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Elexacaftor–Tezacaftor–Ivacaftor improves exercise capacity in adolescents with cystic fibrosis

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Abstract

Objective: Elexacaftor/Tezacaftor/Ivacaftor is a cystic fibrosis transmembrane conductance regulator (CFTR) modulator with the potential to improve exercise capacity. This case series of three adolescents with CF aimed to investigate whether 6 weeks treatment with Elexacaftor/Tezacaftor/Ivacaftor could improve exercise capacity in CFTR modulator naive adolescents with CF.

Methods: Three adolescents (14.0 ± 1.4 years) with CF (FEV_1% predicted: 62.5 ± 17.1; F508del/F508del genotype) completed an exhaustive maximal cardiopulmonary exercise test on a cycle ergometer to determine peak oxygen uptake ($\dot{V}O_{2peak}$) and measure changes in gas exchange and ventilation during exercise at 6 weeks. We also analyzed wrist-worn device-based physical activity (PA) data in two of the three cases. Validated acceleration thresholds were used to quantify time spent in each PA intensity category.

Results: Clinically meaningful improvements in $\dot{V}O_{2peak}$ were observed in all three cases (+17.6%, +52.4%, and +32.9%, respectively), with improvements greatest in those with more severe lung disease and lower fitness at baseline. Although lung function increased in all cases, inconsistent changes in markers of ventilatory and peripheral muscle efficiency likely suggest different mechanisms of improvement in this case group of adolescents with CF. Device-based analysis of PA was variable, with one case increasing and one case decreasing.

Conclusion: In this case series, we have observed, for the first time, improvements in exercise capacity following 6 weeks of treatment with Elexacaftor/Tezacaftor/Ivacaftor. Improvements were greatest in the presence of more severe CF lung disease and lower aerobic fitness at baseline. The mechanism(s) responsible for these changes warrant further investigation in larger trials.

KEYWORDS

cardiorespiratory fitness, CFTR modulator therapy, cystic fibrosis-transmembrane conductance regulator, elexacaftor–tezacaftor–Iacaftor, peak oxygen uptake, respiratory disease

1 | INTRODUCTION

The treatment of cystic fibrosis (CF) has been revolutionized with the introduction of CF transmembrane conductance regulator (CFTR) modulators. These drugs are a new class of small molecules that improve the synthesis, intracellular processing, and function of the CFTR protein.[1] Elexacaftor/Tezacaftor/Ivacaftor is the latest CFTR modulator that was approved in August 2020 for people with CF aged ≥12 and January 2022 for people with CF aged ≥6 years with at least one copy of the F508del mutation. In vitro studies have shown that this triple-therapy combination drug increases the level of mature CFTR proteins and chloride transport.[2] Elexacaftor/Tezacaftor/Ivacaftor's clinical benefits include significant improvements in pulmonary function, respiratory-related quality of life (QoL), and fewer pulmonary exacerbations.[3]

Clinical trials investigating receiving 4 weeks treatment with triple therapy (Elexacaftor/Tezacaftor/Ivacaftor) versus Tezacaftor and Ivacaftor alone[3,4] have demonstrated transformative improvements in spirometry measured lung function, sweat chloride concentration, and the respiratory domain of the CF-Questionnaire-Revised in adults and children aged > 12 years, homozygous for p.Phe508del mutations[3,4] and those with a single Phe508del allele.[5] However, it is currently unknown whether Elexacaftor/Tezacaftor/Ivacaftor improves other functional parameters of disease severity, such as exercise capacity.

Higher levels of aerobic fitness (peak oxygen uptake [$\dot{V}O_{2peak}$] measured by cardiopulmonary exercise testing [CPET]) are associated with improved quality of life,[6] reduced risk of being hospitalized with a pulmonary exacerbation,[7] reduced risk of lung transplant on 10-year follow up[8] and better prognosis[8] in people with CF. Several mechanisms have been hypothesized as to how CFTR modulator therapy might improve the multifactorial exercise dysfunction characterizing people with CF,[9,10] but to date, few studies have evaluated the effects of CFTR modulators on exercise outcomes. Small case studies have reported some promising effects on $\dot{V}O_2$peak following treatment with Ivacaftor[11,12] with a larger randomized, double-blind, crossover trial reporting improved exercise duration but not $\dot{V}O_2$peak.[13] Despite initial case series reports that 2 years of treatment with lumacaftor/Ivacaftor could improve physical activity and exercise tolerance in adults with CF,[14] a more recent pilot study reported no improvements in exercise tolerance[15] and a small study of four adolescents commencing Tezacaftor/Ivacaftor combination therapy demonstrated increased $\dot{V}O_2$peak in only one of four patients at 7–8 months follow-up,[16] with submaximal aerobic fitness (anaerobic threshold [AT]) improved in all cases. To date, there is no data regarding the response to Elexacaftor/Tezacaftor/Ivacaftor.

This case series aimed to report the short-term (6 weeks) effects of Elexacaftor/Tezacaftor/Ivacaftor on prognostically important CPET outcomes and device-based daily physical activity in three CFTR modulator naïve adolescents who participated in a Phase III trial (VX-17-445-103). It was hypothesized that clinically meaningful improvements in aerobic fitness would be observed following treatment.

2 | MATERIALS AND METHODS

2.1 | Participants

Data from three adolescents (two males [Table 1]) with CF disease (F508del/F508del genotype) who were under the care of the Southampton Children's Hospital (UK) are presented. Inclusion criteria comprised a diagnosis of CF based on clinical features, an abnormal sweat test (sweat chloride 60 mmoL. L^{-1}) /100 mg sweat), and genotyping and all participants already consented into the ethically approved Phase III trial (VX-17-445-103). The additional data presented in this case series were all obtained from routine clinical assessments. All cases provided additional informed consent to complete CPET and device-based physical activity assessments at baseline and 6 weeks after receiving Elexacaftor/Tezacaftor/Ivacaftor. All participants were pancreatic insufficient and prescribed regular nebulized rhDNase. Cases 2 and 3 were also receiving nebulized antibiotics, having had recurrent isolates of *Pseudomonas Aeruginosa*. Case 3 had moderately severe lung disease at baseline as indicated by their reduced lung function (Table 1) as a result of previous non-tuberculous mycobacteria infection.

2.2 | Exercise testing procedures

Before and after treatment with Elexacaftor/Tezacaftor/Ivacaftor, participants attended the laboratory to undertake CPET. Participants were advised to arrive rested and hydrated, to be > 2 h postprandial, and having refrained from caffeine for > 2 h. Following anthropometric and pulmonary function measurements, an exhaustive ramp incremental (10–25 W min^{-1}) cycling CPET protocol was undertaken. After a 3 min warm-up (20 W), participants completed an incremental test to the point of volitional exhaustion, maintaining a cadence of 70–80 rpm throughout. Exhaustion was defined as a >10 rpm drop in cadence for five consecutive seconds, despite strong verbal encouragement and confirmed using recommended criteria.[17] A 5 min active cool down (cycling at 20 W) then preceded passive seated recovery (10 min). In only one patient (due to time constraints) a combined ramp and supramaximal verification CPET protocol,[18] previously used to evaluate the response to CFTR modulator therapy[11] (Ivacaftor), was employed. Supramaximal verification consisted of a 3 min warm-up (20 W), followed by a "step" transition to a constant work rate corresponding to 110% peak power output (W_{peak}).

Breath-by-breath changes in pulmonary gas exchange and ventilation (K5, COSMED, Rome, Italy) and beat-by-beat heart rate (Premium HR Monitor, Garmin, USA) were measured throughout exercise, although heart rate could only be measured at 6 weeks due to technical problems at baseline. Heart rate, $\dot{V}O_{2peak}$, carbon dioxide production ($\dot{V}CO_2$), minute ventilation ($\dot{V}_E$), and ventilatory equivalents of O_2 ($\dot{V}_E/\dot{V}O_2$) and CO_2 ($\dot{V}_E/\dot{V}CO_2$) data were interpolated to 15 s averages and peak values taken as the highest 15 s average achieved during the ramp incremental test. The anaerobic threshold

TABLE 1 Clinical and physical activity characteristics of 3 CFTR modulator naïve adolescents with CF before and after 6 weeks of treatment with Elexacaftor–Tezacaftor–Ivacaftor

	Case 1 (male)			Case 2 (female)			Case 3 (male)		
	Pre	Post	%Δ	Pre	Post	%Δ	Pre	Post	%Δ
Age (years)	13.1	–	–	13.3	–	–	15.7	–	–
Clinical parameters									
Weight (kg)	45.4	50.1	+10.4	49.4	51.2	+3.6	51.7	71.3	+37.9
BMI (kg m^2)	18.2	19.5	+7.1	20.5	21.2	+3.4	16.9	22.8	+34.9
BMI centile	40	70	–	67	77	–	7	85	–
FEV_1 (L)	2.3	2.7	+17.4	2.0	2.5	+25.0	1.9	2.3	+21.1
$FEV_{1\%pred}$	79.8	87.3	+9.4	62.1	88.2	+42.0	45.6	53.5	+17.3
FVC (L)	3.0	3.3	+10.0	2.7	3.0	+11.1	2.5	3.3	+32.0
$FVC_{\%pred}$	88.1	92.8	+5.3	74.4	93.6	+25.8	52.4	66.1	+26.1
Baseline SpO_2 (%)	96	97	+1	99	98	−1	96	97	+1
Average [glucose] (mmol L^{-1})		–	–	–	–	–	5.9	5.7	−3.5
Physical activity & exercise capacity									
Total PA, min	+	+	+	145.3	97.7	−32.8	86.3	101.1	+17.1
$\dot{V}\dot{V}O_{2peak}$ (L min^{-1})	2.44	2.87	+17.6	1.43	2.18	+52.4	1.55	2.06	+32.9
$\dot{V}\dot{V}O_{2peak}$ (ml kg^{-1} min^{-1})	28.7	42.5	+48.1	53.8	57.4	+6.7	30.1	28.9	−4.0
$\dot{V}O_{2peak}$ (% predicted)	99.5	111.8	+12.4	74.2	113.1	+52.4	48.4	62.2	+28.5
AT (L min^{-1})	1.01	1.17	+15.8	0.93	1.15	+23.7	1.20	1.41	+17.5
AT (%$\dot{V}$ O_{2peak})[a]	41.4	40.8	−1.3	65.0	52.8	−18.7	77.4	68.4	−11.6
W_{peak} (W)	157	166	+5.7	110	118	+7.3	81	91	+12.3
Relative W_{peak} ($W.kg^{-1}$)	2.2	2.3	+4.5	3.5	3.3	-5.7	1.6	1.3	−18.8
$\Delta\dot{V}O_2/\Delta WR$ (mL. min^{-1} W^{-1})	8.7	11.9	+36.8	13.5	13.7	+1.5	8.3	13.5	+62.7
$\dot{V}_E$/MVV (%)	77.6	95.9	+23.6	80.8	74.4	−7.9	87.2	85.5	−1.9
$\dot{V}_E/\dot{V}O_{2peak}$ (L.min^{-1})	47.7	32.9	−31.0	25.1	27.0	+7.6	49.5	41.8	−15.6
$\dot{V}_E/\dot{V}CO_2$-slope (L.min^{-1})	38.2	37.9	−0.8	28.0	32.5	+16.1	52.0	50.8	−2.3
Exercise ΔSpO_2 (%)	0	−1	–	-3	-1	–	-4	0	–
HR (mL. $beat^{-1}$)	–	191	–	–	204	–	–	173	–
O_2 pulse (mL. $beat^{-1}$ min^{-1})	–	11.4	–	–	11.7	–	–	12.0	–

Note: Self-reported high levels of PA, self-reported football, and CrossFit training 4–5 times per week.

Abbreviations: %Δ, percentage change from baseline following treatment; AT, anaerobic threshold; Av, average; BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MVV, maximal voluntary ventilation; SpO_2, transcutaneous arterial oxygen saturation measured at the fingertip; Total PA, average daily physical activity; $\dot{V}_E$, minute ventilation; $\dot{V}O_{2peak}$, peak oxygen uptake; W_{peak}, peak power output. N.B. +.

[a]AT was expressed as a percentage of measured $\dot{V}O_{2peak}$. N.B.

(AT) was determined using the V-slope method[19] and confirmed through visual inspection of the ventilatory equivalents and subsequently expressed in both absolute terms and as a percentage of $\dot{V}O_{2peak}$. Ventilatory drive ($\dot{V}_E/\dot{V}CO_2$-slope) was determined by plotting a linear regression line through the power output × $\dot{V}_E/\dot{V}CO_2$ response up to the respiratory compensation point. Breathing reserve ($\dot{V}_E$/MVV) was calculated by expressing $\dot{V}_{Epeak}$ as a percentage of predicted maximal voluntary ventilation (MVV = FEV_1 (in L) × 40).

2.3 | Device-based physical activity and glycaemic control

Device-based daily physical activity of Cases 2 and 3 was assessed using GENEActiv™ accelerometers (Active Insights, Kimbolton, Cambridge, UK) worn on the nondominant wrist for 7 consecutive days at baseline and following 6 weeks treatment. Devices were programmed to record at 100 Hz for 7 consecutive days and data. Following the measurement

period, data were downloaded using manufacturers software and processed in R (R Core Team, Vienna, Austria) using the open source GGIR software package (http://cran.r-project.org), using validated threshold values to classify movement as light-, moderate- or vigorous-intensity.[20] Device-based data was unavailable due to poor adherence in Case 1, however they self-reported high levels of baseline physical activity (football and CrossFit training 4-5 times per week). Case 3, who had CF-related diabetes, also wore a Freestyle Libre Pro® (Abbott, Chicago, USA) continuous glucose monitoring sensor for 14 days before and after treatment with Elexacaftor/Tezacaftor/Ivacaftor.

3 | RESULTS

Baseline clinical, exercise testing, and physical activity data and changes after 6 weeks of treatment with Elexacaftor/Tezacaftor/Ivacaftor are shown in Table 1. BMI (Case 1: +7.1%; Case 2: +3.4%; Case 3: 34.9%) and lung function ($FEV_{1\%}$predicted: Case 1: +9.4%; Case 2: +42.0; Case 3: +17.3%) increased in all three cases, irrespective of baseline lung disease severity. Clinically meaningful improvements in $\dot{V}O_{2peak}$ were observed in all three cases, which exceeded the typical error (13.3%) of measurement established over this duration[21] in young people with CF, and the magnitude of response was greater in those with moderate-to-severe lung disease at baseline (Table 1). Although there was an inconsistent relationship between the change in $\dot{V}O_{2peak}$ and physical activity among the three cases, the greatest increase in $\dot{V}O_{2peak}$ was achieved by Case 2, who had a substantial decrease in physical activity over the 6-week study period (Table 1; Case 1: N/A; Case 2: −32.8%; Case 3: +17.1%). Changes in ventilatory function during exercise, measured as $\dot{V}_E/\dot{V}O_{2peak}$, improved in Cases 2 and 3 who had lower fitness levels and moderate-to-severe lung disease (Case 1: +7.7% vs. Case 2: −31.1% and Case 3: −15.6%) and there were inconsistent changes in the $\dot{V}_E/\dot{V}CO_2$-slope (Case 1: +16.2%; Case 2: −0.9%; Case 3: −2.3%), breathing reserve (Table 1) and $\dot{V}_E/\dot{V}CO_{2peak}$ (Case 1: −0.4%; Case 2: +2.3%; Case 3: +5.5%). A variable $\dot{V}O_2$ per unit of power output ($\Delta\dot{V}O_2/\Delta WR$) response was observed, being higher after treatment in the two participants with lower baseline fitness levels ($\dot{V}O_{2peak}$ % predicted) and more advanced lung disease (Case 2: +36.0% and Case 3: +62.1%), but was negligible in Case 1 (+1.6%) who demonstrated greater baseline fitness and mild lung disease at baseline (Figure 1). Predicted maximal heart rates (> 180 bpm) were achieved by Cases 1 and 2 pre- and post-treatment with Elexacaftor/Tezacaftor/Ivacaftor, whereas predicted heart rate maximum was not achieved in either CPET by Case 3 who had a greater degree of ventilatory limitation during exercise and more severe lung disease. Glycaemic control was unchanged after treatment in Case 3 (Table 1).

4 | DISCUSSION

In this case series of three adolescents with CF we have observed, for the first time, improvements in exercise capacity following 6 weeks of treatment with Elexacaftor/Tezacaftor/Ivacaftor, especially in those with more severe CF lung disease and lower aerobic fitness ($\dot{V}O_{2peak}$ %predicted) at baseline. More specifically, clinically meaningful improvements in $\dot{V}O_{2peak}$ were observed in all three cases (+17.6%, +52.4%, and +32.9%, respectively), with improvements greatest in those with more severe lung disease and lower fitness at baseline, which exceeded the typical error of measurement established over this duration in young people with CF.[21] Whilst lung function increased in all cases, inconsistent changes in markers of ventilatory and peripheral muscle efficiency likely suggest different mechanisms of improvement in this case group of adolescents with CF, which warrants further investigation in larger trials.

Exercise intolerance in pwCF is multifactorial with a mechanistic basis that changes across the life course and with disease severity. Ventilatory, cardiovascular and intramuscular abnormalities have been reported.[9] The majority of clinical trials examining the effects of CFTR modulator treatment have studied changes in FEV_1, with relatively few evaluating changes in exercise capacity.[11–16,22] The present findings of clinically meaningful improvements in $\dot{V}O_2$peak are promising given the findings of previous studies. A small case series of Ivacaftor, reported an increase in $\dot{V}O_2$peak in an adolescent with severe lung disease, but no improvement in milder disease following 12 weeks treatment.[11] In contrast, 8 weeks treatment improved $\dot{V}O_2$peak (14%) in an adult with CF; a change that was associated with reduced breathlessness during exercise.[12] A larger randomized, double-blind, crossover trial ($n = 20$) of people with CF and ≥1 copy of the G551D-CFTR mutation showed improved exercise duration but not $\dot{V}O_2$peak following 4 weeks of treatment.[13] Of the evidence available for Lumacaftor/Ivacaftor, despite initial case series reports that 2 years of treatment could improve physical activity and exercise tolerance in adults with CF,[14] a more recent pilot study reported no improvements in exercise tolerance following treatment with Lumacaftor/Ivacaftor.[15] Most recently, a small study of four adolescents commencing Tezacaftor/Ivacaftor demonstrated increased $\dot{V}O_2$peak in only one patient at 7–8 months follow-up, with the remaining three experiencing reductions, although submaximal aerobic fitness (the AT) was improved in all cases.[16] The present case series adds to this evidence base and provides the first exercise-related data in response to eElexacaftor/Tezacaftor/Ivacaftor in modulator naïve patients.

The improvements in $\dot{V}O_{2peak}$ and the AT observed at 6 weeks in the present case series are similar to that observed in a previous study investigating the response to 2 years of treatment with lumacaftor/ivacaftor.[14] In that longer study, the authors speculated that improved fitness might be the consequence of better health enabling increased daily physical activity levels.[14] Our findings were achieved over a much shorter time (6 weeks) and, although there was an inconsistent relationship between the change in $\dot{V}O_{2peak}$ and physical activity among the three cases, the greatest increase in $\dot{V}O_{2peak}$ was achieved by Case 2, who had a substantial decrease in their habitual physical activity, suggesting other underlying physiological mechanisms are responsible.

Elexacaftor/Tezacaftor/Ivacaftor might improve exercise ability through correcting a number of the abnormalities of O_2 transport and

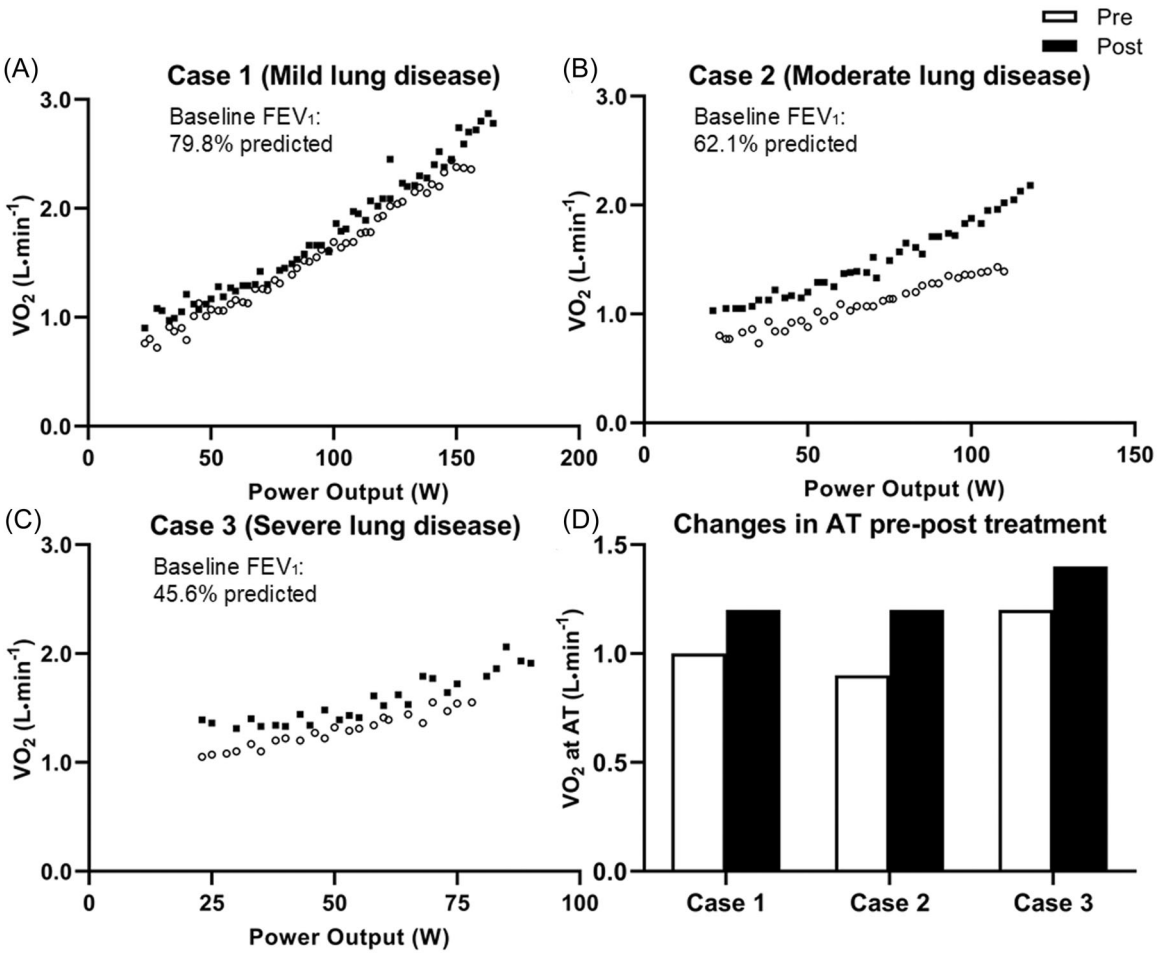

FIGURE 1 Measurements of exercise capacity before and after 6 weeks treatment with Elexacaftor/Tezacaftor/Ivacaftor in three cystic fibrosis CFTR modulator naïve adolescents with CF. CFTR, cystic fibrosis transmembrane conductance regulator

utilization that occur in CF.[9] CFTR is expressed in myocardial cells,[23] vascular smooth muscle,[24] and the sarcolemma and sarcoplasm of skeletal muscle.[25] Although oxygen delivery and abnormal respiratory mechanics might also contribute to exercise limitations in severe lung disease, those with milder lung involvement are more likely limited by peripheral factors such as reduced striated muscle mass and function. In addition, CFTR modulators might also be impacting on many parts of the oxygen delivery, extraction, and utilization pathway.

Although young people with CF are typically not limited by ventilatory factors during exhaustive exercise, the finding that lung function (FEV_1% predicted) increased in all three adolescents in our case series, irrespective of baseline lung function, suggests that improved fitness may partly be due to improved pulmonary function. However, two of the cases also experienced a reduced $\dot{V}_E/\dot{V}O_{2peak}$, suggesting that enhanced O_2 uptake, transport, and/or utilization were mechanistically involved. We previously reported the effect of CFTR activity on endothelial cell function.[26,27] Peripheral factors, such as abnormal macro- and micro-vascular function that impair blood flow and reduce oxygen extraction, and mitochondrial defects that diminish metabolic efficiency might also be important.[10] Since heart rate and O_2 pulse data are not available at baseline and vascular endothelial function was not measured, contributory roles of these cannot be fully excluded. However, evidence did support changes at the peripheral muscle level.

Although not directly measured, the fitness improvements we observed might be due to CFTR modulators directly improving a CFTR-related defect of skeletal muscle. CFTR is expressed within skeletal muscle tissue[25] and CFTR activity might be involve in regulating mitochondrial function.[28] It is possible that CFTR modulators may improve abnormalities at a cellular level, by altering skeletal muscle oxidative metabolism, resulting in improved muscle oxidative capacity. Our findings of a variable response in $\Delta\dot{V}O_2/\Delta WR$ (two increasing and one decreasing), which are in line with a previous case study of Ivacaftor ($n = 2$),[11] support the need for further investigation in larger samples of any potential intramuscular metabolic benefits of Elexacaftor/Tezacaftor/Ivacaftor in people with CF. However, this previous case series[11] did demonstrate, using near-infrared spectroscopy, that the improvement in $\dot{V}O_{2peak}$ in one adolescent was due to improved muscle O_2 extraction and/or utilization.[11] A larger study of Ivacaftor has also suggested that, despite unchanged $\dot{V}O_{2peak}$, increased exercise duration was a result of improved exercise economy.[13]

As reported in other studies,[12,14,16,29] BMI increased in all three of our adolescents. Understanding the pattern of weight gain after modulator treatment is an important area of research. The changes in our case series are unlikely to reflect significant increases in muscle mass given the short duration and unchanged physical activity. This assumption is supported by the modest improvements in W_{peak} compared with the larger improvements in AT and $\dot{V}O_{2peak}$. Further research is needed to examine body composition changes and how these might influence reported changes in exercise physiology, particularly ventilatory function and breathing mechanics during exercise. Increased adiposity on modulator therapy has already been suggested to contribute to the heterogeneity observed to date in $\dot{V}O_{2peak}$ outcomes in CFTR modulator trials.[10] Specifically, if those on modulator therapy gain more fat than others, this might artificially decrease their $\dot{V}O_{2peak}$. This is because fat is noncontributory to $\dot{V}O_{2peak}$ but body mass is generally linearly scaled.[10]

Further research with a larger sample size is now needed to document the long-term effects of treatment with Elexacaftor/Tezacaftor/Ivacaftor and the role of structured exercise training and/or increased physical activity in improving exercise capacity. Considering the small sample in this case series, the possibility of a more variable response, as seen with other CFTR modulators, should also be considered. Current evidence also suggests that people with more severe CF may benefit most in terms of exercise capacity improvements from CFTR modulator therapy.[12,14] If modulator therapy alone is unlikely to improve exercise capacity in some people with CF, structured exercise training will be needed to see more significant benefits.

The present data must be considered in the context of several methodological limitations. A case series approach limits generalizability to the wider CF population. Furthermore, supramaximal verification was only obtained in one case, due to time constraints. However, the use of supramaximal verification at previous annual review CPETs had previously confirmed that all cases were motivated and able to achieve maximal effort during exercise testing. Our participants might have been motivated to work harder knowing they were on active medication, however, this would not have affected effort-independent parameters, such as the AT.

In conclusion, this case series including three adolescents provides insights into how Elexacaftor/Tezacaftor/Ivacaftor might improve prognostically relevant indices of exercise capacity in people with CF. Clinically meaningful improvements in $\dot{V}O_{2peak}$ were observed in all three cases, with greater improvements in those with more severe lung disease and deconditioning at baseline. These changes appear to primarily be due to enhanced efficiency of the exercising peripheral muscle. Further studies with larger sample sized across the disease spectrum might usefully confirm these findings and help clarify the mechanisms whereby CFTR modulators improve O_2 extraction and utilization.

AUTHOR CONTRIBUTIONS

Adam J. Causer: Conceptualization; investigation; writing—original draft; writing—review & editing; formal analysis; project administration; data curation; methodology; visualization. **Janis K. Shute**: Conceptualization; investigation; writing—original draft; methodology; visualization; writing—review & editing; data curation; supervision. **Michael H. Cummings**: Conceptualization; investigation; writing—original draft; methodology; validation; writing—review & editing; data curation; supervision. **Anthony I. Shepherd**: Conceptualization; investigation; writing—original draft; methodology; validation; writing—review & editing; data curation; supervision. **Samuel R. Wallbanks**: Investigation; writing—review & editing; methodology; data curation. **Richard M. Pulsford**: Conceptualization; investigation; writing—original draft; methodology; validation; writing—review & editing; formal analysis; supervision; data curation. **Victoria Bright**: Conceptualization; investigation; writing—original draft; methodology; validation; writing—review & editing; data curation; supervision; resources. **Gary Connett**: Conceptualization; investigation; writing—original draft; methodology; validation; writing—review & editing; data curation; supervision; resources. **Zoe L. Saynor**: Conceptualization; investigation; writing—original draft; methodology; validation; visualization; writing—review & editing; software; formal analysis; project administration; data curation; supervision; resources.

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CONFLICTS OF INTEREST

Professor Connett has been a principle investigator in Vertex clinical trials. The Southampton Children's Hospital has received educational support grants and Professor Connett and Dr Saynor have received speaker fees from Vertex Pharmaceuticals. There are no other conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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