**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

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**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 [pFEV₁], resting SaO₂ 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 pFEV₁ 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 pFEV₁ 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 rehospitalized 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, PCO₂ 70 mmHg, PO₂ 61 mmHg, and HCO₃ 48.7 mEq/L.
with 88% \( \text{O}_2 \) 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% \( \text{O}_2 \) 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 Pharmaceuticals.

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% \( \text{O}_2 \) 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 mmHg, and HCO\(_3\) 32.8 mEq/L with 92.2% \( \text{O}_2 \) 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.

### 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 \textit{ex vivo} study has recently shown that \textit{elexacaftor} is at least an additive co-potentiator with ivacaftor for \( F \) and two gating mutants (\textit{G551D} and \textit{G1244E}), thus increasing its functional effectiveness.\(^11\) Other studies have shown that \textit{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 \textit{Bcc} infection, frequent exacerbations, CF-related diabetes, and female sex.\(^10\)

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### 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.
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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