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Original Article

Recovery of lung function following a pulmonary exacerbation in patients with cystic fibrosis and the *G551D-CFTR* mutation treated with ivacaftor☆

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Abstract

Background: Pulmonary exacerbations (PEx) are associated with acute loss of lung function that is often not recovered after treatment. We investigated lung function recovery following PEx for ivacaftor- and placebo-treated subjects.
Methods: Short- and long-term pulmonary function recovery data after PEx were summarized from a placebo-controlled trial in 161 cystic fibrosis patients ≥ 12 years old with the *G551D-CFTR* mutation (NCT00909532). Short-term recovery was measured 2 to 8 weeks after treatment, and long-term recovery was determined at the end-of-study, both compared with baseline measured just prior to the PEx.
Results: Fewer patients receiving ivacaftor experienced a PEx than patients receiving placebo (33.7% vs. 56.4%; $P = 0.004$) and had a lower adjusted incidence rate of PEx (0.589 vs. 1.382; $P < 0.001$). The proportion of PEx followed by full short-term recovery of percent predicted forced expiratory volume in 1 s was similar (ivacaftor vs. placebo, 57.1% vs. 53.7), as was the proportion of patients having long-term recovery (46.4% vs. 47.7%).
Conclusions: Ivacaftor treatment reduces the frequency of PEx but does not improve on the rate of complete lung function recovery after PEx when compared with placebo.

Keywords: Cystic fibrosis; Pulmonary exacerbations; Ivacaftor; Cystic fibrosis transmembrane conductance regulator; Pulmonary function

1. Introduction

Pulmonary exacerbations (PEx) in patients with cystic fibrosis (CF) are associated with a more rapid decline in lung function [1], poorer quality of life [2], increased healthcare costs [3], and early mortality [4,5]. Although no standardized definition exists [6,7], in general a PEx is considered to have

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occurred when a patient presents with increased signs and symptoms of respiratory tract illness, and the clinician decides to begin (or make changes to existing) antibiotic treatment. Avoiding PEx is a key therapeutic goal. When a PEx does occur, loss of lung function frequently occurs [8], and one goal of treatment is to recover this lost function. However, even following treatment and clinical improvement, recovery of lung function is often incomplete [8–13] and accounts for half of the long-term lung function decline in patients with CF [8].

Several factors may contribute to this unrecovered loss of lung function. Although the underlying factors associated with PEx are not always clear, some causes may be more harmful and difficult to treat than others. For example, patients with *Pseudomonas aeruginosa* infection have greater airway inflammation than patients with other bacterial infections and, theoretically, will experience greater airway damage over time [14]. A second factor contributing to PEx-related loss of lung function may be the treatment, either because it is insufficient or delayed; hence, prevention of PEx becomes a key aspect of chronic management. Although antibiotics are almost universally prescribed for PEx, there are no standard approaches for the choice and duration of antibiotic therapy [13,15]. Finally, host factors, including severity of lung disease, nutritional status, comorbidities, and the use of chronic therapies, may contribute to the impact of PEx. Baseline lung function and the extent of lung function loss associated with PEx may influence the choice of treatment and independently impact the likelihood of recovery [13,16].

Ivacaftor is a CF transmembrane conductance regulator (CFTR) protein potentiator approved for the treatment of patients with CF who have at least one gating mutation (e.g., *G551D-CFTR*). Ivacaftor targets the underlying disease mechanism in CF, potentiating the function of the CFTR protein to increase chloride ion secretion in bronchial (and other) epithelial cells, and thereby reducing excess fluid absorption and increasing ciliary beating [17]. In clinical experience, patients receiving ivacaftor have demonstrated improved lung function, improved mucociliary clearance, and lower sputum culture positivity for *P. aeruginosa* [18]. It is plausible that the improvement in mucociliary clearance observed in patients following ivacaftor treatment may enhance the clearance of infective bacteria and inflammatory material following a PEx event, and in so doing also allow for improvement in recovery of lung function after such an event. A placebo-controlled clinical study of ivacaftor in patients with CF ≥ 12 years old (STRIVE) [19] was of sufficient duration to assess the impact of PEx on lung function. We designed this post hoc analysis to assess lung function recovery following a PEx for ivacaftor- and placebo-treated patients.

2. Methods

Data from patients enrolled in the STRIVE clinical study were used in this analysis (NCT00909532). Methods and results for this study were previously reported [19]. STRIVE included 161 patients with CF who had at least one *G551D-CFTR* gene mutation and were ≥ 12 years old, with a baseline percent predicted forced expiratory volume in 1 s ($ppFEV_1$) of 40 to 90. Patients could not have been treated for PEx in the 4 weeks prior to enrollment. This study lasted 48 weeks, and patients were examined and underwent pulmonary function testing at baseline and at study weeks 2, 8, 16, 24, 32, 40, and 48. Thus, values closest to the PEx were used for analysis. Local ethics committees approved the original protocols, and all patients provided written informed consent or assent, as appropriate.

A PEx was defined a priori as any clinician-determined new or changed antibiotic therapy (intravenous [IV], inhaled, or oral) for four or more protocol-defined signs or symptoms as used by Fuchs et al. [20]. Antibiotic start and stop dates were recorded and were at the clinician's discretion. For analyses of event rates, *P* values were derived from negative binomial regressions that included number of events as the dependent variable, treatment as a fixed effect, adjustments for baseline $ppFEV_1$ severity (< 70 vs. ≥ 70), and age group (< 18 years vs. ≥ 18 years), with log (time on study) as an offset. Regressions were only conducted when the number of patients with events in each treatment group was five or more and when the model converged; otherwise, *P* values were derived from Fisher's exact test on the number of patients with events. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Lung function recovery following PEx was defined as a return to at least 100% of the pre-exacerbation $ppFEV_1$ measurement. Important for this analysis was the lack of pulmonary function testing immediately prior to or at the end of a PEx. In order to be included in the lung function analysis, patients had to have spirometry results obtained during study visits both before and after a PEx; multiple PEx occurring between spirometry measurements were treated as one event for the purposes of lung function recovery analyses. Short-term recovery was calculated for each PEx by comparing the most recent pre-exacerbation $ppFEV_1$ with that measured 2 to 8 weeks after stopping the new or changed antibiotic. Long-term recovery was determined by the change in $ppFEV_1$ from the pre-exacerbation value to the end-of-study value (duration varied depending on when during the study the PEx occurred). Long-term recovery was calculated only once (using the first PEx) for patients with more than one PEx. Lung function recovery data were also summarized according to the number of observed PEx events and from patients treated with IV antibiotics, whether or not they met the a priori criteria for a PEx.

3. Results

Baseline demographics demonstrated that the 83 ivacaftor- and 78 placebo-treated patients were well matched for age, sex, nutritional status, $ppFEV_1$ (mean ± SD, 63.5 ± 16.1 vs. 63.7 ± 16.8), and sweat chloride [19].

Overall, fewer patients in the ivacaftor group had PEx events reported during the study period (n = 28 [33.7%]) than in the placebo group (n = 44 [56.4%]; $P = 0.004$), and more patients in the placebo group experienced three or more PEx (n = 14 [17.9%]) than the ivacaftor group (n = 4 [4.8%]; $P = 0.01$;

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