Apparent Improvement of Airway Injury after Gene-Potentiating Therapy in Cystic Fibrosis

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Abstract

Patients with cystic fibrosis (CF) and suitable genotypes are now able to access gene-potentiating therapy that improves lung function, weight gain, and prolongs the time between pulmonary exacerbations. We report the case of a 74 year old woman who had CF with a R117H gating mutation. Lung function had declined to 38% predicted normal FEV1 and there was progressive bronchiectasis evident on CT scanning. After treatment with ivacaftor over 12 months, lung function has improved to FEV1 of 50% predicted normal. Repeat CF scanning showed marked improvement of bronchiectasis. This case report demonstrated that gene-potentiating therapy may be beneficial in CF patients with advancing age and that structural improvement may occur on treatment.

Keywords: Cystic Fibrosis; Ivacaftor; Gene-Potentiating Therapy

Introduction

Gene-potentiating therapy is now indicated for the treatment of patients with cystic fibrosis, provided specific criteria are met. It was first used in patients with the GD551D CFTR mutation, with clinical trials demonstrating an improvement in lung function, weight gain, and time to pulmonary exacerbations [1].

The R117H mutation affects 2.4% of the cystic fibrosis population internationally and approximately 2.8% of the Australian CF population [2]. Ivacaftor (Kalydeco, Vertex Pharmaceuticals, Cambridge, MA, USA) is an orally-active, cystic fibrosis transmembrane conductance regulator (CFTR) gene-potentiator, which facilitates increased chloride transport [3].

In vitro studies have demonstrated significant chloride channel activity for other mutations, including R117H. In a small, phase III trial specifically following adult patients with the R117H mutation, there was a 5.0% absolute change from baseline in FEV1 after 24 weeks treatment, a non-significant increase in BMI, and time to pulmonary exacerbations [4]. Further studies have reported similar effects [5,6].

Case Report

A 74 year old female with R117H/deltaF508 mutation genotype was commenced on ivacaftor because of low lung function (poly T intron status not available). Despite prior optimal treatment according to recommended practice guidelines [7], her lung function declined significantly in the two months prior to treatment. At the time of assessment for gene-potentiating therapy, her forced expiratory volume in one second (FEV1) was 0.83L (38% predicted) with forced vital capacity (FVC) 1.49L. Her exercise tolerance was poor (NYHA FC II-III), affecting her social activities while chronic abdominal pain, altered bowel habit, and low BMI (21.9) persisted despite pancreatic enzyme replacement. Although acute exacerbations were not a prominent feature of her illness (experiencing one pulmonary exacerbation in 18 months), lung function had declined over the preceding years (Figure 1).

Ivacaftor was commenced at a dose of 150 mg BID, and for the next 12 months she was monitored for objective and subjective clinical response. Lung function progressively improved in the next 12 months (Figure 1): FEV1 0.87L (36% predicted) to 1.09L (50% predicted) and FVC from 1.27L (44% predicted) to 1.66L (59% predicted) at 12 months. The patient reported an improvement in gastrointestinal symptoms including a reduction in abdominal discomfort in association with a weight gain of 6.7kg over 12 months. Laboratory indices are reported in Table 1 showing improved sweat chloride. High resolution CT chest scan demonstrated less mucus impaction and less parenchymal infiltrate at 12 months (Figure 2), however, sputum continued to culture Pseudomonas aeruginosa.

Figure 1: Trend in %FEV1 and %FVC post bronchodilator over time (months) where baseline is at 0 months.

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Subjective improvement in exercise tolerance was reported, (regular exercise 4 times per week) and quality of life, mood and sleep all reported to have improved. There was one pulmonary exacerbation following initiation of ivacaftor. No adverse side effects of ivacaftor therapy were identified (specifically hepatotoxicity).

Discussion

Ivacaftor is the first drug which improves defective CFTR function in gene specific mutations by potentiating CFTR channel gating function. Potentially, access to ivacaftor for patients with severe lung disease (ppFEV1 < 40%) and suitable CF gene mutations (Class III) may be beneficial. Treatment has resulted in improvements in clinical outcomes including lung function, weight gain, and time to hospitalization for pulmonary exacerbations. Reversibility of established injury has not been previously reported.

We report on the oldest documented recipient of ivacaftor showing improvement in lung function, exercise capacity, exocrine sufficiency and quality of life. No significant adverse effects were seen despite the patient’s age. Despite the fibrotic changes in the lung parenchyma, atrophy of the pancreas, and impairment of the liver and kidneys that occur over time, this case report challenges the notion that older patients will have completely irreversible complications of CF disease.

This case report also shows that despite the longstanding nature of the disease the sequelae of CF can be ameliorated, including the improvement in FEV1 and weight which will improve prognosis in CF [8,9]. In the new era of geriatric care for CF patients, gene-potententiating treatment may delay or abrogate the need for lung transplantation in an environment of continued donor organ shortages.

Sweat chloride did not completely normalize suggesting either sub-optimal bioavailability or incomplete efficacy of ivacaftor to restore CFTR function. Additionally, other candidate pathways could explain the dysregulation of CFTR [10] and may respond incompletely to ivacaftor. Sputum culture was unchanged however: Organism load was not assessed and possibly some beneficial effect may have arisen from changes in the respiratory microbiome.

This case identifies the potential benefit in treating all CF patients regardless of age who have a modifiable genotype. Improvements beyond exacerbation rates and FEV1 levels, such as quality of life and exercise capacity, potentially have an economic impact on the healthcare system. The geriatric CF population should be a focus in future research studies to assess the potential benefit, economic and clinical, derived from this new class of treatment.

Conflict of Interest

No conflict of interest to disclose.

References

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