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Original Article

Inhaled alpha$_1$-proteinase inhibitor therapy in patients with cystic fibrosis

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Abstract

Background: Inhaled alpha$_1$-proteinase inhibitor (PI) is known to reduce neutrophil elastase burden in some patients with CF. This phase 2a study was designed to test inhaled Alpha-1 HC, a new aerosolized alpha$_1$-PI formulation, in CF patients.
Methods: We performed a randomized, double-blind, placebo-controlled study and evaluated the safety of 100 or 200 mg of inhaled Alpha-1 HC once daily for 3 weeks in subjects with CF. Thirty adult subjects were randomized in a 2:1 ratio to receive Alpha-1 HC or placebo.
Results: Drug delivery was confirmed by a dose-dependent increase in the sputum alpha$_1$-PI. Seven (20.0%) of the 35 adverse events in the 100-mg dose group, 3 (13.0%) of 23 in the 200-mg dose group, and 4 (14.3%) of 28 in the placebo group were drug-related in these subjects. One serious adverse event occurred in 1 subject within each group.
Conclusions: Alpha-1 HC inhalation was safe and well tolerated.

Keywords: Cystic fibrosis; Alpha-1 HC; Alpha-1 antitrypsin; Prolastin

1. Introduction

Cystic fibrosis (CF) lung disease is characterized by viscous mucus, chronic respiratory infections, and a sustained exaggerated inflammatory response [1]. Airway recruitment of neutrophils causes airway tissue destruction and remodeling through excess release of neutrophil elastase (NE) [2–4]. Endogenous alpha$_1$-proteinase inhibitor (alpha$_1$-PI), which inhibits NE activity, is overwhelmed by excess release of NE in patients with CF [2–5]. This protease/antiprotease imbalance results in a progressive decline in lung function, in part through airway remodeling [2,3,6]. There is no specific antiprotease treatment available for patients with CF [2,7]. The potential protective function of alpha$_1$-PI provides a strong rationale to develop chronic antiprotease therapies to control airway inflammation and tissue damage.

Human plasma-derived alpha$_1$-PI has a well-established safety profile when administered intravenously in patients with alpha$_1$-antitrypsin deficiency, a condition characterized by increased serine protease activation leading to early-stage emphysema [8–11]. Aerosolized delivery of alpha$_1$-PI by inhalation permits

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delivery of drug to the site of active airway disease while limiting systemic exposure [12] and has been shown to reduce NE burden and inflammation in respiratory secretions of alpha$_1$-antitrypsin-deficient patients [13–15]. In previous studies, aerosolized alpha$_1$-PI has been found to be both safe and well tolerated in patients with CF [3,6,16–18]. However, an effective combination of delivery system and drug is required to efficiently deposit aerosolized alpha$_1$-PI in a sufficient dose at the site of CF lung disease. The AKITA^{2}® APIXNEB™ (Vectura Group plc, Chippenham, United Kingdom) electronically regulated nebulizer system increases drug deposition compared with older nebulizer systems and allows for accurate dosing that is independent of lung function impairment. This is achieved by customizing and controlling the patient's breathing pattern [16]. Therefore, it is hypothesized that the combination of a well-tolerated alpha$_1$-PI preparation and an electronically regulated nebulizer system may provide improved deposition of a biologically relevant antiprotease. Here, we report results of a 3-week phase 2a study conducted to evaluate the safety and tolerability of inhaled Alpha-1 Hydrophobic Chromatography Process (HC) in patients with CF.

2. Subjects and methods

2.1. Subjects

This study enrolled men and women aged ≥ 18 years with CF, as evidenced by 1 or more clinical features consistent with the CF phenotype and 1 or both of the following: (1) sweat chloride level ≥ 60 mEq/L by quantitative pilocarpine iontophoresis test and (2) 2 well-characterized mutations in the CF transmembrane conductance regulator (CFTR) gene. Subjects were required to have a prebronchodilator forced expiratory volume in 1 s (FEV_1) ≥ 40% of predicted at screening and have an FEV_1 that was ≥ 40% of predicted and within ± 15% of the screening FEV_1 value prior to study drug administration on day 1 of the study.

Key exclusion criteria included an investigator-defined pulmonary exacerbation either 4 weeks before screening or between screening and randomization that required antibiotic treatment, respiratory insufficiency, significantly elevated liver enzymes, history of smoking, any lung surgery, positive culture for *Burkholderia cepacia* or lower *mycobacterium*, or active allergic bronchopulmonary aspergillosis. Other major exclusions used in this study are provided in the supplementary material.

2.2. Study design and procedure

This was a multicenter, sequential dose escalation, randomized, double-blind, placebo-controlled phase 2a study (ClinicalTrials.gov: NCT01684410). Alpha-1 HC (100 mg and 200 mg) was administered once daily and compared with placebo over a 21-day treatment period. All subjects provided written informed consent. The study was approved by the institutional review board and conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the Declaration of Helsinki [19,20].

Two sequential dosing cohorts (100 mg and 200 mg) were enrolled (Fig. S1). In each cohort, subjects were randomized in a 2:1 ratio utilizing a block size of 3 to receive Alpha-1 HC (50 mg/ml) or a volume-matched placebo delivered once daily via the AKITA^{2} nebulizer system. Inhalation data (e.g., start of inhalation, duration of treatment, daily dose compliance) was recorded by the AKITA^{2} device. Subjects were considered adherent to study medication if they had taken at least 80% of the prescribed dose over the total duration of study drug dosing. A review of unblinded safety results from the Alpha-1 HC 100 mg treatment cohort was conducted by the Cystic Fibrosis Foundation Therapeutics Data Monitoring Committee prior to proceeding to the next cohort. Screening occurred 14 ± 7 days prior to study treatment initiation. A follow-up visit occurred approximately 28 days following the treatment period in each cohort.

2.3. Safety assessments

Data were collected for evaluation of safety from the time of consent until the final study visit. A detailed description of treatment-emergent adverse event (TEAE) and serious adverse event (SAE) data collection are provided in the supplementary material.

Subjects were monitored via weekly telephone calls. Pulmonary exacerbations were graded as mild (increase in 1 or more symptoms [dyspnea, cough, and/or sputum] that was controlled by increasing usual medication), moderate (required outpatient antibiotic treatment), and severe (resulted in hospitalization). Subjects treated with Alpha-1 HC were tested for immunogenicity with an antibody screening enzyme-linked immunosorbent assay to alpha$_1$-PI at screening, study day 22, and at follow-up. Abnormal test values that were judged relevant by the investigator were considered adverse events (AEs). Adverse events, which were related to the AKITA^{2} nebulizer system, were reported based on the investigator's judgment (see supplementary material).

2.4. Exploratory efficacy variables

The exploratory objectives included possible signals of treatment efficacy, subject satisfaction with aerosol treatment, and health-related quality of life (HRQOL). The exploratory variables included assessment of changes from baseline following treatment for pulmonary function tests (PFTs; FEV_1, FEV_1% predicted, and forced vital capacity [FVC]), and sputum analyses of alpha$_1$-PI levels, NE activity, bacterial culture, leukotriene B4 (LTB4) concentration, inflammatory cell counts (absolute and differential counts), pro-inflammatory cytokines (interleukin [IL]-6, -8, and -17; IL-1 beta, and tumor necrosis factor-alpha [TNF-α]), and urine markers of lung injury (desmosine and isodesmosine).

Sputum for alpha$_1$-PI level, sputum biomarkers of inflammation, and blood biomarkers of inflammation were collected at screening, randomization (day 1), day 10, at the end of treatment (day 22), and at the end of the 4-week follow-up phase. Urine samples were collected at screening, day 10, at the end of treatment, and at follow-up. Forced expiratory volume in