OLGU SUNUMU CASE REPORT

DOI: 10.5336/archlung.2022-92967

The First Cystic Fibrosis Case Treated with Elexacaftor/ Tezacaftor/Ivacaftor in Türkiye

Türkiye'de Elexacaftor/Tezacaftor/Ivacaftor ile Tedavi Edilen İlk Kistik Fibrozis Olgusu

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ABSTRACT The recovery process and quality of life with treatment of elexacaftor/tezacaftor/ivacaftor we observed in 32-year-old male cystic fibrosis (CF) patient who showed signs of advanced disease are quite promising. Although our case was receiving 8 L/min oxygen his saturation was still around 80%. Patient was started on triple combination CF transmembrane regulator (CFTR). In the follow-up, the shortness of breath with effort decreased. He became much easier to do his daily work. The patient, who was 51.3 kg at the beginning of the treatment, became 71 kg after 1 year. While forced vital capacity (FVC) was 29%, forced expiratory volume in one second (FEV1) 19% at beginning of treatment, FVC was 62%, FEV_1 37% after 1 year of treatment. The SO_2 value in room air was 94% after 1 year of treatment. Overcoming the high price, reimbursement problems experienced in all countries will increase using of CFTR modulators by the patients with having compatible genetic characteristics

Keywords: Cystic fibrosis; elexacaftor; tezacaftor; ivacaftor

ÖZET İlerlemiş hastalık belirtileri gösteren 32 yaşındaki erkek kistik fibrozis (KF) hastasında gözlemlediğimiz elexacaftor/tezacaftor/ivacaftor tedavisi ile iyileşme süreci ve yaşam kalitesi oldukça umut vericidir. Olgumuz 8 L/dk oksijen almasına rağmen saturasyonu %80 civarındaydı. Hastaya üçlü kombinasyon KF transmembran regülatör (KFTR) başlandı. İzlemde eforla nefes darlığı azaldı. Günlük işlerini yapmak çok daha kolay hâle geldi. Tedavinin başında 51,3 kg olan hasta 1 yıl sonra 71 kg oldu. Tedavi başlangıcında zorlu vital kapasite [forced vital capacity (FVC)] %29, bir saniyedeki zorlu ekspiratuar hacim [forced expiratory volume in one second (FEV_1)] %19 iken tedaviden 1 yıl sonra FVC %62, FEV_1 %37 idi. Oda havasındaki SO_2 değeri 1 yıllık tedaviden sonra %94 idi. Tüm ülkelerde yaşanan yüksek fiyat ve geri ödeme sorunlarının aşılması, uyumlu genetik özelliklere sahip hastalarda KFTR modülatörlerinin kullanımını artıracaktır.

Anahtar Kelimeler: Kistik fibrozis; elexafaktor; tezafaktor; ivafaktor

Cystic fibrosis (CF) is an autosomal recessive inherited disease. The mutation in the CF transmembrane regulator (CFTR) gene, located on the 7th chromosome, plays a role in the formation of the disease. The principal function of the CFTR protein is transporting of chloride and bicarbonate ions across epithelial surfaces. In the airway, CFTR also functions as a negative regulator of the epithelial Na+ channel. Dysfunctional CFTR impairs mucociliary clearance and is associated with persistent airway infection and unresolved inflammation.[1]

In recent years, there have been very important developments in the treatment of CF. ELX/TEZ/IVA combined drugs were approved by Food and Drug

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Peer review under responsibility of Turkiye Klinikleri Archives of Lung.

Received: 19 Aug 2022 ***Received in revised form:*** 24 Oct 2022 ***Accepted:*** 24 Oct 2022 ***Available online:*** 01 Nov 2022

Administration in 2019 for CF patients over 12 years of age and having at least one F508del mutation. These drugs have been shown to increase pulmonary function tests, gain weight in patients, reduce lung infections, and reduce the chlorine concentration in the sweat test. Although it is a newly used treatment and there are not many studies, available data shows that the best results are obtained with the use of the ELX/TEZ/IVA triplet.[2] However, the CFTR modulators have a beneficial effect not only in mild to moderate CF, but also in individuals with advanced pulmonary disease [forced expiratory volume in one second (FEV_1) <40%], including candidates for lung transplantation.[3]

The presented case is CF with advanced pulmonary disease and is the first patient in Türkiye to be treated with ELX/TEZ/IVA.

CASE REPORT

A 32-year-old male patient, was diagnosed with CF at the age of 8 months with gastrointestinal symptom symptoms. Pulmonary symptoms occurred when he was 4 years old. His the most common symptoms in childhood were cough and expectoration. Moderate anorexia was always present and his weight was in 50% percentile. In the periods when purulent sputum was produced with fever, intravenous (IV) antibiotic treatments were also started. He had frequent hospitalizations 2 or 3 times in a year. In the last 10 years, decreased respiratory functions and shortness of breath started. He couldn't sleep at night because of coughing. He also had hemoptysis.

He was admitted to our clinic with signs of infection and respiratory failure. The patient was cachectic and his accessory respiratory muscles were working. On auscultation, there were coarse rhonchi and decreased breath sounds. An informed consent form was obtained from the patient. In the Thorax computed tomography widespread cystic structures, bronchiectasis, bullae, and peribrochial thickenings were seen.

He was taken to the intensive care unit because his saturation was still around 80% while taking 8-10 L/dak O_2 treatment. noninvasive mechanical ventilation (NIMV) and meropenem, Piperacilin/tazobactam, levofloxacin treatment was applied. Since he had advanced CF disease, he was enrolled in the lung transplant program.

The patient had received creon for 30 years, ursodeocycholic acid for 20 years, dornase alfa for 15 years, and inhaler tobramycin and colistin for 20 years. Although he used broad-spectrum antipseudomonal antibiotics at least 4-5 times a year, *Pseudomonas aeruginosa* was grossly growing in his cultures. He was in O_2 therapy at home.

Our patient's CF mutation was heterozygous for F508del and the pulmonary disease was in advanced stage. ELX/TEZ/IVA two tablets in the morning and one tablet IVA 150 mg after fat contained dinner was administered to the patient. The patient's daily intense cough and sputum production decreased from the second day of the drug. In the follow-up, the shortness of breath with effort decreased and he became much easier to do his daily work. He began to sleep uninterrupted and cough-free at night. He gained weight and C-reactive protein (CRP) decreased to normal values. The patient used a home spirometer for pulmonary function tests (Spirohome personel). The improvements in Pulmonary Function Test are seen in Table 1. No side effects were observed during the treatment of the patient in the controls. Liver and kidney function tests were normal. There was an increase in creatin kinase (CK) (normal 205 IU/L) after treatment. Only on the 3rd month it was mildly elevated. There is a gradual decrease in the number of drugs during the treatment period of the patient. In addition, he no longer needed NIMV and daytime O_2 therapy (Table 1).

DISCUSSION

CFTR modulators seems to be changing treatment managements of CF and the effects of them in clinical trials have focused on pulmonary function and quality of life measures, which are important clinical outcomes and are also required for regulatory approval.[2,3] According to the function of the specific mutations the phenotypic expression of disease varies widely. The CFTR2 database lists more than 2,000 different mutations in the *CFTR* gene with potential

TABLE 1: The clinical and labarotory findings and usage of the medicines of the patient before and after the treatment with elexacaftor/tezacaftor/ivacaftor.

	Just before CFTR	After CFTR treament					
Findings	**treament**	**1st month**	**2nd month**	**3rd month**	**7th month**	**9th month**	**1 years**
Weight (kg)	51.1	57	62.5	65	67	69	71
BMI	17	18.8	20.6	21.5	22.1	22.8	23.5
FVC %	29	44	44	47	52	58	62
FEV_1 %	19	28	30	31	33	33	37
FEV_1/FVC	53	52	55	54	48	46	48
PEF %	58	84	86	96	86	106	94
FEF 25-75%	6	6	8	9	9	8	10
O_2 saturation %	With 8 L/ min O2 93%	With 8 L/ min O2 90%	Room air 90%	Room air 91%	Room air 93%	Room air 94%	Room air 94%
CRP (mg/L)	45.8	1.59	1.54	1.9	1.2	NA	3.1
Sputum culture	*P. aeruginosa*	*P. aeruginosa*	*P. aeruginosa*	*P. aeruginosa*	*P. aeruginosa*	*NA*	*P. aeruginosa*
CK (IU/L)	41	144	128	223	181	NA	205
Treatments							
Creon	+	+	+	+	+	+	+
Ursodeocyh olic acid	+	+	+	+	+	+	+
Dornase alfa	+	-	-	-	-	-	-
Dornase alfa	+	-	-	-	-	-	-
Azithromycin 500 mg^3 times in a week	+	+	+	+	+	-	-
Inhaler tobramcycin	+	-	-	-	-	-	-
Inhaler colistin	+	+	+	+	+	+	+
Salmeterol + fluticasone inhaler (100 mikro gr)	+	+	+	+	+	+	+
Piperacilin/tazobactam	+	-	-	-	-	-	-
Amikasin	+	-	-	-	-	-	-
O2 treatment	+	+	+	+	Only at night	Only at night	Only at night
NIVM	+	+	-	-	-	-	-

CFTR: Cystic fibrosis transmembrane regulator; BMI: Body mass index; FVC: Forced vital capacity; FEV1: Forced expiratory volume in one second; PEF: Peak expiratory flow; FEF: Forced expiratory flow; CRP: C-reactive protein; CK: Creatin kinase; NIVM: Noninvasive mechanic ventilation.

to cause disease. The most common pathogenic mutation is F508del (also noted as delta F508, delF508, p.Phe508del), which describe the deletion of three DNA bases coding for the 508th amino acid residue phenylalanine. Hangül et al. found F508del mutation as 17/30 in the central region of Türkiye.[4] It has shown that other research were found the relation between severe CF participants and disease prognosis and genetic mutation in central region of Anatolia in Türkiye.[5,6]

The effects of CFTR modulators on inflammation in general and existing published research is mainly limited to the effects of IVA. Hisert et al. demonstrated that sputum inflammatory markers decreased significantly in the first week of IVA treatment in patients with G551D mutations.[7] Some studies have shown reductions in lung clearance index with CFTR modulation and this indicates reduced mucus plugging and improved air trapping.[8,9]

The CFTR modulators have a beneficial effect not only in individuals with mild to moderate CF, but also in individuals with advanced pulmonary disease, including candidates for lung transplantation. This beneficial impact was clearly demonstrated by randomised controlled trials as well as in open-label studies.[9-12] There was an increase of about 40% in the

respiratory functions of our patient. He got rid of dependence on O_2 treatment, did not have an attack for a year, and did not need IV treatment. Our patient described changes in his life as unbelievable and miraculous like the patients in the study done by Martin et al. about the patient perspectives following initiation of ELX/TEZ/IVA in people with CF and advanced lung disease.[13] He had increase in mobility and muscle strenght with weight gain.

Side effects of ELX/TEV/IVA that were reported are biliary colic, testicular pain, distal intestinal obstruction syndrome, CK elevation.[14] Our patient had no adverse effect during the treatment except CK elevation. The moderate increase in CK may be related to the increase in physical activity and exercise capacity after the treatment.

The existing data that we have summarised in our patient showed that ELX/TEZ/IVA is highly effective in advanced disease. Results of real life studies will show new perspectives for these patients. The problems we experienced regarding the use of inhaler antibiotics in our patient with *P. aeruginosa* colonization may become clear. Overcoming the high price and reimbursement problems experienced in all countries will increase the usage of the CFTR modulators by the patients with having compatible genetic characteristics and more people can have life-changing benefit in the future.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Hatice Canan Hasanoğlu, Hatice Kılıç;* ***Design:*** *Hatice Canan Hasanoğlu, Hatice Kılıç;* ***Control/Supervision:*** *Hatice Canan Hasanoğlu;* ***Data Collection and/or Processing:*** *Habibe Hezer, Fatma Sinem Cander;* ***Analysis and/or Interpretation:*** *Hatice Canan Hasanoğlu, Hatice Kılıç;* ***Literature Review:*** *Habibe Hezer, Fatma Sinem Cander, Hatice Canan Hasanoğlu;* ***Writing the Article:*** *Hatice Canan Hasanoğlu, Hatice Kılıç;* ***Critical Review:*** *Hatice Canan Hasanoğlu, Hatice Kılıç;* ***Materials:*** *Habibe Hezer, Fatma Sinem Cander.*

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