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Elexacaftor/Tezacaftor/Ivacaftor Improves Glycemic Control in Pediatric Patients with Cystic Fibrosis-Related Diabetes

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Abstract

Cystic fibrosis (CF) is an inherited disorder caused by genetic mutations encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) is a CFTR modulator shown to improve lung function in certain patients with CF. We undertook this study to determine its effects on glycemic outcomes in pediatric patients with cystic fibrosis-related diabetes (CFRD). We reviewed the medical records and identified two subjects, referred to as subject A and subject B, with CFRD on insulin therapy at Duke University Hospital between 2019-2020 who were on treatment with ELX/TEZ/IVA for at least one year. The mean hgbA1C pre- and post- treatment was 5.65% (5.6-5.7) and 5.05% (5.0-5.1) respectively with a mean reduction of 0.6% (p value 0.01). Improvement in hgbA1C occurred in the absence of increased insulin requirements, subject B remained on a similar insulin regimen whereas subject A was able to come off insulin completely. In addition, improvements in BMI z-score were seen in both groups with a mean BMI z-score of -0.30 pre-treatment (-0.71-0.11) and z-score of +0.28 post-treatment (0.11-0.45).

Keywords: Cystic Fibrosis, Cystic Fibrosis-Related Diabetes, Diabetes, CF Modulators

Introduction

Cystic fibrosis (CF) is an inherited disorder caused by genetic mutations encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein, leading to decreased or absent CFTR function. The CFTR protein is found in several exocrine tissues and transports chloride and bicarbonate across the apical surface of secretory epithelia. With defective CFTR function, defects in chloride transport cause build-up of viscous secretions in the lungs, pancreas, reproductive tract, and gastrointestinal tract and lead to increased salt content in sweat gland secretions [1]. Most notably, defective chloride transport in the lungs leads to thick mucopurulent secretions and impaired ciliary clearance, this predisposes patients to chronic infections, inflammation and lung damage [2]

With improved treatment modalities in CF, life expectancy has increased and comorbidities have become more prevalent. Cystic fibrosis-related diabetes (CFRD) is the most common comorbidity in CF, affecting 5% of adolescents and as many as 45% of adults in the US [3]. CFRD is a distinct disease from type 1 and type 2 diabetes. In CFRD, there is loss of islet cell mass resulting in insulin and glucagon deficiency, and acute and chronic inflammation leading to insulin resistance [4, 5]. Screening guidelines for CF recommend an annual oral glucose tolerance test starting at 10 years of age. Diabetes is diagnosed when fasting blood sugar is greater than or equal to 126 mg/dL or when blood sugar is greater than or equal to 200 mg/dL randomly or two hours after the oral glucose load. Postprandial hyperglycemia is commonly seen in CFRD and other forms of diabetes due to a loss of first phase insulin secretion [6]. Insulin remains the recommended first line treatment in CFRD, oral hypoglycemic agents are not as effective [7]. Management of CFRD can be challenging due to the need for high caloric intake in CF patients stemming from increased energy expenditure and pancreatic insufficiency.

CFTR modulators are designed to improve CFTR protein function, and have substantially improved care in patients with CF. In 2019, 70% of eligible patients in the US were taking CFTR modulators [3]. In 2019, Elexacaftor-Tezacaftor-Ivacaftor (ELX/TEZ/IVA) was approved for pediatric patients ages 12 years and older who have at least one mutation in the *F508del* gene. Ivacaftor is a potentiator of the CFTR chloride channel and increases chloride conductance across cell membranes. Elexacaftor and Tezacaftor facilitate the folding and presentation of the mature CFTR protein to the cell surface. Recently, randomized control trials demonstrated substantial improvements in lung function, weight, BMI and nutritional status in pediatric patients taking ELX/TEZ/IVA and in June 2021 its use was expanded to include those 6 years and older [8-10]. While it has been shown to improve pulmonary function in patients with CF, there are limited data on its effects on glycemic outcomes in pediatric patients with CFRD. In adults with CFRD, use of Ivacaftor alone or in combination with Lumacaftor, a CFTR corrector, or Tezacaftor enabled patients to come off insulin in a third of the cases [11].

There is a paucity of data on ELX/TEZ/IVA on glycemic control in the pediatric population. After noting improved hemoglobin A1C in patients taking ELX/TEZ/IVA we undertook the present study to determine its effect on CFRD in a pediatric population followed at a multidisciplinary CF clinic.

Methods

A retrospective chart review was performed at a single institution (Duke University Hospital, NC). Inclusion criteria were: 1) confirmed diagnosis of CFRD, 2) pediatric patients up to age 21, 3) ELX/TEZ/IVA start before November 2019 and continued for at least one year, 4) A1C prior to ELX/TEZ/IVA start, 5) on insulin treatment. All patients had at least one F508del mutation in the CFTR gene. ELX/TEZ/IVA was FDA approved in 2019 for CF patients with one F508del mutation. All patients with one F508del mutation were eligible for the medication and started the medication in order to correct the function of their CFTR channel. Standard doses were started for each patient based on successful clinical trials (ELX/TEZ/IVA 100/50/75mg in the morning and a dose of IVA 150mg at night) [8]. CFRD was defined by abnormal oral glucose tolerance test and/or hemoglobin A1C $\geq$ 6.5%. Clinical characteristics such as age, sex, BMI and total daily insulin requirements and hemoglobin A1C pre- and post- treatment were obtained. All procedures were approved by the Duke University Hospital Institutional Review Board. Descriptive statistics and paired Student's *t*-test were performed in Prism graph pad.

Results

We identified 12 pediatric patients with CF who were on ELX/TEZ/IVA for at least one year at time of analysis. Two subjects had CFRD and were on insulin therapy (Table 1). Subject A is a 14-year-old male who was diagnosed with CFRD at the age of 7. His hemoglobin A1C just prior to starting treatment was 5.6% and had required short-acting insulin with meals, roughly 2-3 units per day. After one year of treatment, his hemoglobin A1C decreased to 5% and he stopped insulin therapy (Figure 1). His BMI z-score improved from -0.71 to 0.11 SDS. He remained healthy for the year studied and did not have any CF-related illnesses or hospitalizations. Subject B is a 20-year-old female who was diagnosed with CFRD at the age of 10 years. Her hemoglobin A1C just prior to treatment was 5.7% and she was on a basal-bolus regimen, receiving approximately 14 units per day from basal and meal coverage. After one year, her hemoglobin A1C was 5.1% with stable insulin requirements. Notably, her BMI improved from z-score 0.11 to 0.45 SDS.

	Patient 1		Patient 2	
	Before	After	Before	After
Age at CF diagnosis	6 months		5 months	
Sex	Male		Female	
Mutations	F508del/909delT		F508del/394delT	
Age at CFRD diagnosis	7 years		10 years	
Age at drug initiation	13 years		19 years	
FEV1%	95.2%	107%	76.3%	88.1%
Hemoglobin A1C	5.6%	5%	5.7%	5.1%
BMI (z-score)	-0.71	0.11	0.11	0.45
Total daily insulin requirements (units)	2	0	14	13

Table 1: Summary of CFRD patients before and after Elexacaftor-Tezacaftor-Ivacaftor treatment

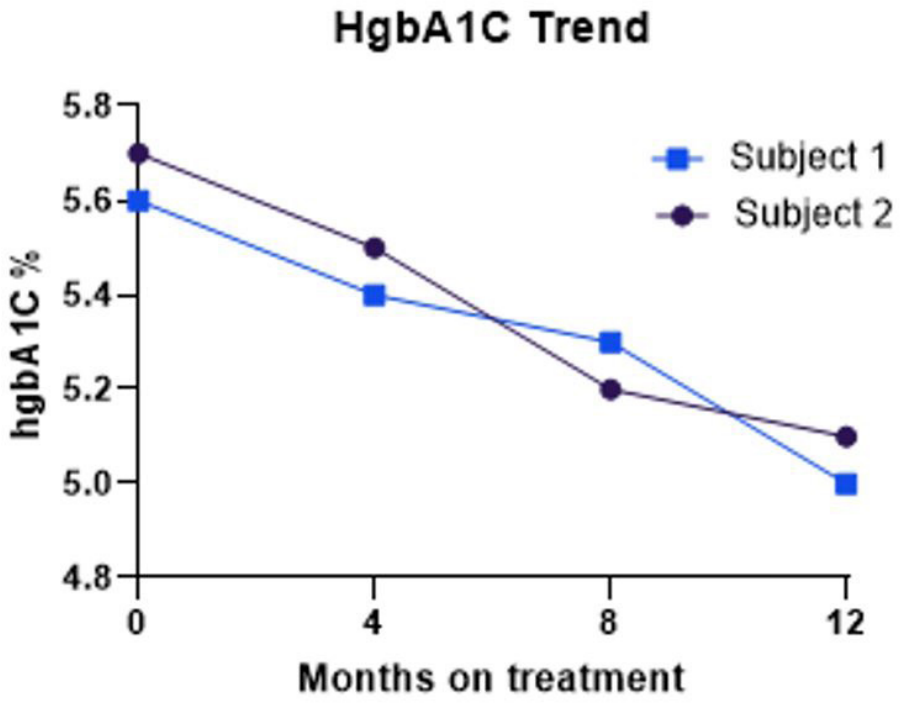

Figure 1: Hemoglobin A1C Trend on Elexacaftor/Tezacaftor/Ivacaftor

Discussion

ELX/TEZ/IVA is a combination CFTR modulator and consists of two CFTR correctors, Elexacaftor and Tezacaftor, which improve CFTR protein processing and tracking, and Ivacaftor which is a CFTR potentiator which enhances channel gating [12]. The efficacy and safety of this triple combination therapy has been established in patients with CF ≥6 years of age with at least one *F508del-CFTR* allele. These studies showed that treatment with ELX/TEZ/IVA led to improvements in lung function, respiratory symptoms, sweat chloride concentrations and BMI for age [8-10]. However, prior studies evaluating the impact of CFTR modulators on glycemic control in those with CFRD have shown mixed results.

Small promising studies have shown improvement in CFRD using Ivacaftor, a CFTR potentiator [13, 14]. Recently, triple therapy ELX/TEZ/IVA demonstrated an improvement in time-in-range in adults with and without CFRD, without changes in total daily insulin in the latter group [15]. Our retrospective chart review study describes two pediatric patients with CFRD on insulin therapy who found improvement in glycemic control while on ELX/TEZ/IVA for one year. Patient A was able to come off insulin while patient B's insulin requirements largely remained the same. Both had an approximate 10% reduction in hemoglobin A1C after one year on treatment. Most notable is that improvements in glycemic control occurred despite increased weight gain, which would typically raise insulin requirements. Both patients had improvements in their CF status as they did not have any CF exacerbations while on ELX/TEZ/IVA treatment for the duration of the study.

Patients with CF who develop CFRD have reduced lung function and nutritional status, and higher mortality than those without CFRD [15]. Understanding the pathophysiology of CFRD is critical for effective treatment of disease. Although there have been many studies investigating the cause of CFRD, the exact mechanism is still unclear. Previous studies have shown reduction in beta cell mass and islet size in CF as a result of pancreatic fibrosis [5,17,18]. This also seems to occur early in the disease process since isolated pancreatic tissue from young children affected with CF and animal models of CF already have reductions in beta cell area prior to the onset of CFRD [19,20]. Separately, while still a matter of debate, pancreatic β-cells have minimal CFTR gene expression implying that intrinsic β-cell defects are less likely to be causing insulin secretion defects [21,22]. CF is also associated with islet inflammation, where higher levels of IL-1β and other inflammatory cytokines were seen in patients with CF and CFRD compared to age-matched controls without CF [23]. Collectively, these data imply that a defect in insulin release is multifactorial and stems from a reduction in beta cell mass as well as intraislet inflammation.

The primary limitations of this study were the retrospective nature, limited sample size, and use of hemoglobin A1C as surrogate marker of beta-cell function and insulin secretion. While the diagnosis of CFRD was made based on oral glucose tolerance test (OGTT), patients were not serially followed with OGTTs. It is recognized that hemoglobin A1C can be falsely low in patients with CFRD due to increased red blood cell turnover. To optimize our study of insulin secretion, we should perform serial glucose tolerance tests rather than rely on hemoglobin A1c values. Insulin levels should be presented as area under the curve (AUC). Further studies should be undertaken with a larger sample size and use of dynamic tests of insulin secretion. This study also focused on patients with CFRD on insulin therapy but we would expand the study to include those without CFRD in order to examine effects of ELX/TEZ/IVA on the development of CFRD.

In these two patients with cystic fibrosis-related diabetes, treatment with ELX/TEZ/IVA led to an improvement in hemoglobin A1C after one year on treatment, not associated with increased insulin utilization. The mechanism by which this occurs still remains elusive but may be related to improved beta-cell sensitivity and reduced pancreatic inflammation from triple CFTR modulation. To our knowledge, this is the first case series demonstrating the positive effects of Elexacaftor/Tezacaftor/Ivacaftor in glycemic control in pediatric patients.

Conclusions

New CF modulator therapies have demonstrated clear improvement in lung function though their effect on CF-related diabetes has not been as well delineated. To our knowledge, this is the first case series to demonstrate the positive effects of Elexacaftor/Tezacaftor/Ivacaftor on glycemic control in pediatric patients with CFRD on insulin therapy. More studies will need to be undertaken to demonstrate how CFTR modulators affect progression of CFRD and if early initiation at a younger age can prevent CFRD.

Author Contributions

MS, MKE and RB designed research study. MS conducted chart review. MS, MKE and RB analyzed data. MS, MKE and RB wrote the manuscript. All authors have read and approved the final manuscript.

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