Case Report

Clinical efficacy of elexacaftor-tezacaftor-ivacaftor in an adolescent with homozygous G85E cystic fibrosis

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A R T I C L E   I N F O

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A B S T R A C T

Eluxacaftor-tezacaftor-ivacaftor (ELX/TEZ/IVA) is a triple combination drug therapy approved for individuals with cystic fibrosis (CF) who possess at least one copy of the F508del cystic fibrosis transmembrane conductance regulator (CFTR) variant. ELX/TEZ/IVA improves lung function and decreases the frequency of CF exacerbations in clinical studies, which has led to investigation of this therapy on rare CFTR variants. Rare mutations have limited research publications; therefore, reporting outcomes is critical to expanding knowledge and understanding of therapeutic efficacy. This case highlights a CF adolescent homozygous for the G85E CFTR variant who had resolution of chronic respiratory symptoms after initiating ELX/TEZ/IVA.

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive, life-limiting genetic disorder [1,2]. The underlying mechanism is an abnormality of the cystic fibrosis transmembrane conductance regulator (CFTR) protein responsible for chloride and bicarbonate transport in epithelial cells. This protein is found in many organs, most notably the lungs, gastrointestinal tract, and sweat glands. CF commonly manifests as progressive lung disease, pancreatic insufficiency, and high sweat chloride levels [2]. There are thousands of variations in CFTR dysfunction categorized into six classes based on the absence or reduction of CFTR protein, abnormal trafficking of the protein channel to the cell membrane, or defective chloride transport across the channel [3]. CFTR modulators, therapies designed to augment the function of CFTR protein, have transformed the lives of individuals with CF. There are four approved modulators: ivacaftor, lumacaftor-ivacaftor, eluxacaftor-ivacaftor, and eluxacaftor-tezacaftor-ivacaftor (ELX/TEZ/IVA) [3]. ELX/TEZ/IVA was initially approved in 2019 for individuals with at least one copy of F508del, the most common genetic mutation [3]. This highly effective modulator therapy (HEMT) is composed of correctors, eluxacaftor and tezacaftor, that improve protein processing and transport to the cell membrane. This is further augmented by ivacaftor, which potentiates CFTR channel opening and improves chloride transport [3]. In a clinical trial for individuals heterozygous for F508del, ELX/TEZ/IVA showed improvement in lung function by 14%, decreased frequency of pulmonary exacerbations by 63%, and improved clinical symptoms [4].

F508del serves as a model for class II CFTR variants and was utilized in preclinical studies to understand the impact of ELX/TEZ/IVA on CFTR restoration in nasal epithelial cultures obtained from individuals with this CF variant [5]. This preclinical data corroborated the positive clinical response noted in the initial clinical trials and laid the groundwork to study modulator efficacy on cell cultures from individuals with rare class II mutations such as G85E. There are 39 homozygous G85E individuals with CF in the CFTR2
database [6]. Based on in vitro data, there was evidence of restoration of CFTR function that led the Food and Drug Administration to broaden HEMT use to include rare CFTR variants without clinical studies [3,5].

This case report describes a Hispanic adolescent female with homozygous G85E CF who had resolution of chronic respiratory symptoms and improvement in CFTR function after initiation of ELX/TEZ/IVA.

2. Case presentation

This is a 16-year-old Hispanic female with homozygous G85E CF diagnosed at birth due to meconium ileus, pancreatic insufficiency, and CF-related diabetes (CFRD). She has been followed by the Nemours Children’s Hospital, Delaware CF team in Wilmington, Delaware since her initial diagnosis. She was ineligible for HEMT until Food and Drug Administration approval expansion in January 2021.

Comparison of clinical data from 10 months before and after initiation of HEMT showed significant improvement in clinical symptoms as shown in Table 1. Prior to HEMT, she had a chronic, productive cough that required cycling of oral antibiotics. Of note, she did not require inpatient hospitalization. After starting HEMT, there was complete resolution of respiratory symptoms within one month of therapy. There was no change in her respiratory microbiome, as she continued to grow methicillin-sensitive Staphylococcus aureus and Haemophilus influenzae on sputum culture. She has never grown gram negative bacteria, specifically Pseudomonas aeruginosa.

Comparison of chest radiographs showed improvement in bilateral patchy airspace opacities, and Brasfield score improved from 20/25 to 23/25, shown in Fig. 1 [7]. The Brasfield score is a radiographic assessment of air trapping, linear markings, nodular cystic lesions, large lesions, and generalized severity. Lung function was not measured due to an inability to perform spirometry. No baseline sweat chloride level at diagnosis was available; however, sweat chloride levels obtained after HEMT were 42 mEq/L and 50 mEq/L. Based on the CFTR2 database, expected sweat chloride level for an individual with two copies of G85E is 100 mEq/L [6]. Additional clinical changes noted after therapy were a change in body mass index from the 89th percentile for age to the 97th percentile for age. CFRD was difficult to control as demonstrated by increase in hemoglobin A1C level of 7.8% to 8.7%.

3. Discussion

This case demonstrates improvement in CFTR function in an individual with homozygous G85E CF on HEMT based on resolution of chronic respiratory symptoms and improvement in sweat chloride levels. There is a need for further research to understand the metabolic effect of modulator therapy given the weight gain observed after HEMT; however, it is additionally possible this outcome was impacted by the patient’s nutritional status. It is important to report positive clinical outcomes of modulator use in rare CFTR variants to support innovative techniques to evaluate drug efficacy in pre-clinical trials. It is challenging to perform clinical trials on
individuals with rare variants due to limited representation of specific CFTR variants [2]. Therefore, clinical case reports are pivotal to demonstrate the therapeutic success of HEMT and facilitates their use in patients with CF caused by rare variants.

4. Conclusion

- This case report shows sustained improvement in respiratory symptoms on HEMT for an individual with severe CF phenotype caused by rare variants.
- There is evidence of CFTR restoration by improvement in sweat chloride levels.
- Further investigation is needed to identify the impact of HEMT on non-respiratory manifestations of CF such as CFRD.
- It is important to report clinical implications of HEMT approved based on in vitro studies to support early utilization in eligible individuals.

Statement of ethics

This case report was prepared and completed in accordance with the guidelines of the revised Helsinki Declaration of 2013. Written informed consent was not required for this case report.

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Declaration of competing interests

The authors have no conflicts of interest to declare.

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