Computed tomography correlates with improvement with ivacaftor in cystic fibrosis patients with G551D mutation

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Abstract

Background: Ivacaftor corrects the cystic fibrosis transmembrane conductance regulator (CFTR) gating defect associated with G551D mutation and is quickly becoming an important treatment in patients with cystic fibrosis (CF) due to this genetic mutation.

Methods: A single-center study was performed in CF patients receiving ivacaftor to evaluate the usefulness of high resolution computed tomography (HRCT) of the chest as a way to gauge response to ivacaftor therapy.

Results: Ten patients with CF were enrolled for at least one year before and after starting ivacaftor. At time of enrollment, mean age was 20.9 ± 10.8 (range 10–44) years. There were significant improvements from baseline to 6 months in mean %FVC (93 ± 16 to 99 ± 16) and %FEV1 (79 ± 26 to 87 ± 28) but reverted to baseline at one year. Mean sweat chloride levels decreased significantly from baseline to one year. Mean weight and BMI improved at 6 months. Weight continued to improve with stabilization of BMI at one year. Chest HRCT showed significant improvement at one year in mean modified Brody scores for bronchiectasis, mucous plugging, airway wall thickness, and total Brody scores. Elevated bronchiectasis and airway wall thickness scores correlated significantly with lower %FEV1, while higher airway wall thickness and mucus plugging scores correlated with more pulmonary exacerbations requiring IV and oral antibiotics respectively.

Conclusions: Based on our findings, HRCT imaging is a useful tool in monitoring response to ivacaftor therapy that corrects the gating defect associated with the G551D-CFTR mutation.

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Keywords: Computed tomography; Cystic fibrosis; Ivacaftor; Pulmonary function; Scan

1. Introduction

Patients with cystic fibrosis (CF) have progressive lung disease leading to bronchiectasis and parenchymal structural changes that is often irreversible with the eventual development of respiratory failure. Technological innovations and drug development have significantly impacted the medical care of the CF population. The majority of these advancements in CF care involve symptomatic therapy ranging from the treatment...
of infection and inflammation to thinning and mobilizing respiratory secretions.

Correcting cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction may prevent disease progression. In addition to the limitations that exist for development of genetic-based therapies, another confounding feature in CF is the variability of genetic mutations that range from little to no CFTR protein reaching the cell surface to other mutations where CFTR protein reaches the epithelial cell surface, but the defective protein results in markedly less chloride transport across the apical cell membrane, the so-called gating defect [1–3]. More recently, there has been some success with the advent of drugs termed CFTR potentiators that can increase the ion-channel function by activating cell surface CFTR and thus restore some transfer of ions and water across the epithelial surface [1]. Ivacaftor (Vertex Pharmaceuticals Inc., Boston, MA, USA), an orally bioavailable CFTR potentiator that targets the G551D mutation, has been shown to increase activity of defective cell-surface CFTR protein leading to increased chloride transport at the cell surface in vitro [4–6]. While treatment with ivacaftor has demonstrated improvements in lung function, lowering of sweat chloride levels, and increasing patient weight [4–6], there has been limited work investigating its effect on lung disease through radiographic imaging.

2. Methods

2.1. Patient population

This single-center, non-blinded, non-randomized prospective cohort study was approved by the Institutional Review Board at Nationwide Children’s Hospital (IRB12-00700). Patients with CF with at least one G551D-CFTR allele were started on ivacaftor 150 mg orally every 12 h for one year. Each patient was instructed to take the drug with a high fat diet (≥20 gram fat and pancreatic enzymes with snack or meal). No other alterations of medical care were done with routine therapy and airway clearance continued according to clinical status and respiratory cultures.

2.2. Data collection

Demographic data including age, race, gender, weight, body mass index (BMI), genetic mutations, pancreatic status, co-morbidities, and tobacco use or secondhand smoke exposure were collected along with information regarding hospitalizations and two weeks courses of antibiotic (oral/aerosolized and intravenous) one year before and after starting ivacaftor. Spirometric measurements performed according to current published standards [7] included forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC ratio, and maximum mid-expiratory flow rate (FEF25–75%). Pulmonary function was monitored at multiple time periods, but the data included for analysis was performed at time of enrollment and 6 months and one year later. Sweat chloride collections were performed at enrollment and then repeated 6 months and one year later according to a standardized protocol using the Macroduct collection device (Wescor, Inc., Logan, UT, USA) [8].

2.3. HRCT imaging

High resolution computed tomography (HRCT) scans of chest were obtained helically at the time of enrollment and then one year later. The HRCT scans were done using a GE Light Speed Ultra® or volume CT (General Electric®, Milwaukee, WI, USA) during voluntary inspiratory breath holding. The settings for the HRCT were 80–100 kilovolts (peak) (kV[p]), 16–32 mA s, (1 CT scan, 3.8 mSv). To assess the lungs, 4 images (reconstructed in bone algorithm at 0.625 or 1.25 mm slice thickness) were evaluated at the following specific anatomic levels: 0.5 cm above the aortic arch, at the carina, halfway between the carina and 1 cm above the higher hemi-diaphragm, and 1 cm above the higher hemi-diaphragm.

HRCT images were scored by an experienced pediatric thoracic radiologist and an experienced pulmonologist using a modified Brody scoring method [9]. They were not blinded to study design but scored each HRCT independently of each other. The scoring system recorded the presence and extent of specific findings of CF lung disease (bronchiectasis, bronchial wall thickening, mucus plugging, parenchymal opacities, and air trapping) in each of the 4 specified levels in the right and left lungs. Bronchiectasis was defined as the diameter of the bronchus greater than the accompanying pulmonary artery. Mucus plugging was defined as the presence of bronchi with opacification of the lumen, centrifibular nodules, or peripheral branching structures. Bronchial wall thickening was subjectively assessed based on comparison with other bronchi throughout the lung. Parenchymal opacities were defined as foci of non-aerated lung at least the size of a subsegment and could include atelectasis as well as pneumonia. The extent of an abnormality was scored as involving ≤10% (score = 1), 11–33% (score = 2), 33–66% (score = 3), >66% (score = 4) of the area of lung or number of visible airways. For all findings, the severity value was multiplied by the extent of the abnormality to produce a score for that finding. These scores were added to produce an overall score with a higher score indicating worsening parenchymal lung disease.

2.4. Statistical analysis

In this cohort, demographic and clinical characteristics were reported as frequency and percentage or mean ± standard deviation. Depending upon the level of measurement of clinical parameters, change between baseline and one year was analyzed by a paired t-test or related samples Wilcoxon signed-rank test. Similarly, change between baseline, 6 months, and one year was analyzed by repeated measures analysis of variance (RM-ANOVA) or related samples Friedman ANOVA by ranks test. CT scan scores were correlated using Pearson correlations. Changes in clinical parameters and changes in CT scores were correlated using spearman correlations. Statistical significance was set at alpha ≤ 0.05.
3. Results

From January 2012 to June 2013, a total of 10 CF patients with G551D-CFTR mutation were started on ivacaftor therapy and had HRCT of the chest done at baseline and one year later and were included in our analysis. At the time of enrollment, the mean age was 20.9 ± 10.8 (range 10–44) years. At enrollment, mean sweat chloride for the cohort was 115 ± 5 mmol/L, which decreased significantly after one year of therapy (50 ± 25 mmol/L, p = 0.023). Other demographics and clinical characteristics are reported in Table 1. All patients were Caucasian. Six of 10 were females. Eight of ten were pancreatic insufficient. None of the patients had cystic fibrosis related diabetes mellitus (CFRDM) and eight of ten were also heterozygous for F508del genotype. There was no specific pattern to respiratory microbiota (Table 1).

Mean weight and BMI improved from baseline to 6 months, weight continued to improve but there was no additional improvement in BMI at one year (Table 2). There were significant improvements from baseline to 6 months in mean %FVC (93 ± 16 to 99 ± 16) and %FEV1 (79 ± 26 to 87 ± 28) (Table 2). Mean %FVC, %FEV1, and %FEF25–75%, returned to baseline levels after one year of therapy.

There were no significant differences in the number of hospitalizations or CF exacerbations that required treatment with intravenous (IV) or oral/aerosolized antibiotics but there was a trend towards improvement in all three (Table 3). Five children (50%) were hospitalized from 1 to 3 times during the year before therapy, while only 1 (10%) child was hospitalized 1 time after a year of therapy. Seven (70%) patients experienced 1 to 3 CF exacerbations that required oral/aerosolized antibiotics before therapy compared to 5 (50%) after 1 year of therapy. The number of patients who had CF exacerbations requiring IV antibiotics decreased from 5 (50%) to 2 (20%).

Structural lung disease was monitored by comparing HRCT scans of the chest done after one year of therapy with the last CT scan done (within one year) before starting therapy. HRCT images were scored separately by an experienced pediatric thoracic radiologist and an experienced pulmonologist using a modified Brody scoring method. Inter-rater reliability between these two readers ranged from ρ = 0.905 to 0.994 (p ≤ 0.001) for bronchiectasis, mucous plugging, airway wall thickness, and total Brody scores. Inter-rater reliability for parenchymal opacity was ρ = 0.732 (p = 0.16) at baseline and ρ = 0.814 (p = 0.004) after one year of therapy. Changes were quantified with modified Brody scores [9] (Table 4, Figs. 1 and 2). One patient had a normal HRCT both at baseline and at one year on therapy. The total mean Brody score significantly improved along with the scores specific for mucus plugging, bronchiectasis and airway wall thickness (Table 4, Figs. 1–5). Mean total modified Brody scores significantly decreased by 13.6 points (bronchiectasis score decreased by 2.7, mucous plugging decreased by 5.6 points, airway wall thickness decreased by 5 points). Few patients had parenchymal opacities or air space disease; thus, scores did not change significantly. However, one patient had a parenchymal opacity score increase from 1 to 2, while no patient experienced worsening of lung disease. Correlations between Brody scores and clinical parameters are shown in Table 5. Higher bronchiectasis and airway wall thickness scores correlated significantly with lower %FEV1. Higher airway wall thickness scores also correlated with more CF exacerbations requiring IV antibiotics. Higher mucous plugging scores correlated with more CF exacerbations requiring oral antibiotics (Table 5). Significant correlations were noted between changes in total Brody CT scores and changes in mean %FVC (r = −0.85, p < 0.01), %FEV1 (r = −0.83, p < 0.01) and courses of intravenous antibiotics/bronchodilators (r = 0.66, p = 0.04).

Table 1
Demographic and clinical characteristics of the cohort (N = 10).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>Genotype F508 heterozygous</td>
<td>8</td>
<td>80</td>
</tr>
<tr>
<td>Respiratory colonization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin-resistant Staphylococcus aureus</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>Methicillin-sensitive S. aureus</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>8</td>
<td>80</td>
</tr>
<tr>
<td>Tobacco use or exposure</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Cystic fibrosis related diabetes mellitus (CFRDM)</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

SD = standard deviation.

Table 2
Alterations in mean weight, BMI, sweat test, and spirometric measurements at baseline and after 6 and 12 months of ivacaftor therapy.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months of therapy</th>
<th>1 year of therapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>46.8 ± 15.2^a</td>
<td>51.9 ± 13.5^ab</td>
<td>54 ± 12.7^bc</td>
<td>≤ 0.001^a</td>
</tr>
<tr>
<td>Body mass index</td>
<td>19.5 ± 3^b</td>
<td>21.1 ± 2.7^a</td>
<td>21.5 ± 2.8^b</td>
<td>0.002^a</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>92 ± 16^a</td>
<td>97 ± 16^a</td>
<td>91 ± 21</td>
<td>0.059</td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>78 ± 27^a</td>
<td>86 ± 29^b</td>
<td>79 ± 30^b</td>
<td>0.021^b</td>
</tr>
<tr>
<td>FEF25–75% % predicted</td>
<td>67 ± 44</td>
<td>79 ± 44</td>
<td>69 ± 43</td>
<td>0.167</td>
</tr>
</tbody>
</table>

SD = standard deviation, FVC = mean forced vital capacity, FEV1 = mean forced expiratory volume in one second, FEF25–75% = mean mid-expiratory flow rate.

aa bb cc values with same superscripts are significantly different from each other.

Significant at alpha ≤ 0.05.

Table 3
Mean number of hospitalizations and CF exacerbations that required antibiotics during one year before and during one year on ivacaftor therapy (N = 10).

<table>
<thead>
<tr>
<th></th>
<th>One year before therapy</th>
<th>One year on therapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>0.6 ± 1.1</td>
<td>0.1 ± 0.5</td>
<td>0.102</td>
</tr>
<tr>
<td>Oral/aerosolized antibiotics</td>
<td>1.5 ± 1.3</td>
<td>0.9 ± 1.2</td>
<td>0.193</td>
</tr>
<tr>
<td>Intravenous antibiotics</td>
<td>0.8 ± 1.0</td>
<td>0.3 ± 0.7</td>
<td>0.177</td>
</tr>
</tbody>
</table>

SD = standard deviation.
4. Discussion

The most important finding in this study is that CF patients with G551D-CFTR mutation have improvement on HRCT imaging with one year of ivacaftor treatment. The majority of the research involving ivacaftor has used various clinical parameters including weight, BMI, sweat chloride levels, nasal potential difference, quality of life scores, and pulmonary function testing [4–6,10–13], but we strongly felt that radiographic changes may be a useful tool in gauging response. In our cohort, ivacaftor therapy was associated with significant reduction in mean sweat chloride levels, weight, BMI and significant improvements in both FVC and FEV1 noted at 6 months but no significant additional improvement in the next 6 months of therapy except in weight. Pulmonary function measures reverted to baseline at one year. HRCT imaging demonstrated an improvement in cohort at one year. Higher HRCT scores correlated with lower %FEV1 and increased use of antibiotics (intravenous and/or inhaled/oral) for pulmonary exacerbations of CF.

In comparison to other studies, Ramsey et al. [6] showed persistent improvement in mean FEV1 throughout 48 weeks of their study and found significant reduction in pulmonary exacerbations compared to placebo. However, their cohort was larger (N = 77), older with a mean age of 25.5 years, and more importantly, suffered from more advanced lung disease (mean FEV1 of 63.6% predicted). Our cohort was smaller (N = 10), younger (mean age of 21 years) and with a milder disease (mean FEV1 of 78% predicted), and these differences may be responsible for lack of significant improvement in %FEV1 after one year of therapy. There was no significant change in hospitalizations and antibiotic use, but there was a trend towards improvement for less need of medical intervention. Improvements in pulmonary function measures were not sustained at one year which raises the possibility that may be HRCT is more sensitive to treatment effects than spirometry especially in patients with mild disease.

Brody scores on HRCT of chest correlated with clinical parameters. Indicators of advance lung disease such as higher bronchiectasis and airway wall thickness scores correlated significantly with lower %FEV1. Higher airway wall thickness scores also correlated with more CF exacerbations requiring IV antibiotics and higher mucous plugging scores correlated with more CF exacerbations requiring oral antibiotics (Table 5). Sweat chloride did not correlate with Brody scores or clinical parameters. Correlation between Brody scores and clinical parameters suggests that change in Brody score was not random but clearly indicative of improvement.

Our study clearly shows significant improvement in parenchymal lung disease with the use of ivacaftor. Improvement in chloride channel function as determined by the decrease in sweat chloride may be responsible for improving hydration of sinus and pulmonary secretions and thinning of mucus. A change in mucus viscosity may lead to a decrease in bacterial density, less infection and inflammation and possibly improvement in airway and sino-pulmonary disease. This drug is the first CFTR modulating medication associated with a reversal of hallmarks of CF. If used in infants and younger children with the appropriate genotype, disease progression may be slowed, but it may also lead to reversal of already developed subtle progressive lung disease as was seen in this small cohort using modified Brody scores in the assessment of alterations on HRCT imaging of the chest.
The current study had several limitations including study design with the lack of placebo group, small sample size and relatively milder clinical disease. Because of these limitations, we cannot demonstrate causality regarding the improvement of parenchymal lung disease on HRCT imaging in these CF patients and ivacaftor treatment.

Ivacaftor is quickly making an impact in the care of patients with CF. Due to limited biomarkers available, we developed this study to assess the utility of HRCT imaging of the chest. Based on our findings, we showed that HRCT imaging is a useful tool in monitoring response to this new therapy that corrects the gating defect associated with the G551D-CFTR mutation. Further research with larger cohorts is needed to determine whether parenchymal lung disease continues to improve beyond the one year period of treatment.

**Conflicts of interest**

The authors report no conflicts of interests and have no relevant disclosures.

**Author contributions**

Dr. Sheikh: contributed to the study design, study conduct, data collection, and manuscript preparation.
Dr. Frederick Long: contributed to the study conduct and data collection.
Dr. McCoy: contributed to the study design, study conduct, and data collection.
Terri Johnson: contributed to the study conduct and data collection.

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**Fig. 3.** Alterations in mucus plugging on high resolution computed tomography imaging of the chest comparing images at baseline and then one year after ivacaftor therapy.

**Fig. 4.** Alterations in bronchiectasis on high resolution computed tomography imaging of the chest comparing images at baseline and then one year after ivacaftor therapy.
Fig. 5. Alterations in airway wall thickening on high resolution computed tomography imaging of the chest comparing images at baseline and then one year after ivacaftor therapy.

Table 5 Pearson correlations between CT Brody scores and clinical parameters after 1 year on ivacaftor therapy.

<table>
<thead>
<tr>
<th>%FVC</th>
<th>%FEV1</th>
<th>%FEF25-75</th>
<th>Oral antibiotics</th>
<th>IV antibiotics</th>
<th>Sweat test</th>
<th>Weight</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>−0.692 (0.039*)</td>
<td>−0.776 (0.014*)</td>
<td>−0.582 (0.100)</td>
<td>0.381 (0.277)</td>
<td>0.611 (0.061)</td>
<td>0.184 (0.408)</td>
<td>0.251 (0.515)</td>
</tr>
<tr>
<td>Mucous plugging</td>
<td>−0.372 (0.325)</td>
<td>−0.385 (0.306)</td>
<td>−0.439 (0.237)</td>
<td><em><em>0.706 (0.023</em>)</em>*</td>
<td>0.480 (0.160)</td>
<td>0.838 (0.081)</td>
<td>−0.151 (0.698)</td>
</tr>
<tr>
<td>Airway wall thickness</td>
<td><em><em>−0.748 (0.021</em>)</em>*</td>
<td>−0.853 (0.003*)</td>
<td><em><em>−0.726 (0.027</em>)</em>*</td>
<td>0.373 (0.289)</td>
<td><em><em>0.840 (0.002</em>)</em>*</td>
<td>0.411</td>
<td>0.254 (0.510)</td>
</tr>
<tr>
<td>Parenchymal opacity</td>
<td>0.163 (0.765)</td>
<td>0.128 (0.744)</td>
<td>0.127 (0.745)</td>
<td>0.200 (0.956)</td>
<td>−0.276 (0.441)</td>
<td>0.304 (0.696)</td>
<td>0.131 (0.736)</td>
</tr>
<tr>
<td>Total Brody score</td>
<td><em><em>−0.851 (0.004</em>)</em>*</td>
<td><em><em>−0.829 (0.006</em>)</em>*</td>
<td>−0.538 (0.135)</td>
<td>0.371 (0.291)</td>
<td><em><em>0.661 (0.037</em>)</em>*</td>
<td>0.442 (0.279)</td>
<td>0.220 (0.570)</td>
</tr>
</tbody>
</table>

Oral antibiotics: mean number of 2 week courses of oral antibiotics/patient.
IV antibiotics: mean number of 2 week courses of i/v antibiotics/patient.
IV = intravenous.
Significant correlations (p ≤ 0.05) are in bold.
* Significant at alpha ≤ 0.05.

Dr. Ryan-Wenger: contributed to the study conduct and data analysis and interpretation.
Dr. Hayes: contributed to the study design, study conduct, data collection, and manuscript preparation.

References