Chronic cough in cystic fibrosis: the effect of modulator therapy on objective 24-h cough monitoring

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To the Editor:

Cystic fibrosis (CF) is an autosomal recessive condition, deletion of phenylalanine at position 508 (F508del) being the most frequent mutation in CF patients. Kaftrio, also called Trikafta in the USA, (Vertex Pharmaceuticals Inc., Germany) is a licensed modulator therapy for CF patients with at least one F508del mutation [1]. Several clinical trials have demonstrated its efficacy [2]. However, the primary outcome measured in these studies was the change in per cent predicted of forced expiratory volume in 1 s (FEV_1), which was in the order of 10%, and thus may have a relatively low sensitivity in predicting efficacy, particularly in more severely affected patients [3].

Cough counting can indicate exacerbations of pulmonary disease [4]. Indeed, it has been long observed that chronic cough is an almost universal phenomenon in adult CF patients [5] and has even been claimed to feasibly replace FEV_1 as an outcome in clinical trials of CF [3]. More convenient subjective scoring is not as reliable in rating coughs when compared with objective cough monitoring [4, 6]. Given this limitation, we used our established cough counting methodology to assess the effect of Kaftrio initiation on cough in CF. We also examined the pattern of cough in CF and its relationships between other outcome measures and patient characteristics.

16 adult CF patients attending the Hull adult CF unit were sequentially studied between July and October 2020. CF diagnosis was based on the standard criteria of clinical presentation, sweat tests or cystic fibrosis transmembrane conductance regulator gene analysis [7, 8]. Current smokers or ex-smokers within 2 years, pregnancy or lactation, and those with known contraindication to Kaftrio were excluded. Those colonised with potentially transmissible agents were also excluded.

Before initiation of Kaftrio therapy, assessments were made including patients' demographic characteristics, cough frequency, health-related quality of life (HRQoL) and pulmonary function testing.

A 24-h ambulatory cough monitor, which has been validated for its reliability in recording coughs, was used for evaluating of cough frequency [9]. 24-h cough counts were subdivided into daytime (defined as 05:00 to 23:00) and night-time epochs (23:00 to 05:00 the next morning), before treatment and ~1 month after treatment. Sound recordings were obtained by using Philips DVT4000 Voice Tracer Digital Recorder (Royal Dutch Philips Electronics Ltd) and a lapel microphone (AT898cW, Audio-Technica Corp.) positioned 30 cm from the mouth, at a sampling frequency of 16 kHz and with an encoding bit rate of 64 kbps. Recordings were analysed on an automated cough analysis system, the Leicester Cough Algorithm software (a kind gift from S Birring, King's College, London, UK) and used to quantify cough.

Cough associated symptoms were scored using the Hull Airway Reflux Questionnaire (HARQ) [10]. Disease-specific HRQoL was measured by an electronic version of the revised Cystic Fibrosis Questionnaire (CFQ-R) [11].

The patients received routine follow-up after a 1-month treatment period and assessments were repeated.

Shareable abstract (@ERSpublications)
This is a prospective observation of the effect of Kaftrio initiation in CF. An early and dramatic improvement in the objective measure of 24-h cough monitoring was observed, providing noninvasive, objective evidence of efficacy and compliance in CF. https://bit.ly/3LpnABB

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The National Health Service Health Research Authority decision tool indicated that this study was not defined as research. Informed consent was obtained from all subjects.

Patients were prescribed oral Kaftrio at the dose of two tablets (each containing ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg) taken in the morning and ivacaftor 150 mg to be taken in the evening.

The primary outcome measure was the objective change in 24-h cough (95% CI). The secondary outcome measures included changes in daytime and night-time cough, pulmonary function testing, and the HARQ and CFQ-R scores.

Normally distributed data are expressed as mean±SD while skewed distributed data are expressed as median with 25–75% interquartile range (IQR). The cough numbers were log-transformed and expressed as geometric mean (95% CI). The comparisons between pre- and post-treatment were made by paired t-test and Wilcoxon signed rank test, where applicable. Pearson and Spearman tests were used for determining the correlation of objective cough improvement with other parameters, where applicable. Software (SPSS 21.0, Chicago, IL, USA) was applied for statistical calculation. A p-value <0.05 was considered statistically significant.

16 CF patients (10 male) with chronic cough were eligible and completed the assessment. Mean age was 31.1±8.5 years. Kaftrio was well tolerated by all patients.

The 24-h cough decreased markedly after treatment from 227 (147–444) to 29 (21–49) (p<0.001) (figure 1a). A single patient with a low baseline cough had a slight increase in cough number.

The temporal distribution of coughing before treatment is illustrated in figure 1b. Both daytime and night-time cough showed similar reductions after treatment (figure 1c and d). Both daytime and night-time cough fell: day-time cough from 188 (122–369) to 27 (20–45) (p<0.001) and night-time cough from 20 (1–74) to 0 (0–2) (p=0.003).

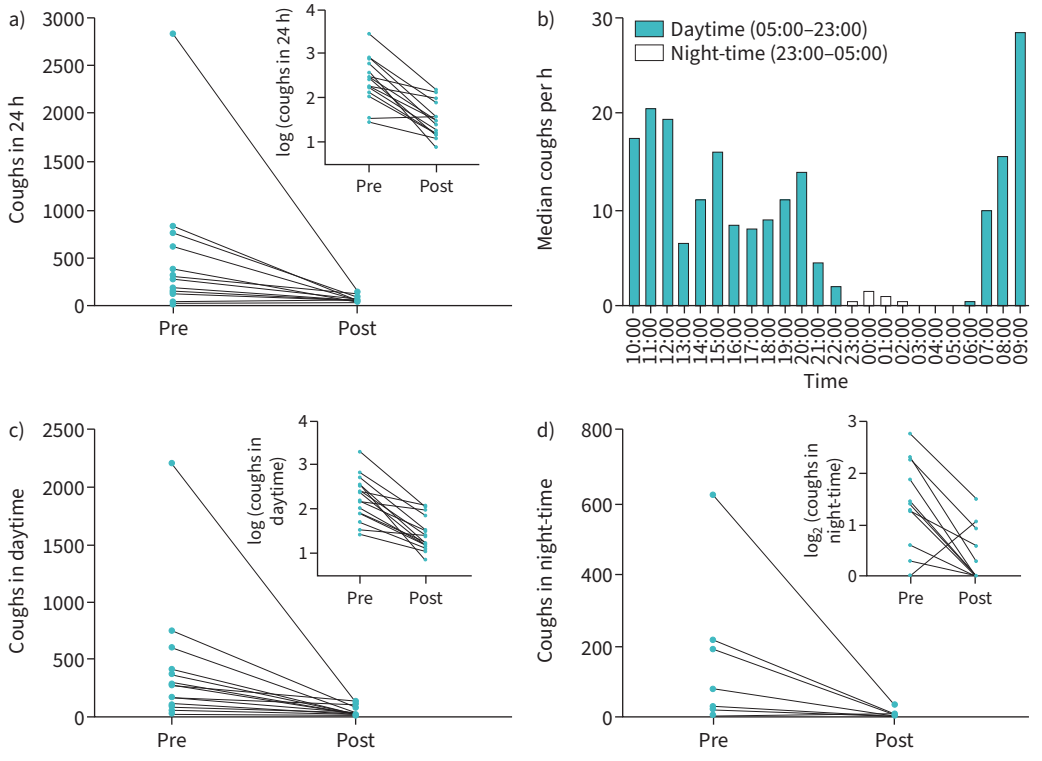

FIGURE 1 Objective cough counts (n=16). a) 24-h cough counts before (pre) and after (post) treatment (insert shows log-transformed data). b) The temporal distribution of coughing before treatment. c) Daytime cough counts before and after treatment. d) Night-time cough counts before and after treatment (to allow log-transformation, 0 coughs was treated as 1 cough).

FEV_1 improved by 9.6%, from 72.04±24.33% to 78.93±21.65% of predicted (p=0.008) and similarly, maximal midexpiratory flow from 43.11±24.60% to 50.50±30.07% (p=0.032).

In those completing patients report outcomes, HARQ scores (n=7) improved after treatment, from 22.43 ±18.54 to 10.14±13.35 (p=0.001). Total CFQ-R scores (n=8) improved significantly from 768.20±126.04 to 944.04±133.01 (p=0.005). In the physical, body, weight and respiratory domains, scores increased from 57.29±20.13, 76.39±17.25, 58.33±38.83 and 52.78±20.14 to 83.33±11.78 (p=0.011), 87.50±16.20 (p=0.007), 100.0±0.0 (p=0.019) and 86.11±13.93 (p=0.005), respectively.

Patients of a younger age tended to show a greater improvement in cough (r= −0.578, p=0.019). There was no correlation between cough reduction and improvement of pulmonary function, or any other assessments. 14 patients were found to have had a significant weight increase (66.34±17.54 to 70.96±17.96 kg, p=0.001).

The introduction of modulators has revolutionised the treatment of CF, effectively curing the pathophysiological defect in ion transport. This has resulted in improvement in a range of clinical parameters; however, this is the first report of objective improvements in cough seen with Kaftrio initiation. Patients reduced their cough to a 10th of baseline levels. No other measure has shown such a dramatic change, suggesting potential as a simple, non-invasive metric of efficacy. This was observed after a single month of treatment.

Excessive gastro-oesophageal reflux is very frequent in CF patients, which may lead to recurrent aspiration and irritation of the airway sensory nerves (cough hypersensitivity) [12]. The profound effects of Kaftrio on the gastrointestinal tract are supported by the weight gain seen in our and other studies [13]. We speculated that the striking and early fall in cough frequency is explicable by improved gastrointestinal function leading to decrease in airway reflux and a consequent reduction of cough. Similar improvements in subjective cough and airway reflux have been observed by others [14]. The major limitations of this report are its small sample size and recruitment from a single centre uniquely experienced in cough counting methodology. A placebo effect cannot be excluded but the magnitude of improvement exceeds that observed in all previous cough counting studies. Whether these observations translate into a reduction in hypersensitivity of the cough reflex is currently unknown.

As yet, cough counting using current technology is impractical outside centres experienced in the technique, but future wearable devices may allow monitoring of exacerbation and compliance [15].

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