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Physical activity levels in cystic fibrosis patients before and after triple modulator therapy: a single-center retrospective pilot study

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Abstract

Background

Regular physical activity (PA) and active lifestyle is associated with health benefits and greater life expectancy in patients with cystic fibrosis (CF). The introduction of new modulators therapy may influence PA level by improving functional health status of patients. This study aimed to investigate whether Elexacaftor/Tezacaftor/Ivacaftor (ETI), had an impact on daily PA level in patients with CF.

Methods

18 patients (7 males, 11 females) participated in the study. PA level and lung function data were measured with accelerometry and spirometry respectively at: baseline (T0), 1 month after receiving ETI (T1) and between 3 and 6 months (T3+) after receiving ETI.

Results

The mean relative forced expiratory volume in 1 second ($FEV_{1\%pred}$) significantly increased from T0 (68.4 ± 18.1) to T1 (78.2 ± 21.2 , $p < 0.05$). The mean relative forced vital capacity ($FVC_{\%pred}$) significantly increased from T0 (88.2 ± 14.9) to T1 (94.0 ± 13.9 , $p < 0.05$). PA parameters at T0 were: 6460.2 ± 2068.8 steps/day and 46.8 ± 35.0 min/day for moderate to vigorous PA (MVPA) time. None of the parameters presented statistical differences throughout all the measurements compared to T0. The mean steps/day were 6253.8 ± 2253.5 at T1 and 7036.0 ± 3177.0 at T3+. The mean MVPA time (min) were 36.2 ± 15.6 at T1 and 48.9 ± 24.4 at T3+.

Conclusions

Despite improved lung function, daily PA levels of patients with CF do not improve after ETI treatment. Therefore, patients with CF, despite being under modulator treatment, still need to be supported and encouraged to be physically active and PA promotional programs are important to achieve an active life in patients with CF.

Keywords: health, mucoviscidosis, well-being

Introduction

Cystic fibrosis (CF) is a disease affecting at least 100 000 people around the world (Shteinberg et al., 2021). This monogenic disease is a multisystem autosomal recessive disorder caused by variants in the gene for cystic fibrosis transmembrane conductance regulator (CFTR) protein, a cell-surface localized chloride channel that regulates absorption and secretion of salt and water across epithelia (Bell et al., 2020). It is the most common life-threatening autosomal recessive disease in Caucasian populations (Gallati, 2013). CF affects mainly the respiratory, gastrointestinal, glandular and reproductive systems (Lopes-Pacheco, 2020).

The treatment for patients with CF has been focused on improving and preventing the symptoms of CFTR dysfunction, mainly recurrent respiratory infections and the pancreatic exocrine failure (Elborn, 2016). Physical Activity (PA) improves exercise capacity, slows down the decline in lung function and improves the quality of life and life expectancy in patients with CF (Hulzebos et al., 2013). In fact, regular PA is recommended in clinical practice and has been included in many treatment programs (Dwyer et al., 2011). Despite all the benefits of PA, scientific literature seems to indicate that patients with CF struggle to adopt a physically active lifestyle (Cox & Holland, 2019). Current recommendations specific for patients with CF state that patients should perform at least 150 minutes per week, and preferably 300 minutes per week, of moderate to vigorous PA (MVPA) (Swisher et al., 2015). The World Health Organization (WHO) refers to meeting the goal of 150 minutes of MVPA spread throughout the week: e.g. 30 minutes of MVPA time, 5 times per week (World Health Organization, 2010).

Ward et al. (Ward et al., 2013) and Dillenhoefer et al., (Dillenhoefer et al., 2022), reported that patients met the minimal PA recommendations. However, some other studies report lower PA level in CF population (Cox & Holland, 2019). This difference of reported PA level in literature could be explained by the method used for PA level assessment. Some studies used questionnaires which frequently measure subjectively the levels of PA in patients with CF, while accelerometers provide a more objective evaluation (Savi et al., 2013). Previous studies measuring PA with accelerometers in CF population reported values of 15 min/day of MVPA time (Troosters et al., 2009), 27 min/day of MPVA (Savi et al., 2013), 43 min/day of MVPA (Ward et al., 2013) and 103 min/day of MVPA (Dillenhoefer et al., 2022). PA level could also be influenced by various facilitators or barriers in CF. These parameters are associated to various domains, like individual, clinical, social or even environmental parameters, as mentioned in the recent literature (Cox & Holland, 2019; Denford et al., 2020). The evolution of some of these factors could possibly have an influence on PA level of patients with CF.

In this way, a new class of therapy directed towards restoring the CFTR protein function has appeared in the past decade (Elborn, 2020; Paterson et al., 2020). This new therapy – the CFTR modulators – conducts to a significantly improved pulmonary function, decreased respiratory infections and improved nutrition (Edmondson et al., 2021). Such leap in the therapies have paved the way for the development of Elexacaftor-Tezacaftor-Ivacaftor (ETI), a new highly effective triple modulator treatment approved by the end of 2020. This treatment is addressed to patients who have at least one F508del mutation in the CFTR gene, which represents approximately 90% of the CF population (*FDA Approves New Breakthrough Therapy for Cystic Fibrosis. Published March 24, 2020. Accessed October 27, 2020. <https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis> Google Scholar, n.d.*). It has been proved to have beneficial effects not only in individuals with mild to moderate CF, but also in individuals with advanced pulmonary disease, including candidates for lung transplantation (Shteinberg & Taylor-Cousar, 2020).

Burns et al. report that ETI does not improve exercise capacity in the majority of patients with CF (VO_{2peak} : 37.7 ml.min⁻¹.kg⁻¹ pre-treatment and 34.5 ml.min⁻¹.kg⁻¹ post-treatment, P =0.07; Burns et al., 2022). The authors state that the performance gains can only occur if matched by training and hypothesize that the lack of improvement may be due to a reduced PA level over the study period as a result of feeling better on ETI and also the SARS-CoV2 pandemic. However, this study did not measure the PA levels of the patients and could only hypothesize about the reasons without an objective measurement. Conversely, a study (Causer et al., 2022) observed for the first time improvements on lung function (FEV_{1%pred}) and exercise capacity (VO_{2peak}) in 3 adolescents, following 6 weeks of treatment with ETI. The improvements in exercise capacity were greater in more severe CF lung disease and lower aerobic fitness baseline. However, it has to be considered that the sample size was small (n=3) and only 2 of them had their device-based PA data analyzed with one case increasing (+17%) and one case decreasing (-32%) the PA time. To date, there is no more data regarding the potential effect of ETI on PA levels. Other studies that showed an improvement on lung function after ETI (Hillen et al., 2022; Krivec et al., 2022; McGrath et al., 2022), did not assess the impact of this improvement on daily PA either.

Therefore, the objective of this study was to investigate the effects of ETI on PA levels in patients with CF. It was hypothesized that patients, after starting ETI treatment, due to a potential improvement of their lung function and exercise capacity, would incur a substantial PA increase along the time.

Material and Methods

Participants

This retrospective cohort study included patients diagnosed with CF that were regularly followed up at the CF center of the University Hospital Center of Limoges. Local ethical approval was obtained for this study and all subjects provided informed consent.

Inclusion criteria were defined as follow: a diagnosis of CF confirmed by identification of genetic mutations and/or a positive sweat test, initiating ETI treatment, age over 6 years old, a stable health status with at least a 6-week period - away from exacerbation or antibiotic therapy and affiliation to a social security plan. Non-inclusion criteria were defined as follow: being part of an interventional research protocol whose intervention could have influenced daily PA level or fitness level, being transplanted or awaiting a transplant and being under judicial protection, guardianship or curatorship.

Study design

In order to determine the effects of new modulator therapy initiation in patients with CF, PA level and lung function data were obtained from routine clinical assessments at baseline (before treatment initiation, T0), one month after receiving ETI (T1) and between three and six months (T3+) after receiving ETI.

Physical activity level

PA level was objectively quantified using accelerometers (ActiGraph GT3X, Actigraph Corporation, Pensacola, FL). Patients were asked to wear the accelerometer on their waist of their dominant side for 7 consecutive days at T0, T1 and T3+.

Devices were programmed to record at a frequency of 30 Hz, meaning that the accelerometer recorded data at every 1/30th of a second. Tri-axial data collected from accelerometers was analyzed using the software Actilife V6.11.9 which converted data to number of minutes per day spent in various PA intensity categories with the goal of measuring minutes per day of MVPA, light PA time and sedentary time. Step counts were based only on accelerometer data collected on the vertical axis. Steps/day was determined by averaging the steps taken per day across valid wear days.

Lung function

According to international guidelines, lung function parameters were assessed using spirometry (NDD Medical Technologies, Inc., Switzerland). Relative forced expiratory volume in 1 s ($FEV_{1\%pred}$) and relative forced vital capacity ($FVC_{\%pred}$) were measured in patients in sitting position, while wearing a nose clip. Data was computed according to sex, age, height, and ethnicity, based on reference regression equations developed by the Global Lung Function Initiative (Quanjer et al., 2012).

Data analysis

Data is presented as mean \pm standard deviation. All analyses were performed using SPSS v.29 for Windows. Kolmogorov-Smirnov test, was used to examine data's normality.

Paired sample t-test was used to show differences, in the lung function and PA data, between T0 (defined as baseline pre-treatment value) and the different measurements (T1 and T3+) when data was normally distributed, and Wilcoxon signed-rank test was used to compare non-normally distributed data.

To further explore PA level over the 7-day period of measurement, data was grouped in 3 periods: data from Monday to Friday (week), data from Saturday and Sunday (weekend) and data from Monday to Sunday (7 days). Significance level was set for $p < 0.05$.

Results

The study population was composed by 18 patients with CF (7 males and 11 females). Because there were no statistically significant differences in the mean values of any of the clinical parameters between adults (n=16) and adolescents (n=2) groups, we did not separate the data by age group. Data of the patient's characteristics at T0 are resumed in Table I.

Table I. Characteristics of the subjects at T0.

| | | |
|----------------------------|--|-----------|
| N=18 | Age (years) | 27.9±10.2 |
| Anthropometric data | Weight (kg) | 57.1±13.7 |
| | Height (m) | 164.9±9.7 |
| | BMI (kg.m ⁻²) | 21.0±3.2 |
| Pulmonary data | Forced expiratory volume in 1s (%) | 68.4±18.1 |
| | Forced vital capacity (%) | 88.2±14.9 |
| GFTR gene mutation | Delta F508 homozygotic (n (%)) | 12 (66.7) |
| | Delta F508 heterozygotic (n (%)) | 6 (33.3) |
| Comorbidities | Nasal polyposis (n (%)) | 9 (50) |
| | Gastroesophageal reflux (n (%)) | 3 (16.7) |
| | Distal intestinal obstruction syndrome (n (%)) | 5 (27.8) |
| | Hemoptysis (n (%)) | 5 (27.8) |
| | Exocrine pancreatic insufficiency (n (%)) | 15 (83.3) |
| | Diabetes (n (%)) | 2 (11.1) |
| | Osteoporosis (n (%)) | 1 (5.6) |

Lung function evolution

In order to see the lung function evolution of the patients before and after the ETI treatment, FEV₁%_{pred} and FVC%_{pred} values for each measurement time are resumed in **Figure I**.

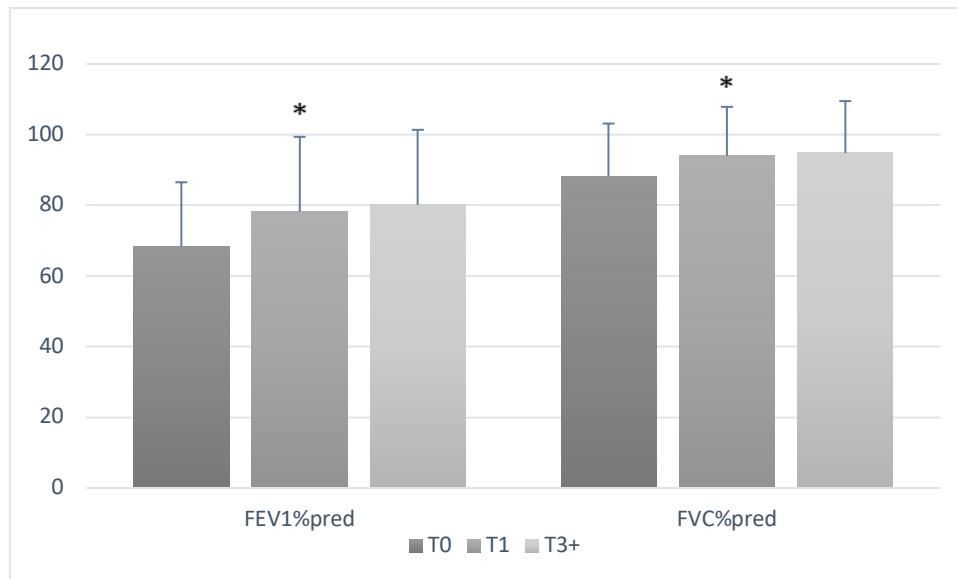


Figure I. Evolution of pulmonary parameters along the measurements (n=18).

Data are presented as mean group values and standard deviation. Difference from previous measurement: * (P < 0.05).

FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, T0: baseline, T1: 1 month after receiving ETI, T3+: between 3 and 6 months after receiving ETI, %pred: percentage of predicted normal values.

Physical activity evolution

In order to see the evolution of PA level of the patients along the ETI treatment, **Table II** presents the mean daily steps, the mean daily sedentary time, the mean daily light PA time and the mean MVPA time.

Table II. Evolution of the physical activity parameters along the measurements.

| Parameter | T0 (n=18) | T1 (n=11) | T3+ (n=10) |
|------------------------------|---------------|---------------|---------------|
| Daily steps | 6460.2±2068.8 | 6253.8±2253.5 | 7036.1±3177.0 |
| Daily sedentary time (min) | 570.2±80.2 | 531.9±133.3 | 552.0±143.8 |
| Daily light PA time (min) | 159.3±50.7 | 166.9±46.1 | 169.4±54.6 |
| Daily moderate PA time (min) | 42.2±30.2 | 32.7±12.7 | 44.1±21.8 |
| Daily vigorous PA time (min) | 4.4±5.5 | 3.4±6.6 | 4.1±5.4 |
| Daily MVPA time (min) | 46.8±35.0 | 36.2±15.6 | 48.9±24.4 |

Data are presented as mean±SD. T0: baseline, T1: 1 month after receiving ETI, T3+: between 3 and 6 months after receiving ETI.

All parameters changes did not reach statistical significance between any period (week, weekend, 7 days) nor any measurement (T1, T3+) compared to T0.

For further comprehension of the individual differences and evolution in MVPA time, data is presented with boxplots and dotplots to see the individual differences between each measurement compared to T0 (**Figures 2 and 3**). A line at 30 minutes has been plotted in each figure for easily identifying which measurements were above and below the international PA guidelines (30 minutes/day).

In **Figure II**, individual MVPA values at T0 and T1 are plotted. Four out of 11 patients did not meet the 30min/day recommended PA before ETI treatment initiation. One month after the treatment, only 3 patients out of 11 remain under the minimum recommended daily PA level, one patient having increased his PA level above the 30min/day threshold.

Overall, among the 11 patients, 6 of them decreased the MVPA time, while 5 increased it after the treatment.

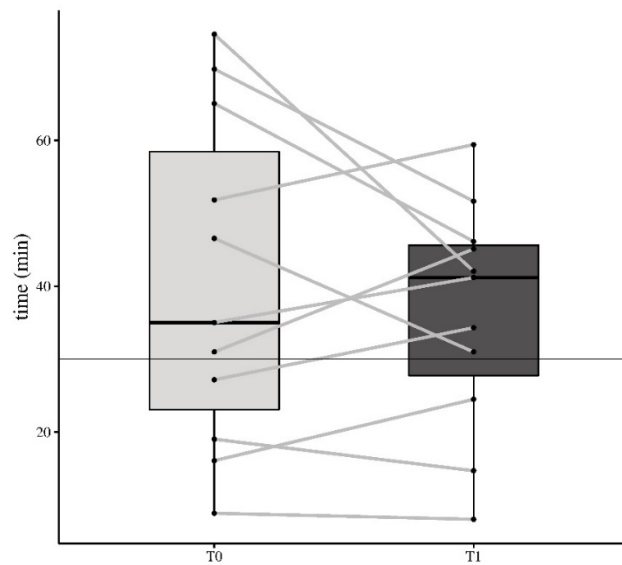


Figure II. Individual evolution of the daily moderate to vigorous physical activity time between T0 and T1 (n=11). Data are presented as mean group values (boxplots) and individual values (dotplots). T0: baseline, T1: 1 month after receiving ETI.

Figure III reports the individual MVPA values at T0 and T3+. Five out of 10 patients did not meet the 30min/day recommended PA before ETI initiation and while 7 of them increased their MVPA time at T3+, 3 of them decreased it.

At T0, one of the patient's values stood out as MVPA time was above 160min/day, and despite a reduction of two thirds at T3+, values were still above 30 min.

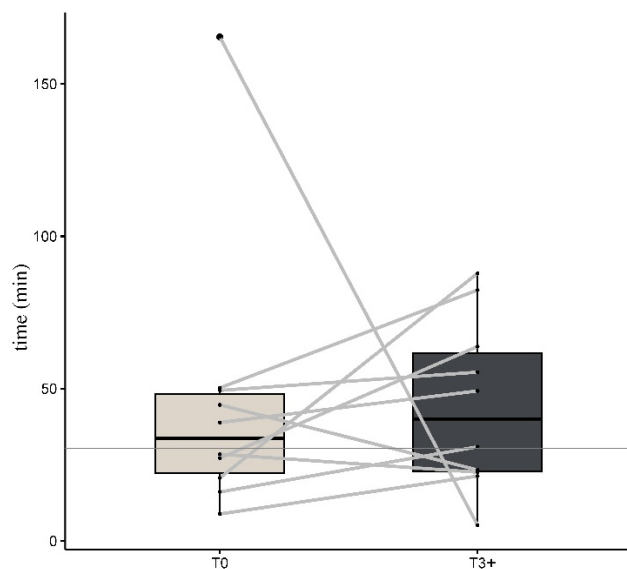


Figure III. Individual evolution of the daily moderate to vigorous physical activity time between T0 and T3+ (n=10). Data are presented as mean group values (boxplots) and individual values (dotplots). T0: baseline, T3+: between 3 and 6 months after receiving ETI.

Discussion

To our knowledge, this study is the first to investigate the effect of ETI on daily PA level in patients with CF. Our results highlight that despite an improvement on lung function parameters after starting the treatment, PA parameters presented no difference between measurements. These results reject our hypothesis in which we stated that patients would benefit from a clinical improvement and incur a substantial PA increase.

PA is not only recommended to patients with CF, but to the population in general for their benefits (e.g., reduced risk of chronic disease, increased pulmonary function, increased muscle endurance, reduced anxiety and depression, improved socialization). In patients with CF, PA is considered as an important part of treatment and disease management (Dwyer et al., 2011; Swisher et al., 2015) and is arguably even more important than for the rest of the population.

In our study we measured the PA at 3 different moments: T0, T1 and T3+. At T0 (before the initiation of treatment), mean MVPA time of our patients was 46.8 ± 35.0 min.day⁻¹. It has to be emphasized that, at a group level, our patients already met the current minimum international PA recommended guidelines of 30 minutes of MVPA per day (World Health Organization, 2010) before the treatment (**Table II**). This result is really interesting as it may provide some potential health benefits for the patients.

This could be explained by the fact that the staff of the CF center where the patients composing the study population are followed up, has a PA professional. This professional has the mission to follow up the patients and help them to achieve a more active lifestyle with some advice, behavioral modification, educational initiatives and physical exercise sessions. The high mean MVPA level value at T0 could be the expression of the effectiveness of the actions of this professional.

The reasons for not seeing statistical differences in any PA parameter after the introduction of the treatment, are likely to represent the already relatively high baseline in all PA parameters. However, it must be noted that data was heterogeneous between patients. For instance, before the treatment (T0), 6 patients had values below 30min/day of MVPA while 12 had values above 30min/day. The rest of the differences and disparities between patients and measurements could be linked to different personal opinions and individual perceptions about PA after the treatment.

Mean daily steps of patients were between 6000 and 8000 steps/day before treatment and in all measurements after treatment (**Table II**). Since the sedentary lifestyle index has a value of $\leq 5,000$ steps per day (Tudor-Locke et al., 2008), our patients could be considered active. However they were within a range of 500-600 min/day of sedentary time in all measurements (**Table II**) which is a quite high value and it is around the 9-hours-a-day sedentary behavior's recommended cut-off (Ku et al., 2018). Mean light PA time was within a range of 150-200 min.day⁻¹ (**Table II**). A decrease of sedentary time, encouraging patients to engage in less sedentary behaviors in exchange of an increase in light PA time or MVPA might be of interest (Bianchim et al., 2022).

With respect to our other findings, it is of interest that globally we found a short-term improvement on lung function after starting the treatment (**Figure I**), and while Burns et al., did not find improvements on lung function after ETI, and stated that performance gains can only occur if matched by training (Burns et al., 2022), our patients did improve the lung function after the first month under treatment. Indeed, FEV_{1%}pred significantly increased from T0 (68.4%) to T1 (78.2%) and FVC_{%pred} as well increased significantly from T0 (88.2%) to T1 (94.0%). After that, values reached a plateau at T3+. These results are in accordance with other studies that showed improvements in lung function after the treatment (Causser et al., 2022; Hillen et al., 2022; Krivec et al., 2022; McGrath et al., 2022) and highlight the profound gains in the health of patients with CF since the introduction of ETI. These gains could be explained by the way ETI inverted CF physiopathological process increasing the F508del mutant CFTR protein's function at the cell surface, leading to an improvement in chloride ion transport (Ridley & Condren, 2020).

According to the literature only one study assessed PA level in 2 patients with CF before and after ETI treatment (Causser et al., 2022). This study reported an increase of PA level in one case (+17%) but also a decrease in the other case (-32%). In our study, only some trend for mean MVPA time improvement could be observed. This major result could emphasize the fact that engagement of patients with CF in an active lifestyle could be explained by individual and environmental factors (Cox & Holland, 2019; Denford et al., 2020), and not only on the basis of clinical factors. As a matter of fact, the PA professional recounted various points of view expressed by the patients during their PA sessions regarding the effect of the treatment on their PA level. While some patients increased their daily MVPA time as a result of an improvement in their physical health and motivation, others reported a reduction in PA. Patients reporting this reduction alleged that since they were already feeling better and PA was being seen as part of their treatment, they didn't need it any more. The different opinions and individual perceptions in this study after ETI are consistent with previous research (Almulhem et al., 2022). Indeed, PA assessment is not commonplace or consistent in clinical practice (Shelley et al., 2019) which leads to a limited understanding of PA in CF population. Dillenhofer et al., proved that supervision was a facilitator to motivate CF patients to improve daily PA and that precise action plans and concrete coping strategies to achieve and active lifestyle are needed

(Dillenhofer et al., 2022). It is consequently of medical interest to quantify actual PA levels in patients with CF to help prescribe individual PA programs designed to improve their health.

Strengths and limitations

A major strength of this study is the careful and objective assessment of PA in patients with CF before and after ETI which was carried out in a field where little information has been provided due to the novelty of this treatment and the lack of PA data in CF patients. Another strength is the individual comparison between periods to better comprehend the inter-individual differences between patients. However, we should also acknowledge some limitations and caveats in this study. Perhaps, due to the retrospective design of the study, the main limitation was the incomplete dataset in all PA measurements and the relatively small sample size. Furthermore, some data about exercise capacity or individual's social and environmental characteristics are missing to further explore the lack of improvement of PA level in the current study, despite an improvement of pulmonary function. A multicentric study to examine differences according to the living area would be as well of interest.

Conclusions and perspectives

Our findings highlight the fact that ETI has no positive effect on the daily PA levels of patients with CF. However, our patients already achieved the recommended daily PA goal of 30 minutes of MVPA. This could be explained by the fact that they were accompanied by a PA professional. Thus, our findings show the importance of PA and sedentary time assessment across the spectrum of age and disease severity for patients with CF and that despite being under ETI treatment and improving lung function parameters, patients with CF may still require assistance and encouragement to engage in PA. Therefore, PA promotion programs, carried out by PA professionals, are crucial to help patients with CF achieve or maintain an active and healthy lifestyle.

We believe that the future of CF care in terms of PA recommendations, will require a paradigm shift away from general recommendations and towards an individualized, holistic approach by a PA specialist.

Conflicts of Interest

The authors declare no conflict of interest.

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