

Long-term effects of ivacaftor on nonpulmonary outcomes in individuals with cystic fibrosis, heterozygous for a S1251N mutation

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Abstract

Objectives: To describe the long-term effects of ivacaftor (Kalydeco®) in individuals with cystic fibrosis (CF) on body mass index (BMI), body composition (BC), pulmonary function (PF), resting energy expenditure (REE), and exercise capacity (EC) after ≥12 months of treatment.

Working Hypothesis: BMI, lean and fat mass, PF, and EC will increase and REE will decrease after treatment.

Study Design: Observational study.

Methodology: Seven individuals with CF (mean age 15.4 ± 5.8 years) heterozygous for S1251N mutation, starting with ivacaftor, were included. Paired *t* tests were performed to assess the effects of ivacaftor. Height and weight were used to calculate BMI and BMI Z-scores. Dual-energy X-ray absorptiometry was used to assess BC. Spirometry and body plethysmography were used to assess PF. Indirect calorimetry was used to measure REE and cardiopulmonary exercise testing (CPET) was used to measure oxygen uptake (VO_{2peak}), peak work rate (W_{peak}), and other CPET variables.

Results: After a median of 15 (interquartile range: 13–16) months of treatment, BMI increased significantly ($P = .03$), but not BMI Z-score ($P = .23$) or BC. Significant improvements were found for several PF variables, especially measures of hyperinflation ($P = .02$). Absolute VO_{2peak} ($P = .01$), VO_{2peak} related to body weight ($P = .00$),

Abbreviations: $BF_{peak}/V_{t_{peak}}$, ratio of breathing frequency to tidal volume at maximal exercise; BF_{peak} , breathing frequency at maximal exercise; BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CO_2 , carbon dioxide; CPET, cardiopulmonary exercise test(ing); DEXA, dual-energy x-ray absorptiometry; IQR, interquartile ranges; $ppFEV_1$, forced expiratory volume in 1 second, in percentage predicted; $ppVO_{2peak}$, maximal oxygen uptake, in percentage predicted; $ppVO_{2peak/kg}$, maximal oxygen uptake, related to body weight, in percentage predicted; ppW_{peak} , peak work rate, in percentage predicted; $ppW_{peak/kg}$, peak work rate, related to body weight, in percentage predicted; REE, resting energy expenditure; RER, respiratory exchange ratio; RV, residual volume; SOP, standard operating procedure; TLC, total lung capacity; $\Delta VO_2/WR$, oxygen cost of work; VO_2 , oxygen uptake; VO_{2peak} , maximal oxygen uptake; $VO_{2peak/kg}$, maximal oxygen uptake, related to body weight; $VO_{2peak/lean}$, maximal oxygen uptake, related to lean body mass; $V_{t_{peak}}$, tidal volume at maximal exercise; W_{peak} , peak work rate; $W_{peak/kg}$, peak work rate, related to body weight; $W_{peak/lean}$, peak work rate, related to lean body mass.

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and oxygen cost of work ($P = .01$) decreased. Absolute W_{peak} ($P = .59$) and W_{peak} related to body weight ($P = .31$) remained stable.

Conclusions: The results showed that long-term treatment of ivacaftor is associated with improvement of BMI and PF, but not of BC and REE. Oxygen uptake reduced after treatment, which may be due to a decrease in work of breathing.

KEYWORDS

body composition, exercise capacity, oxygen uptake, resting energy expenditure

1 | INTRODUCTION

The prevalence of the S1251N mutation in Dutch individuals with cystic fibrosis (CF) is 1.2%.¹ This so-called gating mutation is characterized as a class III mutation² with a defective activity of the CF transmembrane conductance regulator (CFTR) chloride channel.³

Ivacaftor (Kalydeco[®], Vertex Pharmaceuticals Inc) is a CFTR potentiator that partially restores CFTR channel activity.⁴ It has been shown in individuals with gating mutations that during ivacaftor treatment, pulmonary function improves, with a significant decrease of pulmonary exacerbations.^{4,5} In addition, increases of body mass index (BMI), changes of body composition involving increases in fat mass and lean mass, and reductions of resting energy expenditure (REE) after treatment with ivacaftor are reported in literature as well.^{6,7}

Peak oxygen uptake ($VO_{2\text{peak}}$), often used as a measure for exercise capacity, is of particular clinical importance in individuals with CF given as it is associated with quality of life,⁸ reduced risk of hospitalization,⁹ and longevity.¹⁰ Results from other studies indicate that ivacaftor improves exercise duration and capacity.^{5,11,12} However, long-term effects on exercise capacity are unknown. Based on the described results of previous studies, we hypothesized that BMI, both lean and fat mass, and pulmonary function would increase after treatment with ivacaftor, while REE would probably decrease after treatment. These hypothesized effects would result in an improved exercise capacity after treatment as well. The aim of this study was to describe the effects of ivacaftor in individuals with a CFTR gating mutation on BMI in particular body composition, pulmonary function, REE, and exercise capacity after at least 12 months of treatment.

2 | MATERIALS AND METHODS

This was a single center (University Medical Center Utrecht, The Netherlands) observational study in both young and adult individuals with CF with a S1251N mutation. All individuals started a regimen of ivacaftor (two times/day 150 mg) before July 2015, in the context of standard care. All individuals, heterozygous for S1251N mutation, who were at the time under treatment in the CF Center Utrecht were included for this observational study, resulting in a sample size of seven individuals. These individuals were eligible, as ivacaftor was

indicated for this specific mutation. All clinical and demographic data from routine outpatient visits were collected from the electronic patient records. Routine CF care was unchanged and no prescribed exercise program was included. All individuals signed informed consent in context of the Dutch CF registration cohort, which includes the use of standard-care data for scientific research purposes.

2.1 | Anthropometrics and body composition

Measurements of body weight and height were performed, in a fasting state, using a calibrated electronic scale (Seca, Hamburg, Germany) and stadiometer (Ulmer Stadiometer, Ulm, Germany). The subjects were dressed in lightweight clothing and not wearing any footwear while the measurements were taken. BMI was calculated by dividing body weight in kilograms by height in meters squared. Z-scores for body weight, height and BMI were calculated based on the fifth national growth study of TNO (present for ages <21 years) (2010).¹³ Whole-body dual-energy X-ray absorptiometry (DEXA) (type Discovery 4500 APEX 5.4; Philips) was used to measure fat and lean mass to determine body composition. The institutional DEXA standard operating procedure (SOP) was followed.

2.2 | Pulmonary function

Pulmonary function (Geratherm, Bad Kissingen, Germany) was assessed by using spirometry and body plethysmography conform the ERS/ATS recommendations¹⁴ and were used to assess pulmonary function. Global lung function reference equations published in 2012 were used.¹⁵

2.3 | Resting energy expenditure

Indirect calorimetry was used to estimate REE by measuring VO_2 and VCO_2 exhalation. Individuals were measured in a fasted and rested state of at least 8 hours. REE measurements were executed between 08:30 AM and 09:30 AM. For the measurement, individuals breathed through an air-tight face mask that covers both mouth and nose (Hans Rudolph Inc, Shawnee), connected to a calibrated metabolic cart (Geratherm). In the test situation, the individuals were

instructed to lie still in the supine position for 20 minutes. Data of the first 10 minutes were eliminated to achieve data of steady-state ventilation. The institutional SOP was followed. The Weir equation¹⁶ was used to calculate REE.

2.4 | Exercise capacity

Cardiopulmonary exercise testing (CPET) on a bicycle ergometer with gas analysis was used to assess oxygen uptake and peak work rate. Peak oxygen uptake, peak oxygen uptake related to body weight ($VO_{2peak/kg}$), and peak oxygen uptake related to lean body mass ($VO_{2peak/lean}$) were determined. Next to peak work rate (W_{peak}), peak work rate related to body weight ($W_{peak/kg}$), and peak work rate related to lean body mass ($W_{peak/lean}$) were determined as well. Percentages of predicted value for VO_{2peak} , $VO_{2peak/kg}$, W_{peak} , and $W_{peak/kg}$, were calculated based on reference equations: $ppVO_{2peak}$, $ppVO_{2peak/kg}$, ppW_{peak} , $ppW_{peak/kg}$. For all individuals 18 years and younger, reference equations from Bongers et al¹⁷ were used for oxygen uptake and peak work rate. For individuals over 18 years, reference equations from Mylius et al¹⁸ were used for oxygen uptake, and equations from van de Poppe et al¹⁹ were used for peak work rate. Complete gas-analysis variables were collected during CPET. Breathing frequency at maximal exercise (BF_{peak}), tidal volume at maximal exercise (Vt_{peak}) to calculate BF_{peak}/Vt_{peak} , oxygen cost of work ($\Delta VO_2/WR$), and the respiratory exchange ratio (RER) were assessed. In addition, heart rate was measured by electrocardiography. Objective criteria to assess the quality of the performed effort were (a) peak heart rate $\geq 100\%$ ²⁰ predicted, and (b) RER exceeds 1.03 in children and adolescents²¹ and 1.05 in adults.²² Individuals had to meet at least one out of two objective criteria for the test to be considered as maximal effort, as advised in the statement of exercise testing in CF by Hebestreit et al.²³

All participants performed a CPET, according to the Godfrey protocol, on an electronically braked cycle ergometer (Lode Corival, Lode BV, Groningen, The Netherlands).²⁴ During the test, individuals breathed through an air-tight face mask (Hans Rudolph Inc), connected to a calibrated metabolic cart (Geratherm).

2.5 | Statistical analysis

Descriptive statistics were used to summarize demographics and clinical characteristics. Distribution of the data was assessed by Q-Q plots and values are reported with the mean \pm standard deviation (SD) in case of normal distributed data, and with median \pm interquartile ranges (IQR) in case of nonnormal distributed data. Ivacaftor treatment effects were analyzed by two-tailed paired-samples *t* tests (Tables 1 and 2).

Due to the small sample size and the prospective prevention of type I errors in the statistical analysis, we only included the following outcome variables to assess changes in pulmonary function: forced expiratory volume in 1 second in percentage predicted ($ppFEV_1$),

ratio of residual volume (RV) and total lung capacity (TLC) (RV/TLC). For the CPET variables, we included only $ppVO_{2peak}$, $ppVO_{2peak/kg}$, ppW_{peak} , $ppW_{peak/kg}$, and $\Delta VO_2/WR$.

Analysis was performed using SPSS version 25.0 (IBM Corp, Armonk), and differences with a $P < .05$ were considered statistically significant.

3 | RESULTS

Demographic and clinical characteristics at baseline are presented in Tables 1 and 2, respectively. Seven individuals (four male, 57.1%), with a mean age of 15.4 years (range: 9-26 years, SD = 5.8) were included in the analysis. Two of these individuals were adults (≥ 18 years). On average, the individuals had mild disease severity at baseline (mean $ppFEV_1$, $81.7\% \pm 17.8$). Two of the individuals had moderate disease severity. Two of the individuals (28.6%) had CF-related diabetes, four (57.1%) were colonized with *Pseudomonas aeruginosa*, and two (28.6%) had exocrine pancreatic insufficiency.*

3.1 | Outcomes after at least 12 months of ivacaftor treatment

The outcome variables were measured before the start of ivacaftor and after at least 1 year of ivacaftor (median time on ivacaftor 15 months [IQR: 13-16]). BMI increased statistically significant (from 19.9 to 21.2 kg, $P = .03$), but BMI Z-score did not increase significantly (from 0.4 to 0.6, $P = .23$). Both fat mass (from 12.5 to 15.0 kg, $P = .16$) and lean mass (from 34.9 to 37.4 kg, $P = .07$) did not increase statistically significantly. Mean $ppFEV_1$ improved significantly (from 81.7% to 97.7%, $P = .02$). RV/TLC decreased significantly after treatment with ivacaftor (from 31.5% to 16.8%, $P = .02$). During treatment, no significant change was seen in mean REE (from 1966.8 to 1751.7 kcal/day, $P = .43$; Table 1). With regard to CPET variables, both $ppVO_{2peak}$ (from 93.4% to 80.7%, $P = .01$) and $ppVO_{2peak/kg}$ (from 95.6% to 78.8%, $P = .001$) showed a statistically significant reduction. Peak work rate (from 84.2% to 87.5%, $P = .59$) showed a nonsignificant increase, and $ppW_{peak/kg}$ (from 87.5% to 86.6%, $P = .31$) did not change significantly. $\Delta VO_2/WR$ decreased statistically significant after treatment (from 10.7 to 8.5 mL/watt, $P = .01$; Table 2).

4 | DISCUSSION

This is the first report describing the long-term effects of treatment with ivacaftor on BMI, body composition assessed with the DEXA scan, pulmonary function, REE, and exercise capacity in individuals with CF heterozygous with the S1251N mutation. Our results

*Colonization based on presence of *Pseudomonas aeruginosa* in two or more cultures in the preceding year.

TABLE 1 Data of anthropometrics, body composition, pulmonary function, and resting energy expenditure, before and after ivacaftor treatment in seven individuals with CF and S1251N mutation

Variable	Pre-ivacaftor (mean, SD)	Post-ivacaftor (mean, SD)	P value (two-tailed)	95% CI (lower; upper)
Anthropometrics and body composition				
Height/(Z-score) §, cm	160.9 (18.5)/-0.4 (0.8)	164.8 (15.2)/-0.2 (0.8)		
Weight/(Z-score) §, kg	54.0 (19.7)/0.2 (0.7)	59.2 (18.6)/0.6 (0.4)		
BMI/(Z-score), kg/m ²	19.9 (3.4)/0.4 (0.7)	21.2 (3.4)/0.6 (0.8)	*.027/.22	0.2; 2.4/-0.2; 0.6
Fat mass, kg	12.5 (6.1)	15.0 (5.5)	.16	-1.4; 6.4
Lean mass, kg	34.9 (13.9)	37.4 (12.2)	.07	-0.3; 5.4
Pulmonary function				
ppFEV ₁ , %	81.7 (17.8)	97.7 (19.6)	.015*	4.4; 27.6
RV, §, l	1.5 (0.5)	0.9 (0.3)		
RV/TLC, %	31.5 (10.5)	16.8 (5.4)	.016*	21.0; 3.8
Resting energy expenditure				
REE, kcal/d	1966.8 (305.9)	1751.7 (530.9)	.43	-859.5; 429.2

Note: § = not assessed with paired-samples t test. $P < .05$ is considered statistically significant as indicated in bold and with *.

Abbreviations: BMI, body mass index; CI, confidence interval; ppFEV₁, forced expiratory volume in 1 second, in percentage predicted; REE, resting energy expenditure; RV, residual volume; TLC, total lung capacity.

demonstrate improvements in both BMI and pulmonary function, which is in concordance with previous studies.²⁵⁻²⁷ Unexpectedly, VO₂ showed a statistically significant reduction after treatment with ivacaftor, whereas peak work rate was unchanged.

This remarkable decrease in VO₂ was reflected in the decrease of VO_{2peaklean} as well (Table 2) and is higher than the general annual decline of 3.2% as described by van de Weert-van Leeuwen et al²⁸ The most plausible explanation for this change in VO₂ is a lower work of breathing, which is compatible with our finding of an almost 50% reduction in static hyperinflation (RV/TLC) after treatment, mainly as a consequence of reduction in RV (Table 1). This indicates a decrease of small airway disease during treatment and is highly suggestive for a lower work of breathing and a reduced dynamic hyperinflation. Unfortunately, we did not perform flow-volume loops, as our aim was to describe the effects of ivacaftor and this finding was not expected.

Other factors that could explain our findings are less likely. Differences in effort or deconditioning cannot explain the decreased VO₂ as no relevant differences were seen for maximal heart rate, RER, oxygen pulse, and peak work rate. A higher inflammation and infectious state could be the case, however, this was not assessed in our study population. On the contrary, with the use of ivacaftor, a less inflammatory status related to the earlier reported decrease in pulmonary exacerbations is expected.

Other studies have evaluated the effects of ivacaftor regarding exercise capacity,^{5,11,12,29} but none of these studies included individuals with the S1251N mutation and most studies had only a short follow-up period. The results of previous studies are still inconclusive^{5,11,12,29} Noteworthy, similar trends were seen after 12 weeks of ivacaftor for VO_{2peak}, VO_{2peak/kg} and ΔVO₂/WR in a case-report of Saynor et al¹² Information with regard to static hyperinflation and breathing efficiency was unfortunately lacking.

The lower work of breathing, congruent with our finding of RV/TLC ratio measured with body plethysmography, could explain the not statistically significant but clinically relevant, reduction of REE in most of our individuals. A lower work of breathing enables the body to gain body weight, and consequently BMI, and alter in body composition. In our population, the increase in BMI and body composition are not only attributed to weight gain of both fat mass and lean mass, but also to (height-)growth in the pediatric individuals. Similar increases for body weight, BMI and body composition were reported in other studies.^{6,7,11,27,30} Other possible factors which could contribute to lowering of REE are less bacterial infections, less pulmonary exacerbations,²⁶ and a lower systemic inflammation.³¹ Improved fat absorption due to improved pancreatic enzyme secretion,³⁰ dissolved intestinal inflammation,³⁰ and improved glycemic control which is accompanied by the anti-inflammatory effects of insulin^{30,32,33} could result in a positive energy balance and, eventually, a higher body weight especially seen with increased fat mass.

A limitation of this study is our small sample size, which precludes correcting for multiple testing. Consequently, the risk of statistically significant findings by chance, as we assessed many variables, should be taken into account when interpreting these results. However, the prevalence of individuals mutated with S1251N in the Netherlands is 1.2%,¹ which means that we assessed almost half of the Dutch S1251N mutation group. The absence of objective data of physical activity levels and nutritional intake are other limitations. Though, patient records showed no reduction or change in physical activity levels or involvement by an exercise intervention.

Healthcare providers should be aware of the changes during ivacaftor treatment, regarding body composition and REE, but especially exercise capacity. As no exercise intervention or diet intervention was included, we emphasize the importance of an

TABLE 2 Data of cardiopulmonary exercise testing variables before and after ivacaftor treatment in seven individuals with CF and S1251N mutation

Variable	Pre-ivacaftor (mean, SD)	Post-ivacaftor (mean, SD)	P value (two-tailed)	95% CI (lower; upper)
HR _{peak} §, bpm	184.5 (5.4)	186.2 (6.2)		
RER §	1.1 (0.1)	1.3 (0.1)		
VO _{2peak} §, l	2.3 (1.0)	2.1 (0.8)		
ppVO _{2peak} , %	93.4 (16.5)	80.7 (12.0)	.010*	-22.0; -4.91
VO _{2peak/kg} §, mL/min/kg	42.9 (6.6)	36.3 (5.6)		
ppVO _{2peak/kg} , %	95.6 (10.6)	78.8 (9.0)	.000*	-24.4; -13.1
VO _{2peak/lean} §, mL/min/kg	59.2 (7.1)	53.1 (7.5)		
W _{peak} §, watt	174.9 (83.5)	191.3 (86.2)		
ppW _{peak} , %	84.2 (16.0)	87.5 (11.9)	.59	-5.3; 8.4
W _{peak/kg} §, watt/kg	3.2 (0.6)	3.2 (0.6)		
ppW _{peak/kg} , %	87.5 (15.1)	86.6 (11.6)	.31	-12.5; 4.8
W _{peak/lean} §, watt/kg	4.4 (0.9)	4.6 (0.8)		
TV _{peak} §, l	1.6 (1.0)	2.0 (1.1)		
BF _{peak} §, 1/min	48.4 (9.7)	42.5 (17.3)		
BF _{peak} /TV _{peak} §	41.7 (26.4)	30.5 (27.2)		
ΔVO ₂ /WR, mL/kg/watt	10.7 (1.2)	8.5 (0.9)	.005*	-3.2; -1.0

Note: § = not assessed with paired-samples t test. $P < .05$ is considered statistically significant as indicated in bold and with *.

Abbreviations: BF_{peak}/Vt_{peak}, ratio of breathing frequency to tidal volume at maximal exercise; BF_{peak}, breathing frequency at maximal exercise; CI, confidence interval; HR_{peak}, maximal heart rate; ppVO_{2peak/kg}, maximal oxygen uptake related to body weight, in percentage predicted; ppVO_{2peak}, maximal oxygen uptake, in percentage predicted; ppW_{peak}, peak work rate, in percentage predicted; ppW_{peak/kg}, peak work rate related to body weight, in percentage predicted; RER, respiratory exchange ratio; TV_{peak}, tidal volume at maximal exercise; VO_{2peak}, maximal oxygen uptake; VO_{2peak/kg}, maximal oxygen uptake related to body weight; VO_{2peak/lean}, maximal oxygen uptake related to lean body mass; W_{peak/kg}, peak work rate related to body weight; W_{peak}, peak work rate; W_{peak/lean}, peak work rate related to lean body mass; ΔVO₂/WR, oxygen cost of work.

interdisciplinary treatment at the start of CFTR modulating drug therapies. For the upcoming triple therapies, at least equal treatment effects could be expected and the cardiopulmonary system will be even less limited during exercise and training. The limitation will be at the peripheral muscle level. Accordingly, when a training intervention is started simultaneously with the drug therapy, individuals with CF will use their new (pulmonary) capacities, to adapt their exercise capacity to its maximum. Physical therapy and dietetic intervention should be intertwined adequately to guide and advise individuals with CF to achieve an optimal physical and nutritional status. In addition, this collaboration is necessary to achieve an optimal overall treatment for the long-term as well. Increase in extensively amount of fat mass should be prevented to reduce the risk of developing overweight and/or obesity in CF individuals.

Future studies are warranted to improve the knowledge about the effects of novel treatment options such as ivacaftor on body composition, REE, and exercise capacity. These studies should include large samples, broader ranges of disease severity, objective measurements of physical activity levels, nutritional intake, and assessment of breathing patterns (dynamic hyperinflation) during exercise.

5 | CONCLUSIONS

This study demonstrates that 15 months of ivacaftor in a small group of CF individuals with the S1251N mutation improve BMI and pulmonary function. Oxygen uptake reduces after treatment, which may be due to a decrease in work of breathing, as is suggested by the reduction of static hyperinflation.

ACKNOWLEDGMENTS

The authors would like to acknowledge the contribution of the individuals who participated in this study, and thank W. Broeders and S. Michel for their contribution for the data collection. The authors would like to thank C.L.J.J. Kruitwagen for his statistical advice and Y.M. Blom-Huibers for editing of the final manuscript.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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How to cite this article: Burghard M, Berkers G, Ghijsen S, et al. Long-term effects of ivacaftor on nonpulmonary outcomes in individuals with cystic fibrosis, heterozygous for a S1251N mutation. *Pediatric Pulmonology*. 2020;55:1400-1405. <https://doi.org/10.1002/ppul.24745>