Efficacy of elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease

To the Editor:

Cystic fibrosis (CF) is an autosomal recessive disorder which results from mutations in the cystic fibrosis transmembrane regulator (CFTR) gene encoding the CFTR protein. Defects in the production or function of this protein result in multiorgan dysfunction via altered conductance of chloride and bicarbonate across epithelial cell surfaces. Traditionally, the treatment of CF has focused on management of downstream organ dysfunction and symptoms caused by reduced function of this protein. However, with the recent advent of CFTR modulators, this treatment strategy has changed to targeting the primary cause of CF. CFTR modulators are a class of drugs which act to improve production, processing and function of the defective CFTR protein. Since the US Food and Drug Administration (FDA) and European Medicines Agency approved the use of ivacaftor in 2012, followed by the approval of lumacaftor/ivacaftor and tezacaftor/ivacaftor, CFTR protein modulation has revolutionised the management of CF, and has allowed the disease to be treated at a molecular level [1, 2].

In 2019, elexacaftor was approved by the FDA as part of the triple therapy in combination with tezacaftor and ivacaftor (ELX/TEZ/IVA). ELX/TEZ/IVA has delivered transformative improvements to the lives of people with mild to moderate cystic fibrosis who are homozygous for the Phe508del CFTR mutation [3] or who are heterozygous for Phe508del in combination with another minimal function CFTR mutation [4], i.e. a mutation which produces little or no functioning CFTR protein. The safety and efficacy of this drug combination have been established for these groups in large multicentre phase 3 trials which enrolled subjects with baseline forced expiratory volume in 1 s (FEV1) of 40–90% of predicted. Within 4 weeks of commencement of treatment, both heterozygotes and homozygotes exhibited statistically and clinically significant improvements in FEV1 % pred, sweat chloride concentration (SwCl), body mass index (BMI), and CF quality of life scores. Though previously approved CFTR modulators have been shown to improve outcomes in individuals with CF and more advanced pulmonary disease, the effects of ELX/TEZ/IVA on patients living with more severe lung disease has not yet been fully assessed [5].

The Irish National Referral Centre for Adult Cystic Fibrosis is based in St Vincent’s University Hospital, an 836-bed academic health centre in Dublin, Ireland. Since December 2019, patients of this institution who fulfilled inclusion criteria were enrolled on a managed access programme to receive ELX/TEZ/IVA for treatment of their CF. Patients homozygous for Phe508del or heterozygous for Phe508del with a second minimal function CFTR mutation were included if they had severe lung disease (FEV1 <40% pred) and/or they were on an active lung transplantation list. The severity of disease for these patients was greater than that in the phase 3 trials where FEV1 was on average 62% pred.

Between December 2019 and July 2020, 14 CF patients were started on ELX/TEZ/IVA. We present a comparison of their baseline clinical data prior to commencement with data collected after starting this medication. Patients were enrolled as part of a managed access programme and, as a result, the date of commencement of therapy varied, as did their follow up period. SwCl, FEV1 (% pred), BMI (kg·m$^{-2}$), number of pulmonary infective exacerbations, days spent on intravenous antibiotics, and the presence of CF comorbidities (CF-related diabetes (CFRD) and CF-related liver disease (CFLD)) were collected using retrospective chart review. The most recently available measurement for these clinical parameters prior to drug commencement was used and infective exacerbation frequency was calculated from the past...
12 months of data and expressed as exacerbations per month. Paired t-test was used to compare parametric data and chi-squared test was used for categorical variables. A two-sided p-value <0.05 was considered significant. This study was approved by St. Vincent’s University Hospital research and ethics committee.

Of the 14 patients included in this analysis, nine (64%) were female. All received ELX/TEZ/IVA due to the presence of severe lung disease and two patients were on the active lung transplantation list. Eight were homozygous for Phe508del; six had a combination of Phe508del and a second minimal function CFTR mutation. All eight homozygous for Phe508del were previously on CFTR modulator therapy. Average age was 34.4 years (range 19–46 years). Mean±SD follow-up was 4.9±1.94 months, (range 1–8 months). Mean FEV₁ prior to commencement was 27.3±7.3% pred (range 15–38% pred). Nine (64%) had a diagnosis of CFRD, six (43%) had been diagnosed with CFLD, and all were pancreatic insufficient. One of the patients required dose-reduction due to Child–Pugh Score B liver disease. Patients had a median of three hospitalisations in the year prior to commencing this drug (interquartile range 2.0–4.3), during which the total median duration of intravenous treatment was 77 days (interquartile range 43.5–137.5 days). Mean SwCl was 104.9±15.04 mmol·L⁻¹ (range 78–134 mmol·L⁻¹); mean BMI was 20.7±3.6 kg·m⁻² (range 15.8–26.1 kg·m⁻²).

Follow-up measurement dates varied with mean repeat FEV₁ at 26.4±4.2 days, mean BMI at 62±35 days and mean SwCl at 64±84 days after ELX/TEZ/IVA initiation. After treatment with ELX/TEX/IVA, FEV₁ improved (27.3±7.3% pred versus 36.3±16.5% pred; p<0.0001). BMI also improved (20.7±3.6 versus 22.1±3.4 kg·m⁻²; p<0.0001). Sweat chloride results were only available for 11 patients, mainly due to insufficient sweat volume despite multiple attempts, but also revealed significant improvement (104.9±15.04 versus 53.6±23.3 mmol·L⁻¹; p<0.0001). Infective exacerbations requiring hospitalisation reduced in frequency (0.28±0.17 exacerbations per month in 12 months prior versus 0.04±0.07 exacerbations per month during follow-up period of 4.9 months; p<0.001). ELX/TEX/IVA treatment was generally well tolerated. One patient was admitted with distal intestinal obstruction syndrome and a second patient required temporary drug interruption due to acute kidney injury which was not related to the study drug. There were no other significant adverse effects. Figure 1 illustrates the change in FEV₁, BMI, SwCl and infective hospitalisation frequency from baseline to post-treatment status with the median length of follow-up included.

**FIGURE 1** Comparison of outcome measures pre- and post-initiation of elexacaftor/tezacaftor/vacaftor combination therapy (ELX/TEZ/IVA). Mean figures indicated with horizontal bars. 

- a) Comparison of forced expiratory volume in 1 s (FEV₁) % of predicted pre- and post-drug commencement, mean±SD follow-up 26.4±4.2 days. 
- b) Comparison of body mass index (BMI) pre- and post-drug commencement, mean±SD follow-up 61.85±35.2 days. 
- c) Comparison of sweat chloride concentration [SwCl] pre- and post-drug commencement, mean±SD follow-up 64.18±84.43 days. 
- d) Comparison of monthly rate of infective exacerbations pre- and post-drug commencement, mean±SD follow-up 4.9±1.94 months.

https://doi.org/10.1183/13993003.03079-2020 2
In this observational study, ELX/TEZ/IVA improves clinical outcomes for people with advanced CF lung disease. All parameters measured exhibited significant improvement, some within the first 5 months of treatment, with similar improvements to that observed in the pivotal trials. This cohort differed from those of the large phase 3 trials as these patients have more advanced disease with lower FEV$_1$ % pred and BMI, and a higher incidence of pulmonary infective exacerbations requiring hospitalisation and intravenous antibiotic use prior to starting ELX/TEZ/IVA. While it is possible that some of the reduction observed in use of intravenous antibiotics and hospitalisations may be attributable to the effect of seasonal variation, or possibly confounded further by the coronavirus disease 2019 pandemic and related lockdown measures, we feel that the improvement in exacerbation outcomes remains significant for this group. The main limitation of this study is that this is a cohort from a single centre who were administered this unblinded treatment and the results could be influenced by selection bias. Another limitation is the variation in follow-up intervals for each parameter assessed.

The role for previously approved CFTR modulators in CF patients with advanced lung disease has been well established. Ivacafor has been shown to significantly improve lung function and reduce exacerbation rate in patients carrying the G551D CFTR mutation who had baseline FEV$_1$ <40% pred or who were awaiting lung transplantation [6–8]. The seminal phase III trial to investigate this medication found that FEV$_1$ % pred improved by 10.6% and that infective exacerbation frequency decreased by up to 55% [9]. Lumacaftor/ivacafor was assessed in groups of various baseline lung function and though improvements in FEV$_1$ % pred (4.3% to 6.7% improvement) were more modest, there was a clinically and statistically significant reduction in the frequency of exacerbations requiring intravenous therapy across all groups (30–39% reduction) [10]. Recognising the need for assessment of the efficacy of new modulator drugs in patients with severe disease, the large phase III trials of tezacaftor/ivacafor included sub-analyses which showed similar modest improvements in lung function (6.8% improvement) and significant reductions in exacerbation frequency (35% reduction) in those with lower lung function [11, 12]. This was also seen in the phase III trial of ELX/TEZ/IVA, in which MIDDLETON [4] conducted a subgroup analysis on members of the cohort whose lung function fell below 40% between enrolment and randomisation (8.4% of the group). In this cohort with more advanced lung disease, the absolute increase in ppFEV$_1$, % pred (15.2% increase) was comparable to the overall group (13.8% increase) at 4 weeks. The results seen in our study were more modest in magnitude than that of the phase III trial and this potentially relates to the presence of more severe lung disease at the outset, which may be less reversible, but larger studies in patients with FEV$_1$ <30% pred are needed.

This study shows that ELX/TEZ/IVA improves multiple outcome measures in a small cohort of patients with advanced CF lung disease attending a single centre and that these improvements are similar to those seen in patients with milder disease. Most significant were the reduction in requirement for intravenous antibiotic therapy as well as improvements in lung function and sweat chloride. These results were seen in both patients exposed to previous modulator therapies and in those who were CFTR modulator-naïve. There were few significant adverse events. This therapy is expected to improve the disease trajectory for many CF patients with at least one Phe508del mutation and this expectation should also apply to those groups with more advanced disease.

Kate M. O’Shea, Orla M. O’Carroll, Catherine Carroll, Brenda Grogan, Anna Connolly, Lynda O’Shaughnessy, Trevor T. Nicholson, Charles G. Gallagher and Edward F. McKone

1School of Medicine, University College Dublin, Dublin, Ireland. 2Dept of Respiratory Medicine, St Vincent’s University Hospital, Dublin, Ireland. 3Equal contributions.

Correspondence: Edward F. McKone, Dept of Respiratory Medicine, St. Vincent’s University Hospital, Elm Park, Dublin 4, Ireland. E-mail: emckone@svhg.ie

Received: 9 Aug 2020 | Accepted: 6 Oct 2020

Conflict of interest: K.M. O’Shea has nothing to disclose. O.M. O’Carroll has nothing to disclose. C. Carroll has nothing to disclose. B. Grogan has nothing to disclose. A. Connolly has nothing to disclose. L. O’Shaughnessy has nothing to disclose. T. Nicholson has nothing to disclose. C.G. Gallagher has nothing to disclose. E.F. McKone reports grants and personal fees from Vertex Pharmaceuticals, during the conduct of the study; personal fees from Proteostasis, other than from A Menarini, grants from Gilead, outside the submitted work.

References


Copyright ©ERS 2021