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

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Abstract

This study investigated whether Elexacaftor-Tezacaftor-Ivacaftor (Kaftrio ®), a cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulator, could improve exercise capacity in adolescents with CF. After six weeks treatment, Kaftrio ® improved both maximal and submaximal indices of aerobic fitness. Improvements were independent of changes in ventilatory function during exercise and physical activity. Interestingly, pulmonary oxygen uptake per unit of power output was higher in two, out of three, cases who presented with more severe CF lung disease. These findings suggest improved O $_2$ extraction and/or consumption in the exercising muscle and demonstrate, for the first time, that short-term treatment with Kaftrio ® might improve aerobic fitness in people with CF, especially in those with more severe lung disease and deconditioning.

Original Article

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

Running title: Elexacaftor & exercise capacity in CF

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ABSTRACT

This study investigated whether Elexacaftor-Tezacaftor-Ivacaftor (Kaftrio®), a cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulator, could improve exercise capacity in adolescents with CF. After six weeks treatment, Kaftrio® improved both maximal and submaximal indices of aerobic fitness. Improvements were independent of changes in ventilatory function during exercise and physical activity. Interestingly, pulmonary oxygen uptake per unit of power output was higher in two, out of three, cases who presented with more severe CF lung disease. These findings suggest improved O_2extraction and/or consumption in the exercising muscle and demonstrate, for the first time, that short-term treatment with Kaftrio® might improve aerobic fitness in people with CF, especially in those with more severe lung disease and deconditioning.

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INTRODUCTION

The clinical care of cystic fibrosis (CF) has now been revolutionised with CF transmembrane conductance regulators (CFTR) for use in people with a number of specific CFTR gene mutations.

CFTR modulators are a new class of small molecules that aim to improve the production, intracellular processing and function of the CFTR protein[1]. Elexacaftor-Tezacaftor-Ivacaftor (Kaftrio®) is the newest 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], and Kaftrio(r) can significantly improve pulmonary function, respiratory-related quality of life (QoL) and pulmonary exacerbation frequency[3].

Phase II studies of Kaftrio(r) have demonstrated that mean absolute increases in forced expiratory volume percent predicted ($FEV_{1\%pred}$) in adults and children aged > 12 years, homozygous for p.Phe508del mutations, was 10% greater in those receiving four weeks treatment with triple therapy versus Tezacaftor and Ivacaftor alone[3]. However, it is currently unknown whether Kaftrio(r) improves other functional parameters of disease severity, such as exercise capacity, since clinical trials have focused heavily on more traditional outcome measures (e.g. pulmonary function, sweat [chloride], body mass index (BMI)).

Importantly, higher levels of aerobic fitness (peak oxygen uptake [$\dot{V}O_{2peak}$]) are associated with an improved quality of life[4], reduced risk of being hospitalised with a pulmonary exacerbation[5] and better prognosis[6] and a number of changes following the initiation of modulator therapy have been hypothesised[7]. Therefore, in the present study, we report a case-series of three CFTR modulator naive adolescents who participated in the phase III trial (VX-17-445-103). These individuals underwent cardiopulmonary exercise testing (CPET) and device-based physical activity (PA) assessments at baseline and after receiving triple therapy for 6 weeks to explore, for the first time, the short-term effects of this medication on prognostically important CPET outcomes.

METHODS

All cases gave their informed consent to complete CPET and device-based PA assessments at baseline and 6 weeks after receiving Kaftrio(r). All participants were pancreatic insufficient and prescribed regular nebulised rhDNase. Cases 2 and 3 were also receiving nebulised antibiotics, having had recurrent isolates of

Pseudomonas aeruginosa. Case 3 had more severe CF lung disease as a result of previous non-tuberculous mycobacteria infection. Case 1 self-reported high levels of baseline PA (device-based data was unavailable due to poor adherence), whereas Case 2 was less physically active and Case 3 had low PA levels (Table 1).

Before and after treatment with Kaftrio$^{(r)}$, participants underwent CPET as previously described[8-10]. Briefly, breath-by-breath changes in $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) were measured during incremental cycling to exhaustion. Additionally, device-based daily PA of Cases 2 and 3 was assessed using GENEActiv accelerometers (Active Insights, Kimbolton, Cambridgeshire, UK) worn on the non-dominant wrist for 7 consecutive days. Data was downloaded using the manufacturer's software, and validated threshold values were used to classify movement as light-, moderate- or vigorous-intensity[11].

Case 3, who had CF-related diabetes (CFRD), also wore a Freestyle Libre Pro (Abbott, Chicago, USA) continuous glucose monitoring (CGM) sensor for 14 days before and after treatment with Kaftrio$^{(r)}$.

RESULTS

Baseline data and changes after 6 weeks of treatment are shown in Table 1. $\dot{V}O_{2peak}$, peak power output (W_{peak}) and the anaerobic threshold (AT) were all improved following 6 weeks treatment with Kaftrio$^{(r)}$ in all cases. The magnitude of response was greater in those with moderate-to-severe lung disease at baseline (Table 1).

Improvements in exercise capacity were independent of changes in PA. The greatest increase in $\dot{V}O_{2peak}$ was achieved by Case 2, who had a substantial decrease in PA throughout the study period (Table 1). Changes in ventilatory function during exercise, measured as$\dot{V}_E/\dot{V}O_{2peak}$, improved in cases 2 and 3 who had low fitness levels and moderate-to-severe lung disease (Case 1: +7.7% vs. Case 2: -31.1% and Case 3: -15.6%). There were no consistent improvements in ventilatory drive (Case 1: +16.2%; Case 2: -0.9%; Case 3: -2.3%), breathing reserve (Table 1) or$\dot{V}_E/\dot{V}CO_{2peak}$ (Case 1: -0.4%; Case 2: +2.3%; Case 3: +5.5%).

$\dot{V}O_2$ per unit of power output was higher after treatment in the two participants with low baseline fitness levels and advanced lung disease (i.e. the $\dot{V}O_2$-gain; 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 (Figure 1). Predicted maximal heart rates (180 bpm) were achieved by cases 1 and 2 pre- and post-treatment, whereas predicted heart rate maximum was not achieved by case 3 in either CPET, probably because of a greater degree of ventilatory limitation due to more severe lung disease. Glycaemic control was unchanged after treatment in Case 3 (Table 1).

DISCUSSION

In this case-series we have observed, for the first time globally, improvements in exercise capacity following 6 weeks treatment with Kaftrio$^{(r)}$, especially in those with more severe CF lung disease and deconditioning at baseline. In a previous study, 2 years of treatment with Lumacaftor-Ivacaftor (Orkambi$^{(r)}$) improved $\dot{V}O_{2peak}$ and the AT to a similar magnitude to that observed in the present case-series[12]. The authors speculated that these improvements were due to better health enabling increased PA levels[12]. Importantly, our findings were achieved over a much shorter time period and improvements appeared to occur independently of changes in daily PA undertaken. Although the observed improvements in$\dot{V}O_{2peak}$ may be due to improvements in $FEV_{1\%pred}$, parameters of ventilatory function from CPET were mostly unchanged. Furthermore, the 2 participants who experienced the greatest improvements in $\dot{V}O_{2peak}$ also experienced a reduced$\dot{V}_E/\dot{V}O_{2peak}$, suggesting that O_2 uptake, transport and/or utilisation improved independently of ventilation.

Body mass index increased in all of our participants, but this is unlikely to reflect significant increases in muscle mass given the short duration and unchanged PA. This assumption is supported by only modest improvements in W_{peak} compared to the larger improvements in AT and $\dot{V}O_{2peak}$. Our findings of increased $\dot{V}O_2$ per unit of power output in two participants who were deconditioned are consistent with Savi*et al.* [12] and a prior study in two patients treated with Ivacaftor for G551D gating mutations[13]. The latter study showed, using near-infrared spectroscopy, that the improvement in$\dot{V}O_{2max}$ in one adolescent was due to improved muscle O_2 extraction and/or utilisation[13].

Although not directly measured, the fitness improvements we have observed might be due to CFTR modulator treatment directly improving a CFTR-related defect of skeletal muscle. CFTR is expressed within skeletal muscle tissue[14] and CFTR activity may regulate mitochondrial function[15]. Consequently, it is possible that this treatment may improve abnormalities at a cellular level, by altering skeletal muscle oxidative metabolism during exercise, resulting in improved muscle oxidative capacity.

Our results differ from those of a 28 day cross-over trial of Ivacaftor in 20 adults with CFTR gating mutations[16]. Although $FEV_{1\%pred}$ was significantly improved, only time to exhaustion was improved during CPET[16]. Notably, treatment effects over placebo might have been blunted by a carry-over effect in this cross-over design study, despite a 28 day wash out period between treatments. Alternatively, validity concerns when conducting CPET without supramaximal verification may have meant submaximal tests were included[8,9].

Limitations of our case series were a small sample size, and that supramaximal verification was only obtained in Case 3, due to time constraints in the clinics attended by Cases 1 and 2. However, supramaximal verification had previously confirmed that both patients achieved maximal effort at annual CPET. Our participants might also 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.

CONCLUSION

This case series provides insights into how CFTR modulators might improve prognostically relevant indices of exercise capacity in adolescents with CF. Improvements in exercise capacity appear to be independent of changes in PA and ventilatory function during exercise. Future studies might identify mechanisms whereby CFTR modulators improve O_2 extraction and utilisation.

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CONFLICT OF INTERESTS

Prof. Connett has been a principle investigator in Vertex clinical trials. The Southampton Children's Hospital has received educational support grants and speaker fees from Vertex pharmaceuticals. There are no other conflicts of interest.

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Table 1. Clinical and physical activity characteristics of the cases before and after 6 weeks treatment with Elexacaftor-Tezacaftor-Ivacaftor.

Figure 1. Measurements of exercise capacity before and after 6 weeks treatment with Elexacaftor-Tezacaftor-Ivacaftor. AT, anaerobic threshold;$\dot{V}O_2$, pulmonary oxygen uptake.

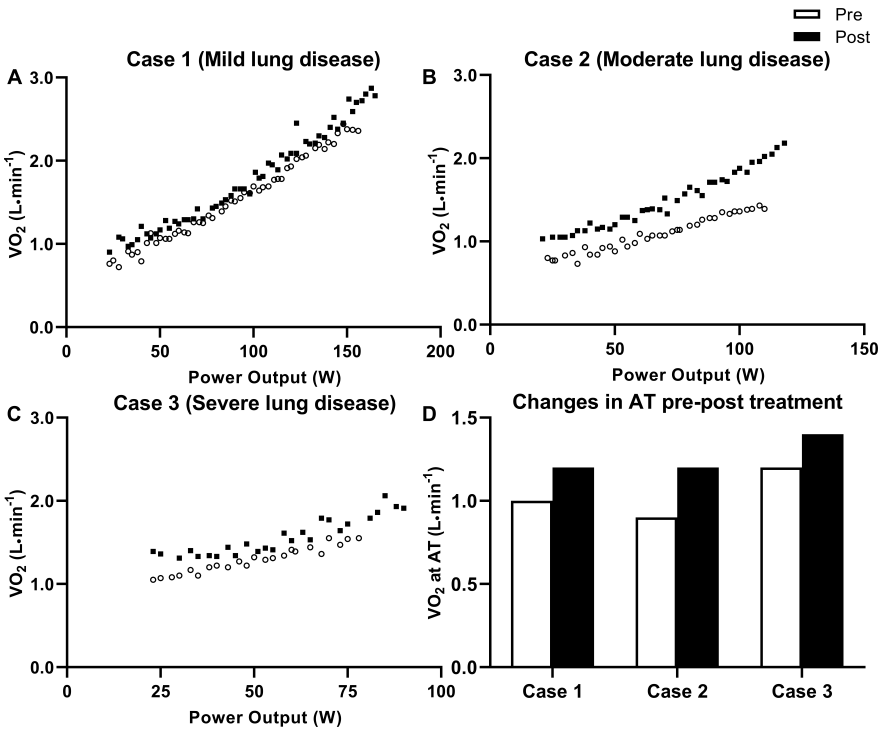

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Table 1, R1.docx available at https://authorea.com/users/476244/articles/565235-elexacaftor-tezacaftor-ivacaftor-improves-exercise-capacity-in-adolescents-with-cystic-fibrosis