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CASE REPORT

Elexacaftor/tezacaftor/ivacaftor as rescue therapy in a patient with the cystic fibrosis genotype *F508DEL/G1244E*

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Abstract

Elexacaftor/tezacaftor/ivacaftor (ETI) is a cystic fibrosis (CF) transmembrane regulator (CFTR) modulator. It is known to be efficacious in stable patients with severe pneumopathy, but there are few data concerning its effectiveness during acute exacerbations. We here describe its use in a woman with CF and respiratory failure.

KEYWORDS

genetics, respiratory medicine

1 | INTRODUCTION

Elexacaftor/tezacaftor/ivacaftor (ETI) is a cystic fibrosis (CF) transmembrane conductance regulator modulator indicated for the treatment of people with CF (pwCF) aged ≥6 years who have at least one *F508del* (*F*) mutation or (only in the USA) any of 177 other mutations that have been shown to be responsive *in vitro*. Clinical trials have demonstrated that it leads to significant and sustained improvement in lung function, nutrition, and the quality of life of pwCF with two *F* (*F*/*F*), or one *F* and one minimal function mutation (*F*/*MF*), or one gating mutation (*F*/*G*), or one residual function mutation (*F*/*RF*).[1-3]

We here describe a case demonstrating the effectiveness of ETI as rescue therapy in a woman with the CF genotype *F508del*/*G1244E* (genotype *F*/*G*) and advanced lung disease.

2 | CASE REPORT

FG is now a 50-year-old woman who was diagnosed as having CF at the age of 23.3 years. Her CF was characterized by severe lung disease (37% of predicted forced expiratory volume in the 1st second [$pFEV_1$], resting SaO_2 95% on 1 L/min of oxygen via a nasal cannula), chronic *Burkholderia cenocepacia* (*Bcc*) infection, pancreatic insufficiency, and CF-related diabetes mellitus. She started treatment with the potentiator *ivacaftor* at the age of 45 years and, during the first year of treatment, gained 3.2 kg in weight, experienced fewer pulmonary exacerbations (PEx), and required less antibiotic therapy; furthermore, her $pFEV_1$ increased from 33% to 41%, and her sweat chloride (swCl) level was 37 mmol/l. Three years later, her health status worsened (weight loss, increased PEx, a progressive decline in $pFEV_1$ to 27%, and a resting oxygen requirement of 5 L/min via a nasal cannula), but *Bcc* colonization excluded a lung transplantation.

In November 2020, she was hospitalized for 24 days because of PEx, and in December of the same year, she was re-hospitalized because of another severe PEx. Upon re-admission, she was febrile, dyspneic, and suffering. Her C-reactive protein level was 43.7 mg/L (normal <5 mg/L); arterial blood gas (ABG) analysis showed a pH of 7.45, PCO_2 70 mmHg, PO_2 61 mmHg, and HCO_3 48.7 mEq/L,

with 88% O_2 saturation on 10 L/min of oxygen via a nasal cannula. Bi-level positive airway pressure (BiPAP) ventilation was started with an FiO_2 of 50% in order to obtain 92% O_2 saturation. A chest X-ray showed diffuse bronchiectasis and fibrotic changes with infiltrates in all lung lobes. Blood cultures and a molecular SARS-CoV-2 swab test were negative, but a sputum culture was positive for *Bcc*. Intravenous (i.v.) *meropenem* and *ceftazidime*, i.v. *methylprednisolone*, and intensive airway clearance were started in addition to *ivacaftor* and standard therapies. During the first two weeks, her respiration slightly improved but, as she remained BiPAP dependent, an urgent request for individual compassionate access to ETI treatment was sent to Vertex Pharmaceutics.

She started ETI on hospitalization day 22, when she was unable to perform spirometry and had a body mass index (BMI) of 22.18 kg/m^2. Within a few days, her thick and sticky mucus became more fluid and abundant, and her respiration improved. *Methylprednisolone* was tapered and discontinued, and she was discharged 19 days after starting ETI. Her discharge ABG analysis showed a pH of 7.46, PCO_2 61 mmHg, PO_2 58 mmHg, and HCO_3 39.6 mEq/L with 91.6% O_2 saturation on 6 L/min of oxygen via a nasal cannula. She required less time on BiPAP and, during the day, received 5 L/min of oxygen via a nasal cannula. Spirometry showing her forced vital capacity (FVC) was 0.76 L (29.02% of predicted) and FEV_1 0.65 L (30.47% of predicted). Her mucus became increasingly transparent and scarce.

Three months after starting ETI, her oxygen requirement had decreased; ABG analysis showed a pH of 7.47, PCO_2 45 mmHg, PO_2 60 mm Hg, and HCO_3 32.8 mEq/L with 92.2% O_2 saturation on 4 L/min oxygen via a nasal cannula; her FVC was 0.92 L (35.18% of predicted) and FEV_1 0.73 L (34.29% of predicted), and swCl was 31 mmol/L. The respiratory domain of the revised CF Questionnaire (CFQ-R) increased by 11 points in comparison with the discharge value (minimum important difference 4). Her BMI was 23.63 kg/m^2 (a weight gain of 3.0 kg). The walked distance in 6 minutes increased from 360 m at discharge to 415 m after the three months of treatment (Table 1). She had not required antibiotic therapy during the previous three months, and no treatment-related adverse events were reported.

TABLE 1 Comparison of change over treatment period with elexacaftor/tezacaftor/ivacaftor.

Characteristics	Baseline*	After 3 weeks	After 12 weeks
Sweat chloride (mmol/L)	37	n.a.	31
$ppFEV_1$	26.41	30.47	34.29
BMI (Kg/m^2)	22.18	23.15	23.63
6MWT (m)	n.a.	360	415
$PaCO_2$	70	61	45
CFQ-R respiratory domain	50.0	72.2	83.3

Abbreviations: 6MWT, 6-minute walking test; BMI, body mass index; n.a, not available; $PaCO_2$, Partial pressure of carbon dioxide in the arterial blood; $ppFEV_1$, percentage of predicted forced expiratory volume in the 1st second.
*treatment with ivacaftor; 12 weeks before hospitalization

3 | DISCUSSION

The clinical trials of ETI in pwCF who were *F*/*F* or heterozygous for *F* and *MF*, *RF*, or *G* involved patients with mild-moderate lung disease,[1-3] but improvements have also been obtained in pwCF with advanced lung disease, and these have often obviated the need for lung transplantation.[4-8]

Our patient had an *F*/*G* genotype and had been previously treated with *ivacaftor* but, after an initial improvement, experienced rapid disease progression (as has been previously described in *ivacaftor*-treated adults with *G* mutations),[9] possibly aggravated by *Bcc* colonization.[10] During her subsequent hospitalization, she did not improve significantly until ETI was administered, and, as all her other treatments remained unchanged, this suggests it played a role in her recovery. Furthermore, her lung disease continued to improve after she was discharged: There was no recurrence of PEx, no need for antibiotics, and her lung function and ABG parameters improved.

An *ex vivo* study has recently shown that *elexacaftor* is at least an additive co-potentiator with *ivacaftor* for *F* and two gating mutants (*G551D* and *G1244E*), thus increasing its functional effectiveness.[11] Other studies have shown that *ex vivo* models, based on nasal brushing, have a high predictive power of the pharmacological response of CF patients, even regardless of the patient's genotype.[12-14] Our case highlights the potential of ETI in patients with severe CF-related lung disease, particularly those for whom lung transplantation is contraindicated. It seems to stabilize and partially reverse progressive lung disease even in the presence of risk factors for an adverse prognosis such as a requirement for supplementary oxygen, complex *Bcc* infection, frequent exacerbations, CF-related diabetes, and female sex.[10]

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CONFLICT OF INTEREST

DS has been a Principal Investigator of Vertex trials and has received fees from the same company for speaking engagements. CC, MD, GM, and DP have no competing interests to declare.

AUTHOR CONTRIBUTIONS

DS: involved in conceptualization, writing the original draft, supervision. CC: involved in conceptualization, investigation, formal analysis, writing the original draft. MD and GM: involved in investigation, formal analysis, manuscript review & editing. DP: involved in investigation, formal analysis.

ETHICAL APPROVAL

The collection of data for the patient was an integral part of the approval by the local Ethic Committee (Ethic Committee of Region Basilicata on December 28, 2020) of the compassionate use program.

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