. There was no correlation between the change in LCI and the change in FEV_1 (r=−0.37, p=0.32). LCI at a 5% cut-off of the washout (LCI_5) 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_1 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 similar to that previously observed in patients with mild lung disease. While the overall response was similar for FEV_1 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_1 for detecting treatment response, which may be particularly relevant in patients in which lung function abnormalities are influenced by changes in peripheral airways.

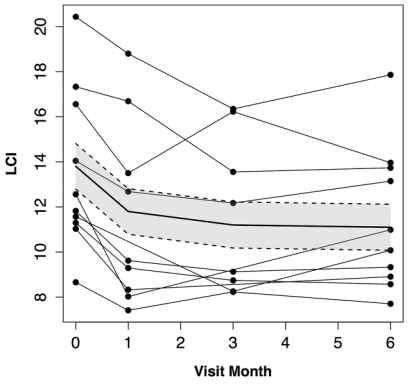

Figure 1 Changes in the lung clearance index (LCI) over the 6-month study period associated with ivacaftor treatment. Closed circles connected by lines represent each patient; the average response and 95% CIs from the unadjusted generalised estimating equation model are shown by the solid line and grey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

Mica Kane,[1,2] Tanja Gonska,[2,3,4] Renee Jensen,[1,2] Julie Avolio,[1,2,3] Michelle Klingel,[1,2] Sanja Stanojevic,[1,2,5] Felix Ratjen[1,2,4]

[1]Division of Respiratory Medicine, Department of Pediatrics, Toronto, Ontario, Canada
[2]Physiology & Experimental Medicine, The Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada
[3]Division of Gastroenterology and Nutrition, Department of Pediatrics, Toronto, Ontario, Canada
[4]Department of Pediatrics, University of Toronto, Ontario, Canada
[5]Institute of Health Policy, Management and Evaluation, University of Toronto, Ontario, Canada

Correspondence to Professor Felix Ratjen, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8; Felix.ratjen@sickkids.ca

Funding This study was funded in part by Vertex Pharmaceuticals Incorporated.

Disclaimer The funder had no role in the collection and interpretation of the data, nor the writing of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Hospital for Sick Children.

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2015-207894).

CrossMark

To cite Kane M, Gonska T, Jensen R, *et al*. *Thorax* 2016;**71**:476–477.

Published Online First 4 March 2016

Thorax 2016;**71**:476–477.
doi:10.1136/thoraxjnl-2015-207894

REFERENCES

1 Van Goor F, Hadida S, Grootenhuis PDJ, *et al*. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. *Proc Natl Acad Sci USA* 2009;106:18825–30.

2 Accurso FJ, Rowe SM, Clancy JP, *et al*. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N Engl J Med* 2010;363:1991–2003.
3 Ramsey BW, Davies J, McElvaney NG, *et al*. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011;365:1663–72.
4 Barry PJ, Plant BJ, Nair A, *et al*. Effects of Ivacaftor in cystic fibrosis patients carrying the G551D mutation with severe lung disease. *Chest* 2014;146:152–8.
5 Davies JC, Wainwright CE, Canny GJ, *et al*. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *Am J Respir Crit Care Med* 2013;187:1219–25.
6 McKone EF, Borowitz D, Drevinek P, *et al*. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study (PERSIST). *Lancet Respir Med* 2014;2:902–10.
7 Quittner A, Suthoff E, Rendas-Baum R, *et al*. Effect of ivacaftor treatment in patients with cystic fibrosis and the G551D-CFTR mutation: patient-reported outcomes in the STRIVE randomized, controlled trial. *Health Qual Life Outcomes* 2015;13:1–9.
8 Davies J, Sheridan H, Bell N, *et al*. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial. *Lancet Respir Med* 2013;1:630–8.
9 Jensen R, Stanojevic S, Gibney K, *et al*. Multiple breath nitrogen washout: a feasible alternative to mass spectrometry. *PLoS ONE* 2013;8;e56868.