Use of hyperpolarized helium-3 MRI to assess response to ivacaftor treatment in patients with cystic fibrosis

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Abstract

Background: This pilot study evaluated the effect of short- and long-term ivacaftor treatment on hyperpolarized 3He-magnetic resonance imaging (MRI)–defined ventilation defects in patients with cystic fibrosis aged ≥12 years with a G551D-CFTR mutation.

Methods: Part A (single-blind) comprised 4 weeks of ivacaftor treatment; Part B (open-label) comprised 48 weeks of treatment. The primary outcome was change from baseline in total ventilation defect (TVD; total defect volume:total lung volume ratio).

Results: Mean change in TVD ranged from −8.2% (p = 0.0547) to −12.8% (p = 0.0078) in Part A (n = 8) and −6.3% (p = 0.1953) to −9.0% (p = 0.0547) in Part B (n = 8) as assessed by human reader and computer algorithm, respectively.

Conclusions: TVD responded to ivacaftor therapy. 3He-MRI provides an individual quantification of disease burden that may be able to detect aspects of the disease missed by population-based spirometry metrics. Assessments by human reader and computer algorithm exhibit similar trends, but the latter appears more sensitive.

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Keywords: cystic fibrosis transmembrane conductance regulator modulator; forced expiratory volume; pulmonary

Abbreviations: AE, adverse event; BMI, body mass index; CF, cystic fibrosis; CFQ-R, Cystic Fibrosis Questionnaire—Revised; CFTR, CF transmembrane conductance regulator; CT, computed tomography; FEV1, forced expiratory volume in 1 s; 3He, hyperpolarized helium-3; MRI, magnetic resonance imaging; ppFEV1, percent predicted forced expiratory volume in 1 s; q12h, every 12 h; SD, standard deviation; TVD, total ventilation defect; TVDc, total ventilation defect by computer algorithm; TVDh, total ventilation defect by human reader.

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Data from this study were presented in part at the 37th Meeting of the European Cystic Fibrosis Society, June 11-14, 2014, Gothenburg, Sweden, and at the 35th European Cystic Fibrosis Society Conference, June 6-9, 2012, Dublin, Ireland.

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1. Introduction

Forced expiratory volume in 1 s (FEV₁) is the primary measure used for characterizing lung function in patients with cystic fibrosis (CF). However, FEV₁ and other pulmonary function tests have limitations [1,2]. For example, FEV₁ reflects total airway resistance and is relatively insensitive to obstruction in small airways, which contributes to ≈10% of overall resistance in healthy adults [3]. Additionally, spirometry is a population-based metric by means of which the disease burden in an individual cannot be determined in absolute terms; it can only be estimated by evaluating the standing of the patient’s spirometric results in a Gaussian distribution. Therefore, in patients with high percent predicted FEV₁ (ppFEV₁) values, it can be difficult to determine whether damage exists and if further improvements in lung function are possible with treatment. Furthermore, reliable spirometry results are difficult to obtain in patients younger than 6 years of age because it requires concentration, cooperation with the spirometry technician, and control of breathing, tasks that may be difficult for young children [4]. Therefore, more sensitive techniques for assessing lung function, which can be performed by patients of all ages, are needed for assessing disease status and response to treatment in patients with CF.

Hyperpolarized helium-3 (³He), an inhaled contrast agent for magnetic resonance imaging (MRI), helps to distinguish well ventilated from poorly ventilated regions of the lung (termed “ventilation defects”) by means of images that have high temporal and spatial resolution [5]. It does not expose patients to ionizing radiation, in contrast to computed tomography (CT) [5]. In prior studies, ³He-MRI revealed ventilation defects in patients with CF [5–13], including those with normal spirometry [5,8], as well as children younger than 6 years [9,10,12,14]. In one study, the ventilation abnormalities seen using ³He-MRI correlated well with structural abnormalities on CT [11]. These data suggest that ³He-MRI may be a sensitive test for depicting lung disease in CF.

In patients with CF, ventilation defects identified by ³He-MRI have responded to conventional treatments, including bronchodilator and mechanical airway clearance [5,7–9]. We hypothesized that ³He-MRI would be appropriate for evaluating response to ivacaftor (Kalydeco; Vertex Pharmaceuticals Incorporated, Boston, MA), a CF transmembrane conductance regulator (CFTR) potentiator in patients with the gating mutation G551D [15]. In clinical studies, ivacaftor has been shown to improve lung function, pulmonary exacerbations, and symptoms of CF in eligible patients [15–19]. In these studies, pulmonary outcomes were assessed using traditional spirometry (ie, FEV₁); thus, it is possible that the full extent of the deficit in lung function or response to treatment was not captured.

The objectives of this pilot study were to determine whether ³He-MRI is a reliable indicator of lung function in patients aged 12 years and older who have CF and a G551D mutation, and who are treated with ivacaftor, and to investigate the effects of ivacaftor therapy on lung function, as measured by ³He-MRI.

2. Methods

2.1. Study design

This single-center, Phase 2 study was conducted in 2 parts. Part A was a single-blind (patients were blinded to the identity of treatment they were receiving), single-arm feasibility phase comprising 4 weeks of ivacaftor treatment (one 150 mg ivacaftor tablet every 12 h), with placebo run-in and placebo washout periods (Fig. 1). This design was selected to avoid study effect bias, as patients with CF commonly adhere more closely to maintenance therapies during clinical trials and consequently experience disease improvement. Part B, which commenced approximately 3 months after Part A concluded, was a 48-week, open-label, single-arm phase evaluating the long-term effect of ivacaftor treatment (Fig. 1). Patients in Part B were either newly enrolled or had participated in Part A. Study assessments were conducted approximately every 12 weeks and at study follow-up at week 50.

![Study Design](image)

Fig. 1. Study design. *Screening visit (on the day before day 1 visit). q12h, every 12 h.
2.2. Patients

Patients aged 12 years or older with CF ([1] sweat chloride ≥ 60 mmol/L or 2 CF-causing mutations and [2] chronic sinopulmonary disease or gastrointestinal/nutritional abnormalities) were eligible for study inclusion. Patients were required to have at least 1 G551D mutation and ppFEV1 of at least 40 at screening. In Part B, no more than 3 patients with ppFEV1 greater than 90 could be enrolled.

Key exclusion criteria included abnormal liver function (liver function tests indicating values ≥ 3 times the upper limit of normal), documented sputum colonization with selected organisms (eg, *Burkholderia cenocepacia*, *Mycobacterium abscessus*), and any potential contraindications to an MRI. Patient treatment regimens must have been stable for at least 14 days before screening and were required to be maintained throughout the study, although patients on cycling inhaled antibiotics were allowed to switch the type of inhaled antibiotic. In Part A, the use of inhaled hypertonic saline was not permitted.

The study protocol (www.clinicaltrials.gov identifier: NCT01161537) was approved by the local institutional review board. Patients or parents/guardians provided written informed consent, and patients younger than 18 years provided assent.

2.3. Study assessments

At each study visit, patients performed spirometry according to American Thoracic Society guidelines (Koko and Koko Legend Spirometers; nSpire, Longmont, CO), underwent 3He-MRI and a sweat chloride test, and completed the Cystic Fibrosis Questionnaire—Revised (CFQ-R) [20,21]. Three CFQ-R versions were used: Child, Adult/Adolescent, and Parent/Caregiver (of patients aged 12 or 13 years). Clinical chemistry and hematology testing and urinalysis were performed at all visits except day 1. Height and weight were assessed at the screening visit in Part A and at every visit in Part B.

2.3.1. MRI acquisition and analysis

3He-MRI was administered under an FDA-approved investigational new drug treatment protocol # 57,866. 3He was polarized to between 20% and 40% using a prototype commercial system (Magnetic Imaging Technologies Inc.; Durham, NC). MRIs were analyzed using both a human reader (C.L.-S.) and an automated method to quantify poorly ventilated lung volume. See online supplementary material for additional details regarding the MR image acquisition and analysis.

2.4. Outcome measures

The primary efficacy variable was change in total ventilation defect (TVD) from baseline (Part A, day 15; Part B, day 1) to the end of ivacaftor treatment (Part A, day 43; Part B, week 48). TVD was manually scored and analyzed by the automated Ventilation Segmentation algorithm [22,23].

Secondary efficacy variables were absolute change from baseline to end of ivacaftor treatment in ppFEV1, sweat chloride, and CFQ-R respiratory domain score. Safety evaluations included adverse events (AEs), clinical laboratory assessments (serum chemistry, hematology, coagulation studies, and urinalysis), clinical evaluation of vital signs and physical examinations, and electrocardiographs. AEs were collected after consent or assent was obtained from all patients enrolled and continued through the follow-up telephone call in Part A or the follow-up visit in Part B.

3. Results

3.1. Study population

Eight patients were enrolled in Part A and completed dosing. Four of these also participated in Part B, which enrolled a total of 9 patients. Eight patients completed dosing in Part B (1 patient refused further dosing), 7 of whom completed Part B through the safety follow-up visit (Supplemental Fig. 1). Patient characteristics for both Parts A and B are summarized in Table 1.

3.2. Primary outcome

3.2.1. Part A

Volume of lung tissue showing ventilation defect as judged by human reader (TVDH) was reduced by 8.2% from baseline (day 15) after short-term ivacaftor treatment (day 43; p = 0.0547) (Fig. 2A). When calculated by computer algorithm (TVDC), a 12.8% reduction was observed (p = 0.0078; Fig. 2B). TVD

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<th>Table 1 Baseline characteristics.</th>
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<td>ppFEV1, mean (SD)</td>
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BMI, body mass index; ppFEV1, percent predicted forced expiratory volume in 1 s; SD, standard deviation; TVD, total ventilation defect.

a Out of the 9 patients who consented in Part B, 2 with G551D/F508del-CFTR mutations withdrew. One of these patients withdrew after completing the day 15 visit because the drug was approved and the patient could receive it outside of the clinical trial. The other patient withdrew after completing the week 48 visit; this patient was unwilling to stop ivacaftor treatment for the washout period of the study. Neither withdrawal was attributed to a perceived lack of efficacy.

b Patients with G551D-CFTR and a mutation previously identified as the F508del-CFTR mutations (although this mutation was not part of the screening panel for either part of this study). The patient with this mutation is the same patient in both Parts A and B of the study.
values returned to baseline levels during the washout period (TVD<sub>C</sub> increase was 8.5%; p = 0.0078).

3.2.2. Part B

The reduction in TVD from baseline (day 1) at the end of ivacaftor treatment (week 48) was 6.3% (TVD<sub>H</sub>; p = 0.1953) and 9.0% (TVD<sub>C</sub>; p = 0.0547), respectively (Fig. 3A and B). By the week 50 safety follow-up visit, mean (SD) TVD values returned to near baseline levels (43.7% [11.93] at baseline vs. 44.8% [8.23] at follow-up TVDH; 33.1% [10.87] at baseline vs. 34.7% [6.71] at follow-up TVDC).

3.3. Secondary outcomes

3.3.1. Part A

At the end of short-term ivacaftor treatment (day 43), mean ppFEV<sub>1</sub> increased by 12.8 percentage points (minimum, maximum: 2.8, 30.5; p = 0.0078; Fig. 2C) and sweat chloride values decreased by 42.3 mmol/L (p = 0.0078; Fig. 2D) from baseline (day 15). Percent predicted FEV<sub>1</sub> and sweat chloride values returned to near-baseline levels at the follow-up evaluation (day 57). The 7.6-point change in CFQ-R respiratory health domain score was not statistically significant (p = 0.8125) although a greater than 4 point change in CFQ-R score is commonly considered clinically significant [21] (Fig. 2E).

3.3.2. Part B

At the end of ivacaftor treatment (week 48), the increase in ppFEV<sub>1</sub> from baseline (day 1) was 5.2 percentage points (minimum, maximum: −7.1, 18.1; Fig. 3C) and was not significant. Sweat chloride decreased by 48.9 mmol/L (p = 0.0078; Fig. 3D), and CFQ-R respiratory health domain score increased by 15.1 points (p = 0.0156; Fig. 3E). By week 50, all variables measured had returned to baseline levels.
3.4. Correlation analyses

Improvement in TVD_{H} (reduction) and in ppFEV_{1} (increase) showed moderate correlation (Spearman correlation for Part A, day 15 through day 43: −0.5238; Part B, day 1 through 48 weeks: −0.6679). Correlations between change in TVD_{H} and change in sweat chloride and CFQ-R respiratory domain scores were weak. The Spearman correlations were the following: Part A: change in TVD_{H} and sweat: 0.0240; TVD and CFQ-R score: 0.0976; Part B: TVD and sweat: 0.2293; TVD and CFQ-R score: −0.2048. The strongest correlation seen in post-hoc analysis was that between the absolute change in MRI measured ventilated lung volume (by computer algorithm) and the absolute change in FEV_{1} (both expressed in liters) measured at every visit compared with the prior visit in Part A. Decreases in TVD matched closely with increases in FEV_{1} (Spearman −0.85, p < 0.0001).

3.5. Images

To illustrate the finding, the imaging results of two representative patients from Part A are shown in Fig. 4 and Supplemental Fig. 2. During Part A, 1 patient (patient 002) had a marked reduction in TVD from baseline to the end of short-term ivacaftor treatment (−24.6 [TVD_{H}] and −31.0 [TVD_{C}] percentage points, Fig. 4). This patient also had a marked improvement in ppFEV_{1}, from 62 at baseline to 83 at the end of treatment. After a 2-week placebo washout period, ppFEV_{1} worsened and ventilation defects returned on imaging. Another patient from Part A (patient 005) had normal spirometry at baseline (day 15; ppFEV_{1}, 113) but had substantial ventilation defects on imaging (TVD_{H}, 29.0%). Following 4 weeks of ivacaftor treatment (day 43), this patient had only a small increase in FEV_{1} to 116 but clear improvement in lung ventilation on imaging (TVD_{H}, 16.0%; Supplemental Fig. 2).
The longer duration of Part B provided additional information about the time course and durability of the changes in lung ventilation. One representative patient from Part B (patient 910) had sustained improvement in ventilation defects from baseline (ie, day 1; ppFEV1, 64; TVDH, 48.0%) through week 24 (ppFEV1, 77; TVD, 17.1%) (Supplemental Fig. 3). At week 36, ppFEV1 (77) was stable; however, a worsening in lung ventilation defects was apparent on imaging (TVD, 28.0%). Shortly after the week 36 study visit, this patient was treated for a mild pulmonary exacerbation. At week 48, the patient had recovered, and ventilation was improved on imaging (TVD 22.0%) and ppFEV1 was again stable (76). At the week 50 visit following the 2-week washout, lung ventilation worsened (TVD 35.0%) and ppFEV1 declined (65) to near-baseline values.

3.6. Safety and tolerability

The incidence of AEs in Parts A and B is summarized in Supplemental Table 1. During the placebo run-in and washout phases of Part A, 2 patients (25.0%) reported 3 AEs of mild severity: dry throat, oropharyngeal pain, and generalized pain. During the ivacaftor treatment phase, 3 patients (37.5%) reported 3 AEs: mild pulmonary exacerbation that required treatment, headache of mild severity, and abdominal distention of moderate severity. These findings are consistent with clinical events observed in patients with CF and with the established safety profile for ivacaftor [16,17].

In Part B, 6 patients (66.7%) had a total of 32 AEs, most commonly (≥ 3 patients) upper respiratory tract infection (n = 4; 44.4%) and pulmonary exacerbation of CF (n = 3, 33.3%). Eighteen AEs were moderately severe: pulmonary exacerbation of CF (n = 2), pyrexia (n = 2), and 1 each of upper respiratory infection, bronchitis, cellulitis, labyrinthitis, nasopharyngitis, pharyngitis streptococcal, vulvovaginal mycotic infection, positive bacterial test, nausea, cerumen impaction, stress fracture, tendonitis, cough, and rash. One patient experienced a severe, serious AE of pulmonary exacerbation and required hospitalization and intravenous antibiotics; the AE resolved by the end of the study. These findings are also consistent with clinical events observed in patients with CF and with the established safety profile for ivacaftor.

No clinically significant safety signals were related to the use of 3He-MRI.

4. Discussion

Part A of this pilot, exploratory study evaluated the feasibility of using 3He-MRI to evaluate short-term (4-week) responses to ivacaftor in patients with CF who had a G551D-CFTR mutation on at least 1 allele. In Part B, examination of ventilation defects using 3He-MRI assessed the efficacy of long-term ivacaftor administered up to 48 weeks [16,17]. TVD, ppFEV1, sweat chloride levels, and CFQ-R scores returned to near-baseline values after treatment with ivacaftor was stopped in both parts of the study. No new safety signals were identified for ivacaftor, and no safety concerns were associated with the use of 3He-MRI.

Confirming previous studies [6,10], TVD and ppFEV1 were only moderately correlated, as exemplified by patient 005.
(images in Supplemental Fig. 2), who had normal spirometry at baseline (ppFEV1, 113) but had ventilation defects on imaging. It is notable that all patients began Parts A and B of the study with obvious ventilation defects as assessed by 3He-MRI, even though some had spirometry measures within the normal range. Furthermore, improvement in lung ventilation following ivacaftor treatment was apparent on 3He-MRI, even in some patients with only small improvements in FEV1. In previous studies of healthy children and young adults, 3He-MRI depicted few, if any, ventilation defects that might predict underlying lung disease [24,25]. The combination of the finding in the current study and prior studies in healthy children suggest that 3He-MRI may be useful in understanding disease progression at the individual patient level. This further provides a complementary approach to population-based spirometry metrics in gauging treatment of CF early in disease.

An advantage of 3He-MRI is that, by identifying areas of poor ventilation, it allows physicians to determine whether subclinical abnormalities exist and whether therefore improvement may be possible. This is especially critical for young, asymptomatic children. 3He-MRI may prove to be an important tool for following the evolution of CF lung disease by detecting earlier declines in lung health that traditional spirometry may not capture. In addition, changes in the 3He ventilation are revealed within the lungs of young children in whom spirometry is not reliable. A second possible advantage of this technique is a fuller assessment of response to treatment. An improvement in spirometry cannot reveal if further improvement is attainable with additional treatment, as the best spirometric values possible for any individual patient cannot be known. 3He-MRI assessment of ventilation defects is quantitative in absolute units, however, and the degree of possible remaining improvement is determined in every case. For example, patient 2 in Part A responded to ivacaftor therapy with resolution of approximately 70.0% of lung ventilation defects. Thirty percent remained however, suggesting that some additional improvement might still be possible. Patient 3, by contrast, responded with a reduction in defect volume (TVD) of only approximately 15.0%, with 85.0% of the defect volume remaining, showing that much further improvement would be possible for this patient with additional therapies. The combination of 3He-MRI and spirometry can also be complementary. For example, the strong correlation between absolute change in TVD and absolute change in FEV1 (in liters) argues that the change in FEV1 with ivacaftor treatment comes primarily from the ventilation of additional lung volume, rather than changes in compliance, airway dilation, or other factors that could influence FEV1.

In this study, 3He-MRI images were analyzed by a human reader and by computer algorithm. Both methods showed similar trends, but the computer algorithm detected statistically significant differences at more time points. The computer algorithm may vary less in judgment than a human reader with regard to the position of the boundary between well- and poorly-ventilated regions of the lung. Within-reader variability of scores was not determined in this study.

The results of this study should be interpreted in the context of certain limitations. The apparent greater effect of ivacaftor treatment in Part A than Part B may be due to the shorter observation period in Part A. Exacerbations and other respiratory illnesses were more likely to occur during the longer treatment period in Part B. The small number of subjects in this proof-of-concept study limits the ability to perform subgroup analyses such as comparing patients with mild to moderate disease and may explain the lack of statistically significant improvement in FEV1 after 48 weeks of treatment in Part B. Furthermore, the number of CF treatment centers currently equipped to perform 3He-MRI is small; additional experience in larger, multicenter studies is needed. A study with a larger sample size may better determine the correlation between lung function based on 3He-MRI and other measures such as FEV1 or perhaps small airway flow rates. In addition, improved image analysis methods may be needed and may improve the sensitivity of the 3He MRI technique which in this study matched the statistical power of spirometry. 3He is currently an investigational contrast agent, which may limit its use in clinical trials until it is approved and recognized as an agent that can help with assessing clinical outcome. Indeed, the need for alternative outcome measures that can detect early lung disease and assess disease progression from childhood into adulthood has been widely recognized [26–28].

In conclusion, this study demonstrated the feasibility of using 3He-MRI as an efficacy measure in clinical trials of emerging treatments for CF. 3He-MRI may be useful for assessing the regional lung ventilation, something that cannot be done using spirometry. Further, the technique allows for assessing the disease at the local level within the lung and can provide a quantification of the disease burden within the individual patient. Ventilation defects observed in patients are not uniform, and regionalizing the analysis (e.g., lobar analysis) would be a way of personalizing monitoring and represents a significant advance beyond current tools. Although not yet mature, such tools are under development and permit both the visualization of the 3D treatment response and the regional quantification of the treatment response [23]. The study also confirmed that the local response to ivacaftor within the lung can be determined by means of 3He MRI and showed that the agent was effective in improving the local and overall lung ventilation in patients with CF who have at least 1 copy of the G551D-CFTR mutation.

Authorship

TA Altes designed the study in collaboration with the sponsor and collected study data. All authors interpreted the data and collaborated in the preparation and critical review of the manuscript, supported by a medical writer provided by Vertex Pharmaceuticals Incorporated. All authors had access to the data and approved the article for submission.

Role of the funding source

Vertex Pharmaceuticals Incorporated participated in designing the study, analyzed the data, and reviewed the manuscript for data accuracy. The authors were responsible for the decision to submit this manuscript.
Conflicts of interest

TAA received a grant from Vertex Pharmaceuticals Incorporated and the Hartwell Foundation during the study. MJ and MF are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. MB is a former employee of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company. DF received a grant from Vertex Pharmaceuticals Incorporated during the study. JM reports grants from Siemens Healthcare, outside the conduct of the study; other from Siemens Healthcare, outside the submitted work. E deL, CLS and NT have nothing to disclose.

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Appendix A. Supplementary data

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