Correlation between chest CT findings and change in lung function on CFTR modulating treatment in CF patients

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November 3, 2020

Abstract

Objective: To verify if the extent of structural lung damage visible on chest CT is correlated with change in ppFEV1 after start of CFTR modulating therapy in CF patients. Methods: In our retrospective observational study, we included patients aged [?]6 years starting ivacaftor or lumacaftor/ivacaftor treatment who were in routine follow up. FEV1 and BMI were recorded every 3 months. From the group of patients who had started lumacaftor/ivacaftor, patients were selected who underwent chest CT within 18 months before or after start of treatment. Patients who had started ivacaftor all underwent chest CT just before the start of treatment. These CT scans were reviewed to determine Brody score. ppFEV1 data was retrieved. To assess correlations, Spearman R and Pearson R tests were applied. Results: Thirty patients met the inclusion criteria, with Brody scores between 0.46-55.30 (median: 19.97, normalized score out of 100) and ppFEV1 before treatment of 19-113 (median: 67). Twenty-three and 7 patients had started lumacaftor/ivacaftor and ivacaftor respectively. Change in ppFEV1 after 6 months of treatment ranged from -19 to +24 (median: +5). For patients using lumacaftor/ivacaftor, the correlation between Brody score and change in ppFEV1 was not significant: Spearman R=-0.213, (p=0.164), but for patients using ivacaftor, there was a significant correlation between Brody score and ppFEV1 change, with a Spearman R=0.679 (p=0.029). Conclusion: The extent of structural damage to the lungs of CF patients is correlated with the response in ppFEV1 to ivacaftor, however this correlation was not demonstrable in patients treated with lumacaftor/ivacaftor.

Introduction

Despite the fact that Cystic Fibrosis (CF) affects various epithelia throughout the body, its effects on the airway epithelium are usually the most evident, resulting in structural damage to the airways and lung parenchyma that can be clearly visualized on computed tomography (CT) scan of the chest, which is widely used as an additional follow up tool in CF care[1].

F508del is the most common CF causing mutation, present on 66.7% of alleles in CF patients in Europe, and is even more frequent in the Netherlands[2]. It affects folding, trafficking, and function of the CFTR protein usually leading to a severe CF phenotype[3]. Targeted therapy for this mutated protein consists of a combination of a CFTR corrector, enhancing processing and trafficking and a potentiator, increasing the open probability of the chloride channel[4]. The first available combination therapy for treatment of F508del homozygous patients regardless of ppFEV$_1$ is lumacaftor/ivacaftor. In the phase III randomized clinical trials for this drug, a modest improvement in FEV$_1$ and BMI and a significant decrease in pulmonary exacerbations was observed in comparison to placebo. However, the effects of this drug proved to be highly variable in the phase III studies, as well as in clinical practice[5,6].

The effect of ivacaftor for patients with gating mutations such as G551D and S1251N, is overall better in comparison with lumacaftor/ivacaftor, especially on sweat chloride concentrations and lung function, but these effects also vary between individuals[7,8].

As the structural damage in CF lung disease involves longstanding remodeling of airways and lung parenchymal fibrosis, we do not expect this structural damage, nor its effect on FEV_1, to change after the initiation of therapy. Therefore, the aim of this study was to evaluate if the extent of structural damage to the lungs visible on chest scans is correlated with the response in ppFEV1 after initiation of CFTR modulatory (ivacaftor or lumacaftor/ivacaftor) therapy in CF patients.

Methods

We included patients with CF who had been using lumacaftor/ivacaftor or ivacaftor for at least 6 months, and who underwent chest CT within 18 months before or after start of therapy. All patients had been in standardized follow up since the moment before start of the CFTR modulator: just before start, patients completed a CFQ-R, underwent pilocarpine iontophoresis sweat chloride testing and pulmonary function testing and measurement of weight and height. All of these measurements were repeated after 6 months of treatment.

In patients starting ivacaftor, a low dose high resolution (HRCT) scan of the chest was performed before the start of treatment in all patients. In the patients starting lumacaftor/ivacaftor, CT scan of the chest was performed by indication only, usually for the exclusion of pulmonary embolism (CT pulmonary angiogram, CTPA: with IV contrast), for evaluation of actual bleeding in patients with hemoptysis (CTPA), or when a patient was screened for lung transplant (HRCT).

Due to the scanning protocol and indication, CTPA did not include expiration slides for evaluation of air trapping. Therefore we calculated total Brody score without air trapping for the group of patients starting with lumacaftor/ivacaftor. In the group of patients who started ivacaftor however, complete Brody score, including air trapping, was available for all patients and this has been used for analysis.

For this study, assessment of Brody score was performed by a board-certified chest radiologist. Brody score was recorded as a total score, total score excluding air trapping, and separate scores on all subdomains[9]. Total scores and subdomain scores were normalized to a 0-100 scale.

Spirometry was carried out according to the current European Respiratory Society (ERS) guidelines using reference data from the Global Lung Function Initiative (GLI) to calculate $ppFEV_1$[10,11].

For analysis of the data, IBM SPSS 25 analysis software was used. To assess correlations, the commonly used Pearson R was calculated. In addition Spearman R was calculated. We consider the latter the best applicable method for our purpose, as this method is less sensitive to outliers and suitable for non-linear correlation. To determine statistical significance, the cut-off for p-value was set at 0.05.

Results

Thirty patients met the inclusion criteria. Brody scores from the CT scans of these patients ranged from 0.46 to 55.30 (median: 19.97, Q1-Q3: 13.80-26.10) out of 100, and $ppFEV_1$ before treatment from 19 to 113 (median: 67, Q1-Q3: 36-83.5). Twenty-three patients with a F508del/F508del genotype had started lumacaftor/ivacaftor, 7 patients with F508del and a gating mutation on the second allele had started ivacaftor. Baseline characteristics for both groups are presented in table 1. Change in $ppFEV_1$ after 6 months of treatment ranged from -19 to +34 (median: +5.0, Q1-Q3: -4.25 - +13). Median change $ppFEV_1$ on ivacaftor was +7 (Q1-Q3:+3 - +27) versus +3 (Q1-Q3:-6 - +11) on lumacaftor/ivacaftor. In the lumacaftor/ivacaftor group, 12 and 11 patients underwent chest CT before and after the start of treatment, respectively.

Brody score (total score without air trapping) correlated significantly with baseline $ppFEV_1$ in patients starting lumacaftor/ivacaftor: Spearman R=-0.514 (p=0.006), Pearson R=- 0.517 (p=0.006).

The correlation between Brody score (total score without air trapping) and change in $ppFEV_1$ after 6 months

was not significant: Spearman R=-0.213, (p=0.164), Pearson R=-0.057, (p=0.398). Scatterplots are shown in figure 1.

In patients using ivacaftor, Brody score also correlated significantly with $ppFEV_1$ at baseline, Spearman R=-0.739 (p=0.029), Pearson R=-0.734 (p=0.028). Moreover, in this group there was a significant positive correlation between Brody score and $ppFEV_1$ change after 6 months, with a Spearman R=0.679 (p=0.029) Pearson R = 0.822 (p=0.012). Scatterplots for these correlations are shown in figure 2.

As Brody score in this group is correlated with both $ppFEV_1$ at baseline and $ppFEV_1$ change at 6 months, $ppFEV_1$ at baseline and after 6 months are expected to be interconnected. Therefore we performed a post-hoc analysis calculating the correlation coefficient between $ppFEV_1$ change and Brody score, corrected for $ppFEV_1$ at baseline. The corrected correlation coefficient of R=0.576 in the ivacaftor group still suggests an association, however this result is not statistically significant (p=0.231).

Discussion

This study provides a first insight into the association between extent of structural damage in the lungs and airways in people with CF and the FEV_1 response to treatment with CFTR modulators during real life follow up. There is no previous literature about this association.

Unsurprisingly, our data confirm the correlation between baseline $ppFEV_1$ and Brody score derived from chest CT, as has been established before by Helbich et al. for an earlier CT score in adult and pediatric CF patients, and by Brody et al. for Brody score in children with CF. [12,13]

This study shows different findings concerning the correlation between Brody score and lung function change for treatment with ivacaftor versus lumacaftor/ivacaftor: we find a positive correlation between Brody score and $ppFEV_1$ response to ivacaftor treatment, whereas we do not find any correlation between these same parameters for treatment with lumacaftor/ivacaftor.

This contrast in findings could be explained by the differences in treatment efficacy of the CFTR modulating drug; lumacaftor/ivacaftor for F508del homozygous patients is known to be far less effective compared to ivacaftor for patients with a gating mutation[5,14]. This difference adds to the difficulties in the assessment of factors correlated with magnitude of response.

Notably, the ivacaftor group consisted of patients with a relatively well-preserved lung function and low Brody scores, reflecting only minimal structural changes in the lungs. This may explain why a positive correlation between Brody scores and lung function change on treatment was found; in patients whose lungs are not severely affected by the disease, an increase in lung function cannot be expected after the start of treatment; the goal of treatment would be to preserve lung function and to prevent lung damage rather than to reverse it. In a group of patients with more severely affected lungs, it is possible that the correlation would be absent or even negative, if extensive structural damage proves to be irreversible by CFTR modulating therapy.

Also the fact that the timing of the CT scans was just before start of therapy in the ivacaftor group, while this was anywhere in the 18 months before or after start of therapy for the lumacaftor/ivacaftor group, could in part account for the difference in findings. The decision to include scans within the time span of 18 months before or after start, was based on literature about the progression of structural damage visible on CT scan in CF, showing no relevant progression in 18 months on most parameters[15].

This study faced several limitations, most of these concerning the group of patients who had started lumacaftor/ivacaftor, as we use clinically indicated CT scans in this group. Firstly, this implicates that differences in scanning protocol occurred with variation of the clinical indications that warranted the chest CT. This resulted in missing air trapping scores in 5 patients in this group. We therefore used Brody score excluding air trapping score for this analysis. As air trapping (together with mucus plugging) would be the aberrance most likely to improve on treatment, also influencing FEV_1, this could decrease the potential of the Brody score to pick up a possible correlation between baseline CT anomalies and FEV_1change on

therapy. Another consequence of using indicated CT scans, is that the timing of the scans is imperfect in comparison with CT scans in the ivacaftor group (where CT was timed just before start of the treatment as part of the regular follow up protocol). This might lead to differences in the findings, as theoretically, some anomalies (such as air trapping, mucus plugging) might improve quickly after initiation of therapy. No information about short term effects of CFTR modulators on CT findings is available in literature however.

A third limitation that the use of clinically indicated scans brings along, is the fact that these scans may show more (possibly reversible) abnormalities than would be present in a stable situation, as the scan is carried out due to respiratory complaints. Also purely based on CT scan it is not easy to discriminate between reversible and irreversible structural abnormalities. For example, a CT scan could show consolidations or increased bronchial thickening, reflecting an exacerbation, in a patient undergoing CT scan because of hemoptysis. The ivacaftor group on the other hand is small, making the data more prone to be influenced by outliers, troubling calculation of partial correlations, and making it impossible to tell if the correlation found is in fact linear, or curved. An advantage was that in this group CT scans were timed optimally and included expiration slides for air trapping analysis.

Verification and closer analysis of this correlation in a larger patient cohort would be favorable. Another additional approach could be to evaluate if Brody scores from follow up CT scans improve in patients while they are using CFTR modulators, and whether or not this improvement is in line with the change in $ppFEV_1$.

Conclusion

The extent of structural damage to the lungs of CF patients is correlated with the response in $ppFEV_1$ on ivacaftor, however this correlation was not demonstrable in patients starting on lumacaftor/ivacaftor. It would take a larger drug effect size and/or larger sample size to see if this correlation also stands after correction for baseline $ppFEV_1$. Brody score derived from chest CT in CF patients correlates with $ppFEV_1$ before the start of CFTR modulating treatment.

Conflict of interest statement

BL Aalbers has assisted in clinical trials for Vertex as a sub-investigator.

KM de Winter-de Groot works as an investigator in clinical studies for Vertex.

HGM Arets is member of the advisory board, speaker and investigator in several clinical studies for Vertex.

CK van der Ent reports grants from Vertex, outside the submitted work.

HGM Heijerman has provided assistance to Vertex pharmaceuticals, the manufacturer of lumacaftor/ivacaftor, as member of the advisory board, speaker and investigator in clinical studies.

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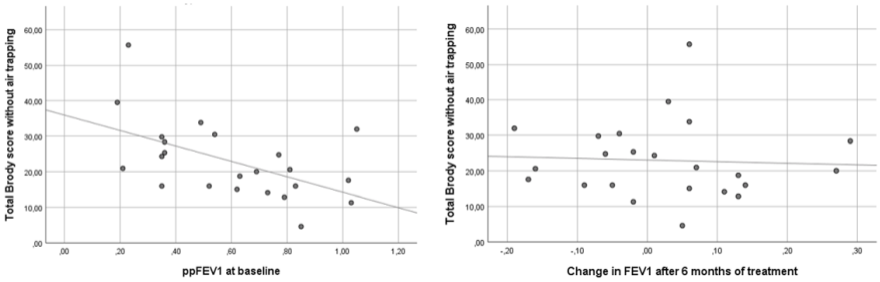

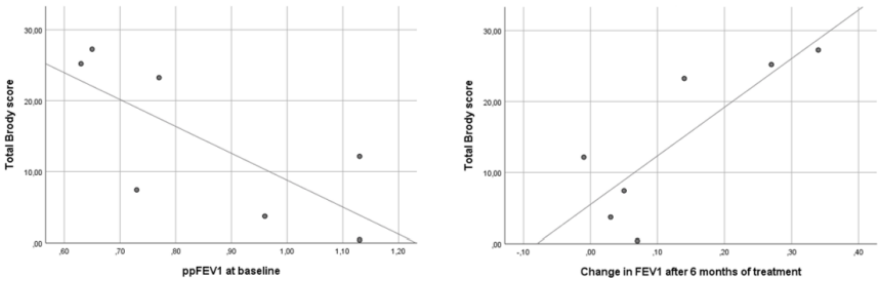

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Table 1.pdf available at https://authorea.com/users/372478/articles/490503-correlation-between-chest-ct-findings-and-change-in-lung-function-on-cftr-modulating-treatment-in-cf-patients