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LETTER TO THE EDITOR

Changes in exercise endurance and inspiratory capacity after lumacaftor/ivacaftor therapy in cystic fibrosis

Dear Editor,

The long-term positive effects of the combination of the corrector lumacaftor (LUM) with the potentiator ivacaftor (IVA) on physical activity and oxygen uptake values obtained during a symptom-limited incremental cardiopulmonary exercise test (CPET) in cystic fibrosis (CF) have been described.[1] Among available exercise-testing protocols, constant work-rate exercise tests, such as a cycle endurance test, deliver a reliable assessment of changes in exercise capacity following intervention (both pharmacologic and nonpharmacologic).[2] As previously demonstrated, one-month LUM/IVA therapy did not increase exercise endurance or modify dyspnea or leg discomfort in adult CF patients[3] and no data are available on the longer-term effects of such modulator therapy on exercise endurance and symptoms of exertion. The aim of this study was to examine the potential impact of LUM/IVA therapy (400 mg/250 mg administered orally every 12 h) on exercise endurance time (EET) and symptoms of exertion during constant work-rate cycle ergometry (CWRCE) after six months treatment. This was a prospective, observational, multicenter study, involving three CF centers in Italy (Rome, Milan, Orbassano). The study (number 853/18) was approved by the ethics committee of Policlinico Umberto I Hospital, Sapienza University of Rome, Italy, and other local ethics committees. All patients provided written informed consent for this study. During the study period from April 2019 to March 2020, we recruited three stable adult CF patients ($\geq$ 18 years old, homozygous for Phe508del) who were about to initiate LUM/IVA treatment. We used a protocol consisting of two visits: 3-4 weeks prior to initiation of LUM/IVA treatment (visit 1) and 6 months afterwards (visit 2). During each visit, in the morning patients performed spirometry and a symptom-limited incremental CPET using cycle ergometry to determine peak work rate (defined as the highest work rate maintained for $>$ 30 s). In the afternoon, all subsequent symptom-limited CWRCE tests were conducted at 80% of peak work rate. Inspiratory capacity and intensity of breathing discomfort and leg discomfort (Borg scale[4]) were measured prior to exercise, every 2 min during exercise and at the point of symptom limitation (end-exercise). Minute ventilation (V'E) and oxygen uptake ($V'O_2$) were measured using a calibrated metabolic system (Cosmed K5). After completing each exercise test, patients identified the primary reason for stopping (due to leg and/or breathing discomfort or another reason). Patients were asked to continue any respiratory-related medications before the visits. Assessment was conducted at the same place and time of day for all subjects. The number of pulmonary exacerbations were prospectively collected throughout the 6- month period. For each patient we calculated the percentage of change between “pre” and “post” the start of LUM/IVA therapy for each variable.

Patient 1 is a 28 - year-old man of Caucasian origin diagnosed with CF at birth (Table 1). He commenced LUM/IVA treatment in May 2019. During six months treatment, he presented with one pulmonary exacerbation, which was treated with oral antibiotics. He reached his peak exercise at a higher oxygen uptake than that measured prior to therapy (Table 2). Patient 1 showed an improvement in oxygen pulse (V O_2/HR) following treatment, as well as slightly higher values of ventilation ($V'E_{peak}$), while mean maximal ventilation was less than the predicted MVV (208 L) and breathing reserve (BR) was reduced (Table 2). Ventilatory efficiency ($V'E/V'CO_2$ slope) and partial pressure of end-tidal CO_2 ($PETCO_2$) were slightly lower. After six month treatment, there was an increase in EET (344 s *vs* 644 s, 87%) and an improvement in inspiratory capacity prior to exercise of 520 mL, +17% (Table 2). The improvements in inspiratory capacity were sustained during exercise and end-exercise (160 mL, 4%, Table 2). There was a reduction in breathing discomfort and leg fatigue.

Patient 2 is a 34-year-old man of Caucasian origin diagnosed with CF at birth (Table 1). He commenced LUM/IVA treatment in July 2019. During six months treatment, the patient did not have exacerbations. He reached peak exercise at a higher oxygen uptake uptake than prior to treatment (+5%, Table 2). There was an improvement in V O_2/HR by + 6%. We observed lower values of $V'E_{peak}$, a mean maximal ventilation less than the predicted MVV (130 L) and a higher BR following treatment, suggesting that ventilation limit was not a limiting factor. $V'E/V'CO_2$ slope and $PETCO_2$ were slightly reduced. There was an increase in EET (416 s *vs* 635 s, 52%) and an improvement in inspiratory capacity prior to exercise of 350 mL, 16% (Table 2). The improvement in inspiratory capacity was sustained during exercise and end-exercise (540 mL, 23%, Table 2). There was a reduction in breathing and leg discomfort as indicated in Table 2.

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Table 1 Anthropometric and clinical characteristics of adult CF patients.

Characteristics	Patient 1			Patient 2			Patient 3		
	Pre	Post	% change	Pre	Post	% change	Pre	Post	% change
BMI, Kg/ m2	24.2	25.1	+4	23.9	24.6	+3	21.3	21.1	-0.93
Pseudomonas aeruginosa colonization	no	no	0	yes	yes	0	yes	yes	0
Staphylococcus aureus colonization	yes	yes	0	yes	yes	0	yes	yes	0
Burkholderia cepacia colonization	no	no	0	no	no	0	no	no	0
Pancreatic insufficiency	yes	yes	0	yes	yes	0	yes	yes	0
CF-related diabetes	no	no	0	no	no	0	no	no	0
FEV1, % predicted	106	109	+3	75	82	+10	72	65	-9.7
FVC, %predicted	123	118	-4	102	101	-0.9	98	84	-14.2

Definition of abbreviations: BMI = body mass index; FEV1 = Forced expiratory volume in 1 second; FVC = forced vital capacity; CF = Cystic Fibrosis.

Patient 3 is a 30-year-old man of Caucasian origin diagnosed with CF at birth (Table 1). He commenced LUM/IVA treatment in June 2019. During the following 6 months, the patient had one pulmonary exacerbation requiring IV antibiotic therapy. He reached peak exercise at a lower oxygen uptake (17% less, Table 2) and there was a marked reduction in V O_2/HR of 29%. He showed lower V'E_{peak} and BR values, with maximal ventilation less than the predicted MVV (107 L). The V'E/V'CO_2 slope improved marginally. There was an increase in EET (371 s *vs* 460 s, 23%). Althought the patient showed dynamic hyperinflation both before and after treatment (ICΔ pre − 0.37 L, post − 0.3 L), there was an improvement in inspiratory capacity prior to exercise of 180 mL (+6%) and at end-exercise 250 mL (+10%; Table 2). There was a reduction in breathing and leg discomfort (Table 2).

Results from these case series demonstrate a longer EET after six months LUM/IVA treatment. Improvements in exercise endurance were accompanied by improvements in inspiratory capacity prior to exercise and additional serial

Table 2 Measurements at peak symptom-limited incremental cycle exercise and at constant work-rate cycle ergometry (CWRCE) of adult CF patients.

Variables at Peak CPET	Patient 1			Patient 2			Patient 3		
	Pre	Post	% change	Pre	Post	% change	Pre	Post	% change
Work rate, watt	180	172	-4.4	180	210	+16.6	120	125	+4.1
V'O_2, ml/min	2084	2328	+11.7	2650	2786	+5.1	1699	1384	-18.5
V'O_2, ml/min/Kg	25.41	27.39	+7.8	38.41	39.24	+2.1	26.97	22.14	-17.9
V'O_2, % predicted maximum	67	69	+3	97.6	102.2	+5	62.2	51.3	-17.5
HR, beats·min−1	179	175	-2.2	150	148	-1.3	134	156	+16.4
V O_2/HR, ml O_2/beat	11.6	13.3	+15	17.7	18.8	+6.2	12.7	8.9	-29
ΔSpO_2	0	0	0	-1	-1	0	0	0	0
V_T *peak* (l)	2.6	2.5	-3.8	3.84	3.7	-3.6	1.9	1.7	-10.5
V'E, l/min	88.4	96	+8.6	86.5	81.4	-5.8	50.5	48.3	-4.3
BR (%)	115	112	-2.6	28.3	49	+73	64.7	59.3	-8
V'E /V CO_2 slope	36.9	35.4	-4	30.3	28.9	-4.6	27.5	30.5	+10
PET_{CO2} *peak* (mmHg)	34	32	-5.8	42	41	-2.3	43	38	-11.6
Dyspnea, Borg scale	8	7	-12.5	7	8	+14.2	5	4	-20
Leg discomfort, Borg scale	9	7	-22.2	7	8	+14.2	8	7	-12.5
Variables at CWRCE									
EET,s	445	644	+87	416	635	+52	371	460	+23
IC baseline, l	3.05	3.57	+17	2.1	2.45	+16	2.82	3	+6
IC end-exercise, l	4.31	4.47	+4	2.36	2.9	+23	2.45	2.7	+10
Dyspnea, Borg scale	6	5	-17	6	5	-17	5	4	-20
Leg discomfort, Borg scale	9	7	-22	9	7	-22	9	8	-11

Definition of abbreviations: V'O_2 = oxygen uptake; HR = heart rate; V O_2/HR = oxygen pulse; ΔSpO_2 = arterial oxygen saturation delta from rest to peak exercise; V_T= tidal volume; V'E = minute ventilation; BR= breathing reserve; V'E/V'CO_2 = ventilatory equivalent for carbon dioxide. CWRCE = constant work-rate cycle ergometry; EET = exercise endurance time; IC = inspiratory capacity; Pre = Measurements pre treatment with lumacaftor/ivacaftor; Post = measurements after 6 months treatment with lumacaftor/ivacaftor.

assessment of inspiratory capacity during exercise demonstrated that these improvements were maintained at end-exercise. All three patients experienced less dyspnoea and less leg discomfort, while exercise limitation was often related to peripheral muscle fatigue and not to ventilatory constraints. Finally, in two patients we observed improvements in oxygen uptake values obtained during an incremental CPET, which is an important result as $V'O_2$ peak is an excellent general predictor of survival in CF.[5]

As a wide variety of exercise testing protocols is currently available with their own strengths and weaknesses, the decision about the most appropriate exercise test should be guided by the objective of the measurement. Incremental exercise protocols (incremental cycle or treadmill exercise tests) are more appropriate in the evaluation of the degree of exercise limitation, in the assessment of mechanisms of exercise limitation and/or in the prescription of training programs. Constant work-rate exercise test (CWRET) tLIM is considered more responsive for detecting improvement in exercise tolerance after an intervention.[2,6] In COPD patients, exercise training and interventions designed to improve ventilatory function (i.e. bronchodilators) showed an increase in endurance time.[2,6]

Improving dyspnoea and exercise tolerance are recognised as important goals in the treatment of CF, with the measurement of exercise endurance also considered a valuable component of CF assessment, particularly in response to treatment interventions with new drugs as modulators. In this case series we found evidence that LUM/IVA can increase inspiratory capacity, reduce exertional breathlessness and improve EET in patients with CF. Slowed increases in operating lung volume provided reductions in exertional breathlessness and improvements in symptom-limited exercise endurance. These improvements include sustained lung volume reduction as a result of enhanced tidal expiratory flow rates and lung emptying, with reduced resting and exercise lung hyperinflation observed in patient 3, together with a delay in the mechanical limitation to ventilation. Consequently, exertional dyspnoea was alleviated, leading to increases in EET. In addition to changes in dyspnoea, our patients who showed an increase in endurance time also experienced less leg discomfort. Although we recognize that both peripheral muscle dysfunction and deconditioning could be related to exercise limitation in CF, we did not evaluate muscle function in this study. We acknowledge that this is a case series with no control arm, so only interesting observations can be made. Constant work-rate exercise test, such as a cycle endurance test, confirmed its utility to assess change in exercise capacity following longer-term therapy with modulators.

CRediT authorship contribution statement

Conception and design: DS. Acquisition of data: DS, AG, MV, MDP, BM. Analysis and interpretation: DS, MDP. Drafting the article: DS, AG, MV. All authors revised the intellectual content of the work and gave final approval of the version to be submitted.

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Availability of data and materials

Available upon request.

Declaration of Competing Interest

The authors declare that they have no financial and personal relationships with other people or organisations that could inappropriately influence their work.

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