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Early View

Research letter

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

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Introduction

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 US) 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 percent predicted of forced expiratory volume in one second (ppFEV1), which was in the order of 10% and thus may have a relatively low sensitivity in predicting efficacy, particularly in more severe 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 FEV1 as an outcome in clinical trials of CF[3]. More convenient subjective scorings are 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.

Methods

16 adult CF patients attending the Hull adult CF unit were sequentially studied between July 2020 and October 2020. CF diagnosis was based on the standard criteria of clinical presentations, sweat tests, or CFTR 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 colonized 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, and pulmonary function testing.

A 24-hour ambulatory cough monitor, which has been validated for its reliability in recording coughs, was used for evaluating of cough frequency[9]. 24-hour cough counts were subdivided into day-time (defined as 5 a.m. to 11 p.m.) and night-time epochs

(11 p.m. to 5 a.m. the next morning), before treatment and approximately 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 16kHz and with an encoding bit rate of 64kbps. Recordings were analyzed on an automated cough analysis system, the Leicester Cough Algorithm software (a kind gift from Prof. S Birring) and used to quantify cough.

Cough associated symptoms were scored by the Hull Airway Reflux Questionnaire (HARQ)[10]. The disease specific health-related quality of life (HRQoL) was measured by an electronic version of the Cystic Fibrosis Questionnaire-Revised (CFQ-R)[11].

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

The NHS 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® (Vertex Pharmaceuticals Inc, Germany) at the dose of two tablets (each containing ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg) taken in the morning, and Ivacaftor 150mg to be taken in the evening.

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

Normally distributed data were expressed as mean ± standard deviations (SD) while skewed distributed data were expressed as median with 25%-75% interquartile range (IQR). The cough numbers were log-transformed and expressed as geometric mean with 95% confidence interval (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.

Results

Sixteen 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-hour cough decreased markedly after treatment from 227 (147 to 444) to 29 (21 to 49), $p < 0.001$ (Figure 1a). A single patient with a low baseline cough had a slight increased cough number.

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

ppFEV1 improved by 9.6%, from 72.04 ± 24.33 to 78.93 ± 21.65 ($p = 0.008$), and similarly maximal mid-expiratory flow (MMEF) 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 kg ± 17.54 kg to 70.96 kg ± 17.96 kg, p = 0.001).

Discussion

The introduction modulators have revolutionized 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 tenth 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 gastroesophageal reflux (GOR) 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 is 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 consequence 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. 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 centers experienced in the technique, but future wearable devices may allow monitoring of exacerbation and compliance[15].

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Figure Legend

Figure 1. Objective cough counts (n = 16). (a) 24-hour cough counts before and after treatment (insert is log-transformed data). (b) The temporal distribution of coughing before treatment. (c) Day-time cough counts before and after treatment. (d) Night-time cough counts before and after treatment (to allow log-transformation, zero cough was treated as 1).