Annals of Clinical Case Reports

Research Article
Published: 17 Aug, 2022

Effects of Lumacaftor/Ivacaftor Therapy on Exercise Endurance and Inspiratory Capacity in Cystic Fibrosis

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Abstract

Rationale: Since the combination of the corrector Lumacaftor (LUM) with the potentiator Ivacaftor (IVA) has been approved, no reports about the long-term effects of CFTR modulators on exercise endurance and exertional symptoms are available.

Methods: We performed a symptom-limited constant load cycling test with assessments of inspiratory capacity, dyspnea and leg discomfort ratings pre- and post 6 months initiation of LUM/IVA in three patients with Cystic Fibrosis (CF).

Results: Exercise endurance time improved by +87% in patient 1, +52% in patient 2 and +23% in patient 3. There was an improvement in inspiratory capacity prior to exercise (+17%, +16%, +6% in patient 1, patient 2 and patient 3, respectively) and at end-exercise (+4%, +23%, +10% in patient 1, patient 2 and patient 3, respectively), associated with improvements in exertional dyspnea and leg discomfort.

Conclusion: Endurance time, inspiratory capacity and exertional symptoms improved after 6 months of LUM/IVA.

Keywords: Cystic fibrosis; Lumacaftor-Ivacaftor; Endurance time; Exercise tolerance; Longer-term treatment benefits

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Received Date: *19 Jul 2022*
Accepted Date: *10 Aug 2022*
Published Date: *17 Aug 2022*

Citation:
Savi D, Gramegna A, Vicenzi M, Di Paolo M, Rota I, Biglia C, et al. Effects of Lumacaftor/Ivacaftor Therapy on Exercise Endurance and Inspiratory Capacity in Cystic Fibrosis. Ann Clin Case Rep. 2022; 7: 2287.
ISSN: 2474-1655.

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Introduction

The long-term positive effects of the combination of the corrector Lumacaftor (LUM) with the potentiator Ivacaftor (IVA) on Physical Activity (PA) and exercise tolerance in Cystic Fibrosis (CF) patients homozygous for Phe508del CFTR mutation have been recently described in a single report [1]. Among available exercise-testing protocols, constant work-rate exercise test, as cycle endurance test, is considered sensitive for detecting change in exercise capacity following intervention (both pharmacologic and non-pharmacologic) [2]. As previously demonstrated, 1 month LUM/IVA therapy did not increase exercise endurance or modify dyspnea or leg discomfort [3] and no data are available about the longer-term effects of such modulator therapy on exercise endurance and exertional symptoms.

For this purpose, in this preliminary study, we used Constant Work-Rate Cycle Ergometry (CWRCE) to evaluate the efficacy of LUM/IVA (400 mg/250 mg administered orally every 12 h) in CF adults that initiated LUM/IVA as part of clinical care. Specifically, we examined the potential impact of LUM/IVA therapy on Exercise Endurance Time (EET) and exertional symptoms during CWRCE after 6 months of treatment.

Methods

In this prospective, observational, multicenter study, we recruited 5 stable adult CF patients (≥ 18 years old, homozygous for Phe508del) who were about to initiate LUM/IVA in the study period

Table 1: Measurements at peak symptom-limited incremental cycle exercise.

Characteristics	Patient 1			Patient 2			Patient 3		
	Pre	Post	% change	Pre	Post	% change	Pre	Post	% change
BMI, Kg/m^2	24.2	25.1	4	23.9	24.6	3	21.3	21.1	-0.93
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
Peak exercise									
Work rate, watt	180	172	-4.4	180	210	+16.6	120	125	+4.1
V'O2, ml/min	2084	2328	+11.7	2650	2786	+5.1	1699	1384	-18.5
V'O2, ml/min/Kg	25.41	27.39	+7.8	38.41	39.24	+2.1	26.97	22.14	-17.9
V'O2, % 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'O2/HR, ml O2/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'CO2 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

Abbreviations: 1: Patient number 1; 2: Patient number 2; 3: Patient number 3; V'O2: Oxygen Uptake; HR: Heart Rate; V'O2/HR: Oxygen Pulse; ΔSpO2: Arterial Oxygen Saturation Delta from Rest to Peak Exercise; VT: Tidal Volume; V'E: Minute Ventilation; BR: Breathing Reserve; V'E/V'CO2: Ventilatory Equivalent for Carbon Dioxide. Pre: Measurements pre-treatment with Lumacaftor/Ivacaftor; Post: Measurements Post- 6 Months of Treatment with Lumacaftor/Ivacaftor

from April 2019 to January 2020. The study was stopped in March 2020 for the ongoing pandemic of Coronavirus Disease 2019 (COVID-19). Patients were excluded if they had unstable medical conditions that could cause or contribute to breathlessness (i.e. cardiovascular, metabolic, or other respiratory diseases) or other disorders that could interfere with exercise testing, such as neuromuscular diseases or musculoskeletal problems. The study was approved by the ethics committee of Policlinico Umberto I Hospital, Sapienza University of Rome, Italy with the number 853/18 followed by the approval of the other local ethical committees. All patients provided written informed consent for this study. We used a protocol consisting of 2 visits: 3 to 4 weeks prior to initiation of LUM/IVA (visit 1) and 6 months after (visit 2). During each visit, in the morning patients performed spirometry and symptom-limited incremental Cardiopulmonary Exercise Test (CPET) on 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'O2) were measured through calibrated metabolic system (Cosmed K5). Oxygen saturation, heart rate and blood pressure were also registered at baseline, at peak of the exercise and throughout. After completing each exercise test, patients identified the primary reason for stopping (due to leg and/or breathing discomfort or other reason). HRQoL was assessed by the adult version of the revised Italian CFQ-R questionnaire. Finally, at the end of the visit, patients wore a multi-sensor armband (SenseWear Pro3 Armband (SWA), BodyMedia, Pittsburgh, USA) to assess daily habitual Physical Activity (PA) over seven consecutive days. The characteristics and the validation of the device in CF have been previously described [5,6]. 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 numbers of pulmonary exacerbations were prospectively collected through 6 months. Two of 5 participants were excluded from the analysis because the 6-months follow-up visit was prevented due to a strict lockdown during the COVID-19 pandemic in Italy. For each patient we calculated the percentage of change between "pre" and "post" the start of LUM/IVA therapy for each variable.

Results

Patient 1 is a 28-year-old man of Caucasian origin diagnosed with CF at the birth. He has been colonized with *Staphylococcus aureus* and *Aspergillus fumigatus*. He commenced LUM/IVA in May 2019. During six months of treatment, he presented with one pulmonary exacerbation treated with oral antibiotics. The change from baseline in BMI was +4% and ppFEV1 was +3%. He reached his peak exercise at a higher oxygen uptake (+3%) (Table 1). Patient showed an improvement in oxygen pulse (V′O2/HR) by +15%, slightly higher values of ventilation (V′Epeak), mean maximal ventilation less than the predicted MVV (208 L) and lower Breathing Reserve (BR) were observed. Ventilatory efficiency (V'E/V'CO2 slope) and partial Pressure of End-Tidal CO2 (PETCO2) were weakly reduced. After six months of treatment, there was an increase in EET (344 sec *vs.* 644 sec, Figure 1) and an improvement in inspiratory capacity prior to exercise of 520 mL, +17% (Figure 2A). The improvements in inspiratory capacity were sustained during exercise and end-exercise (160 mL, +4%, Figure 2A). There was a reduction in breathing discomfort and leg fatigue as indicated by reductions in both the slope and intensity of breathing discomfort and leg fatigue (Figure 3A, 3B). Daily PA

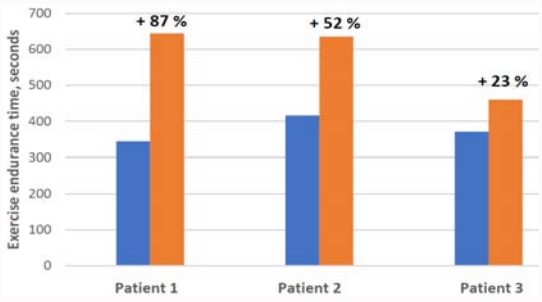
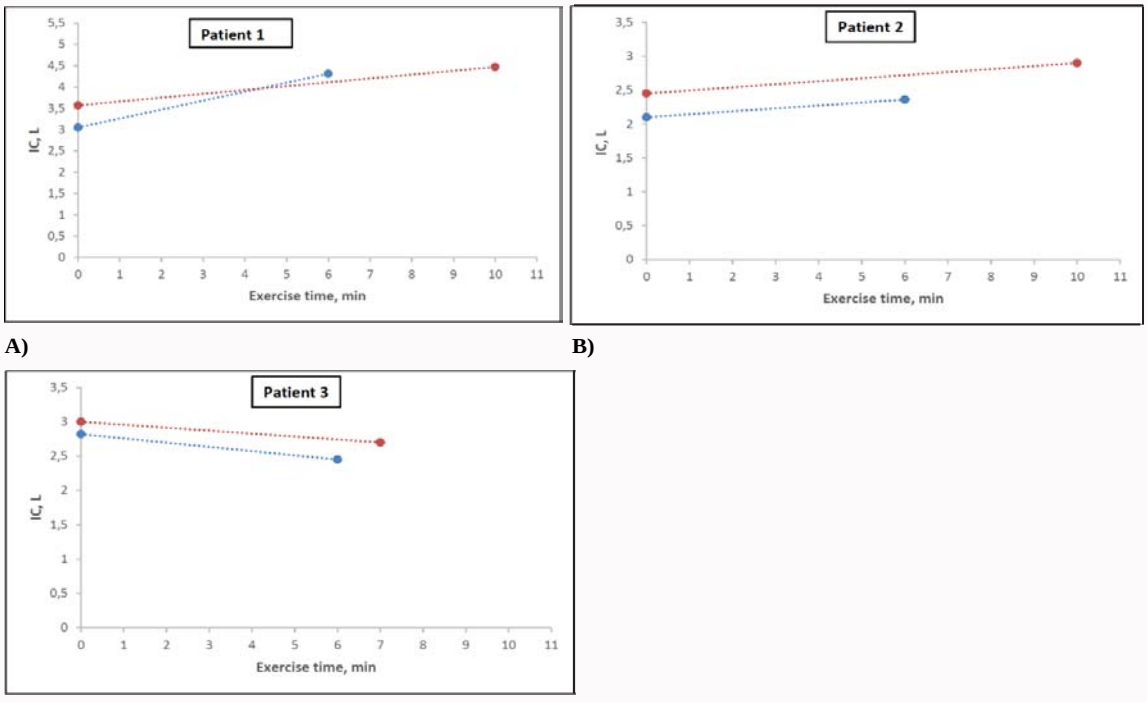


Figure 1: Exercise Endurance Time (EET) during constant work-rate cycle ergometry pre- and post-treatment with lumacaftor/ivacaftor.
Abbreviations: 1: Patient number 1; 2: Patient number 2; 3: Patient number 3; Measurements pre- treatment with Lumacaftor/Ivacaftor; Measurements post- 6 months of treatment with Lumacaftor/Ivacaftor

was not collected at visit 2 for problems related to the accelerometer. Finally, his CFQ-R revealed higher scores indicating a higher patient-reported quality of life with regard to "treatment burden" +14%, "health perception" +12%,"role limitations" +9%, "social limitations" +16%, "digestive symptoms" +16%.

Patient 2 is a 34-year-old man of Caucasian origin diagnosed with CF at birth, and he has been infected with *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Aspergillus fumigatus*. He commenced LUM/IVA in July 2019. During six months of treatment, the patient did not have exacerbations. The change from baseline in BMI was +3% and ppFEV1 was +10%. He reached peak exercise at a higher oxygen uptake (+5%, Supplementary Table 1). There was an improvement in V′O2/HR by +6%. Lower values of V′Epeak, mean maximal ventilation less than the predicted MVV (130 L) and higher BR were observed, suggesting that ventilation limit could be not a limiting factor. V'E/V'CO2 slope and PETCO2 were weakly reduced. There was an increase in EET (416 sec *vs.* 635 sec, Figure 1) and an improvement in inspiratory capacity prior to exercise of 350 mL, +16% (Figure 2B). The improvements in inspiratory capacity were sustained during exercise and end-exercise (540 mL, 23%, Figure 2B). There was a reduction in breathing and leg discomfort as indicated by reductions in both the slope and intensity of breathing and leg discomfort (Figure 3C, 3D). After treatment, patient increased the number of steps in daily life (5141 *vs.* 13374 steps/day, +160%) while duration of daily PA slightly decreased (410 *vs.* 388 min/day, -5%). His CFQ-R revealed higher scores indicating a higher patient-reported quality of life with regard to "emotional state" +27%, "vitality " +24%, "health perception" +33%, "body image" +28% ", "respiratory symptoms" +6%,"digestive symptoms" +33%.

Patient 3 is a 30-year-old man of Caucasian origin diagnosed with CF at birth. He has been infected with *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Mycobacterium abscessus*. He commenced LUM/IVA in June 2019. During the 6 months, the patient had one pulmonary exacerbation requiring IV antibiotic therapy. The change from baseline in BMI was -0.9% and ppFEV1 was -9%. He reached peak exercise at a lower oxygen uptake (-17%), supplementary file Table 1. The patient showed an important reduction in V′O2/HR by -29%. He showed lower values of V′Epeak and lower BR, with maximal ventilation less than the predicted MVV (107 L). V'E/V'CO2 slope was weakly improved. There was an increase in EET (371 sec *vs.* 460 sec, Figure 1). Although 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% (Figure 2C). There was a reduction in breathing and leg discomfort as indicated by reductions in both the slope and intensity



Abbreviations: 1: Patient number 1; 2: Patient number 2; 3: Patient number 3; Measurements pre-treatment with Lumacaftor/Ivacaftor; Measurements post- 6 months of treatment with Lumacaftor/Ivacaftor
Figure 2: Inspiratory capacity (IC) pre- and post-treatment with lumacaftor/ivacaftor at pre-exercise and at end-exercise.

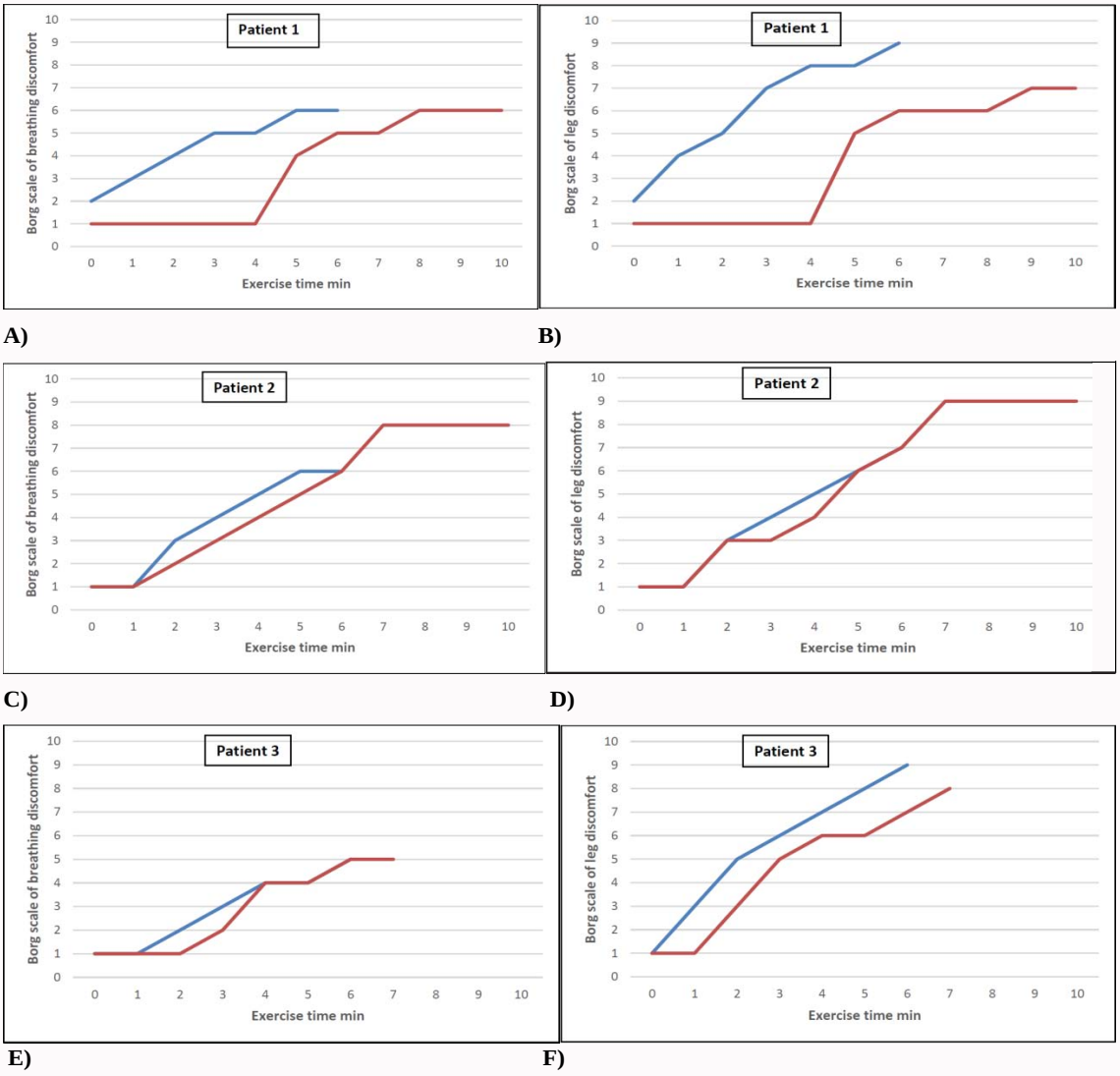


Figure 3: Intensity of breathing and leg discomfort (Borg scale) pre- and post-treatment with lumacaftor/ivacaftor at pre-exercise and end-exercise.
Abbreviations: 1: Patient number 1; 2: Patient number 2; 3: Patient number 3; Measurements pre- treatment with Lumacaftor/Ivacaftor; Measurements post- 6 months of treatment with Lumacaftor/Ivacaftor.

of breathing and leg discomfort (Figure 3E, 3F). Duration of daily PA and number of steps decreased after treatment (-56% and -64%, respectively). His CFQ-R revealed higher scores indicating a higher patient-reported quality of life with regard to "health perception" +16%, "body image" +28%.

Discussion

In this preliminary study, we observed the long-term effects of LUM/IVA on exercise capacity. Results from these three CF patients demonstrate longer EET after six months of LUM/IVA. Improvements in exercise endurance were accompanied by improvements in inspiratory capacity prior to exercise and additional serial assessment of inspiratory capacity during exercise demonstrated that these improvements were maintained at end-exercise. All three patients experienced less dyspnea and less leg discomfort, showing exercise limitation often related to peripheral muscle fatigue and not related to ventilatory constraints. Finally, we observed in two patients improvements in oxygen uptake values obtained during incremental CPET that is an important result as V′O2 peak is an excellent general predictor of survival in CF [7].

Design a study with Constant Work-Rate Exercise Test (CWRET) tLIM to assess the efficacy of interventions is considered to be sensitive and clinically relevant [8]. CWRCE is now often used in efficacy evaluations of long-acting bronchodilators because it allows a thorough evaluation of the physiological response during exercise and due to its documented responsiveness to treatment [8,9]. Improving dyspnea and exercise tolerance are recognized 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 study there is evidence that LUM/IVA can increase inspiratory capacity, reduce exertional breathlessness and improve EET in patients with CF. We have provided insights into the mechanistic factors responsible for reductions in exertional breathlessness and improvements in symptom-limited exercise endurance in CF following LUM/IVA treatment. These improvements include sustained lung volume reduction as a result of improved tidal expiratory flow rates and lung emptying, with reduced resting and exercise lung hyperinflation as observed in patient 3 and a delay in

the mechanical limitation to ventilation. Consequently, exertional dyspnea is alleviated, leading to increases in exercise endurance time. In addition to changes in dyspnea, our patients who had 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, in this study we evaluate daily PA but not muscle function. When we observed PA measurements pre- and post-treatment, only one patient increased the number of steps during his daily life. Further larger studies are likely required in CF to observe effects of such therapy in PA.

The present study has important limitations. Firstly, recruitment was less than calculated due to ongoing pandemic of COVID-19. Secondly, only three of five enrolled patients were able to complete the six months follow-up due to nationwide lockdown. We recognize this is a case series with no control arm, so only interesting observations can be made.

Constant work-rate exercise test, as cycle endurance test, should be considered in clinical trials when assessing change in exercise capacity following longer-term therapy with modulators.

Acknowledgement

The authors would like to express their gratitude to medical student Alessandro Porcella for the stimulating discussion we had on this case report.

Authors' Contribution

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

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Policlinico Umberto I Hospital, Sapienza University of Rome, Italy with number 853/18. All patients were asked to sign an informed consent form authorizing inclusion of their clinical data in the study database.

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