Received: 31 July 2024 | Accepted: 22 January 2025

DOI: 10.1002/jpr3.70007

Journal of Pediatric Gastroenterology and Nutrition JPGN REPORTS

SHORT COMMUNICATION

Nutrition

Effect of cystic fibrosis modulator therapies on serum levels of fat-soluble vitamins

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Funding information
None

Abstract

This is a prospective, multicenter study of a cohort of 224 cystic fibrosis (CF) patients treated with CF transmembrane conductance regulator (CFTR) modulators (CFTRm). Our aim was to prospectively analyze the effect of CFTRm treatment on fat-soluble vitamin serum levels. Demographic and clinical data were recorded, and fat-soluble vitamin levels were analyzed at baseline, and at 6 and 12 months after starting treatment. Two groups were analyzed separately: patients receiving dual therapy lumacaftor/ivacaftor or tezacaftor/ivacaftor (Lum/Tez+Iva), and those on triple therapy with elexacaftor/tezacaftor/ivacaftor (ETI). We found that treatment with ETI produced a significant increase in vitamin D and A levels within the first 6 months, which was maintained at 12 months. However, with dual therapy, we observed an increase only in vitamin A levels within the first 6 months, which was not maintained at 12 months. No differences were found in vitamin E serum levels between the groups.

KEYWORDS
CFTR modulators, nutritional status, vitamin supplementation

1 | INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive genetic disorder caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which results in CFTR deficiency or dysfunction. These changes produce a multiorgan disease involving the lungs, the pancreas, the liver, the gallbladder, and the intestines.[1,2]

Classically, patients with CF are at risk of having fat-soluble vitamin deficiencies, especially due to fat malabsorption, which is higher in the presence of exocrine pancreatic insufficiency (EPI). These fat-soluble vitamin deficiencies are common, affecting around 10%–35% of children with CF and pancreatic insufficiency[1]; therefore, their serum levels should be monitored, and supplements should be given based on the results.

In recent years, therapeutic advances have substantially improved the prognosis and quality of life of patients with CF.[3] CFTR modulators (CFTRm) are one of the promising therapies in which improvements have been observed both at the pulmonary, nutritional, and gastrointestinal outcomes.[4] CFTRm have been shown to improve nutritional status through different mechanisms, one of them being improving fat absorption[5]; therefore, it would be expected that fat-soluble vitamin levels would improve with CFTRm. Several studies have evaluated the effect of both dual therapies with lumacaftor/ivacaftor or tezacaftor/ivacaftor (Lum/Tez+Iva) and triple therapy with elexacaftor/tezacaftor/ivacaftor (ETI) on fat-soluble vitamins (A, D, and E) serum levels. The results are not uniform, with some studies showing increases in the levels of vitamins A and D, while others find no changes, and the results regarding vitamin E are very variable from one study to another.[6] Furthermore, these studies have small sample sizes, and most are retrospective. For all these reasons, the objective of the present study was to prospectively analyze the effect of treatment with CFTRm on fat-soluble vitamin serum levels in patients with CF in a large sample of patients.

What is Known

- Treatment with cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulators improves nutritional status in CF patients.
- The effect of CFTR modulators on fat-soluble vitamin levels remains unclear.

What is New

- Treatment with dual therapy lumacaftor/ivacaftor or tezacaftor/ivacaftor has no significant effect on fat-soluble vitamin levels.
- Treatment with triple therapy (elexacaftor/tezacaftor/ivacaftor) results in a significant increase in vitamin D and A levels.

2 | METHODS

2.1 | Study design

This is a prospective, multicenter study that includes CF patients treated with CFTRm, dual therapy with Lum/Tez+Iva, or triple therapy with ETI. Fourteen Spanish CF Units participated in the project. Inclusion criteria were patients diagnosed with CF who were candidates to start

CFTRm treatment. All visits took place in the outpatient setting, during routine check-ups. The study data were collected between May 2019 and November 2023.

2.1.1 | Ethical statement

The study was approved by the Clinical Research Ethics Committee of the University Hospital Ramón y Cajal (Madrid) and ratified by the committees of the other participating hospitals. All participants aged 12–18 years, their guardians, and adult patients consented to participate in the study and signed informed consent.

2.2 | Clinical and demographic data

Demographic and clinical data were recorded: sex, diagnosis by neonatal screening, age at baseline, anthropometric data, pancreatic status, CF genotype, history of meconium ileus, and the presence of CF-related liver disease or abnormal glucose metabolism. Reference values used for anthropometric data were the World Health Organization 2006 (WHO; https://www.who.int) for children under 6 years and Carrascosa 2010 [7] for patients over 6 years.

Regarding vitamin supplementation, all CF units in this study follow a uniform protocol. Patients receive supplementation with specific CF polyvitamins that include fat-soluble and water-soluble vitamins, and the supplementation started when they present exocrine pancreatic insufficiency. After that, changes are made based on serum levels monitored during follow-up, according to the European Cystic Fibrosis Society Guidelines published in 2016.

Levels of fat-soluble vitamins were analyzed at baseline (before starting CFTRm), at 6 months, and at 12 months. Vitamin D was measured as serum 25-hydroxyvitamin D (calcidiol), vitamin A was measured as retinol, and vitamin E as serum alpha-tocopherol. Serum vitamin K levels were not analyzed, as is not considered a reliable marker for deficiency.

The reference values considered for vitamin levels were[8–10]:

1. 25(OH)D: normal values ≥30 ng/mL; vitamin insufficiency 20–29 ng/mL; vitamin deficiency <20 ng/mL; toxicity >100 ng/mL.
2. Vitamin A: normal values: 30–70 mcg/dL.
3. Vitamin E: normal values: 500–2000 mcg/dL.

2.3 | Statistical analysis

Study data were collected and managed using REDCap,[11] electronic data capture tool hosted at SEGHNP (www.seghnp.org). Technical support was provided by AEGREDCap Support Unit, shared with the Asociación Española de Gastroenterología (AEG). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing an intuitive interface for validated data entry; audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to common statistical packages; and procedures for importing data from external sources.

All eligible patients were recruited into the study. Statistical analysis was performed using STATA, version 13.0. Results were stratified into subgroups according to the modulator used with dual (Lum/Tez+Iva) or triple therapy (ETI). Demographic, clinical, and serum vitamin values were expressed as medians and interquartile ranges (IQRs) or percentages.

Data were checked for normality using the Kolmogorov–Smirnov test. Differences in serum vitamin levels after treatment were determined by Wilcoxon signed-rank test, and McNemar's test for paired proportions. For all analyses, $p < 0.05$ was considered statistically significant.

3 | RESULTS

Two hundred twenty-four patients were recruited. Demographic and clinical characteristics are summarized in Table 1. All patients were carriers of DF508 mutation (61% homozygous). The remaining descriptive data and comorbidities at the beginning of the study are summarized in Table 1. As shown, the clinical and demographic characteristics of the two groups analyzed—dual or triple therapy—were similar, except for age, genotype, and isolation of *Pseudomonas aeruginosa*.

Table 2 shows the levels of fat-soluble vitamins at baseline and at 6 and 12 months in all participants, as well as in subgroups stratified by modulator use.

Overall, we observed an increase in vitamin D levels from baseline to 6 months and from baseline to 12 months. When separating the results by therapy type, the ETI group showed statistically significant changes in vitamin D levels from baseline to 6 and 12 months, but not from 6 to 12 months. No differences in serum vitamin D levels were observed in the Lum/Tez+Iva group.

In the ETI group, we noted a progressive decrease in the proportion of insufficient vitamin D values (<30 ng/ml), from baseline to 6 months (64% vs. 45%, $p = 0.0003$), and from baseline to 12 months (61% vs. 48%, $p = 0.0288$). A similar decrease was found in the proportion of deficient vitamin D values (<20 ng/mL) from baseline to 6 months (23% vs. 10%, $p = 0.0037$), and from baseline to 12 months (28% vs 15%,

TABLE 1 Demographical and clinical characteristics.

Item	Overall ($n = 224$)	Lumacaftor/ivacaftor or tezacaftor/ivacaftor ($n = 51$)	Elexacaftor/tezacaftor/ivacaftor ($n = 173$)	p*
Ages (years)—Mn (IQR)	14.0 (11.4–16.3)	10.8 (7.2–14.7)	14.0 (12.0–17.0)	<0.001
Sex male, *n* (%)	120 (53.8%)	28 (54.9%)	92 (53.5%)	0.859
Genetic, *n* (%)				
DF508 homozygous	138 (61.6%)	47 (92.2%)	91 (52.6%)	
DF508 heterozygous	86 (38.4%)	4 (7.8%)	82 (47.4%)	<0.001
Meconium ileus, *n* (%)	25 (11.1%)	9 (17.7%)	16 (8.3%)	0.094
Newborn screening, yes, *n* (%)	149 (66.5%)	35 (68.6%)	114 (65.9%)	0.716
Z score height – Mn (IR)	−0.43 (−0.93 to 0.17)	−0.49 (−1.04 to 0.1)	−0.41 (−0.93 to 0.18)	0.718
Z score BMI—Mn (IQR)	−0.37 (−1 to 0.18)	−0.35 (−1.01 to 0.27)	−0.38 (−1 to 0.16)	0.423
EPI, yes, *n* (%)	203 (90.6%)	47 (92.2%)	156 (90.2%)	0.669
PERT (UI lipase/kg/day), Mn (IQR)	5555 (3750–6926)	5833 (4074–7500)	5532 (3761–7376)	0.895
CF-related liver disease, *n* (%)				
No CF-related liver disease	138 (62.2%)	27 (54.0%)	111 (64.5%)	
CF-related liver disease, no cirrhosis	78 (35.1)	23 (46.0%)	55 (32.0%)	
Cirrhosis	6 (2.7%)	0 (0%)	6 (3.5%)	
Abnormal glucose metabolism, *n* (%)				
No	147 (66.5%)	39 (78.0%)	108 (63.2%)	
Other no CFRD	44 (19.9%)	7 (14.0%)	37 (21.6%)	
CFRD	30 (13.6%)	4 (8.0%)	26 (15.2%)	
Bronchopulmonary *Pseudomonas aeruginosa* isolation, *n* (%)	44 (19.6%)	5 (9.8%)	39 (22.5%)	0.044

Note: Values were expressed as Mn and IQR or as percentages.

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFRD, CF-related diabetes; EPI, exocrine pancreatic insufficiency; IQR, interquartile range; Mn, median; PERT, pancreatic enzyme replacement therapy.

*Student's *t* test and chi-squared test *p* value.

$p = 0.0072$). No differences were found between 6 and 12 months. No differences were observed in the Lum/Tez+Iva group.

It is important to note that no differences were found in vitamin D doses (UI/day) during the follow-up period.

Regarding vitamin A, overall, we observed an increase from baseline to 6 months and from baseline to 12 months. In the ETI group, the increase was higher than in the Lum/Tez+Iva group. Moreover, this increase was maintained at 12 months in the ETI group, while in the Lum/Tez+Iva group, the increase was not sustained at 12 months. In the ETI group, we also observed a decrease in the proportion of deficient vitamin A values (<30 mcg/dL) from baseline to 6 months (21% vs. 6%, $p = 0.0034$). As an additional finding, it should be noted that the ETI group showed an increase in vitamin A toxic levels at 6 months compared to baseline (3% vs. 11%, $p = 0.0117$). No differences were found in the Lum/Tez+Iva group.

All patients had normal vitamin E values, and no significant differences in serum vitamin E levels were found in any of the groups.

4 | DISCUSSION

In patients with CF, adequate nutrition plays a crucial role, positively associated with lung function and survival.[1,8,12] Over the past five decades, the nutritional status of individuals with CF has significantly improved, mainly due to factors such as early CF diagnosis through newborn screening, the use of pancreatic enzyme replacement therapy, optimization of fat-soluble vitamin supplementation and, more recently, the availability of the highly effective CFTRm.[5]

Fat-soluble vitamins A, D, E, and K are increasingly recognized for their various functions as antioxidants, immunomodulators, and disease biomarkers.

TABLE 2 Fat-soluble vitamin values at baseline and after 6 and 12 months in the overall population and stratified by modulator use.

	0–6 months				6–12 months				0–12 months			
	N	Baseline	6 months	*p**	*N*	6 months	12 months	*p**	*N*	Baseline	12 months	*p**
Overall												
Vitamin A (Retinol mcg/dL)	149	41 (32–52)	47.6 (39–57)	<0.001	52	49.5 (41–60.5)	49.2 (38–61)	0.447	108	39.5 (31–49)	47 (38–57)	<0.001
Vitamin D (calcidiol ng/mL)	167	26 (20–33)	30 (21–36)	<0.001	70	30 (25–37)	29.3 (22–38)	0.503	127	27 (19–34)	29.8 (22–39)	<0.001
Vitamin E (alfa tocoferol mg/dL)	124	1030 (774–1274)	1035.5 (818–1289)	0.236	46	894 (780–1274)	1032 (790–1335)	0.205	98	945 (750–1230)	974.5 (797–1250)	0.715
Lumacaftor/ivacaftor or tezacaftor/ivacaftor												
Vitamin A (Retinol mcg/dL)	39	38 (32–48)	42 (35–49)	0.035	11	42 (27–44)	30.2 (25–44)	0.449	20	34.8 (25–41)	36 (27–43)	0.433
Vitamin D (calcidiol ng/mL)	43	26 (20–33)	29 (21–34)	0.885	14	27.5 (19–32)	26 (20–30)	0.706	22	25 (19–30)	27 (21–32)	0.660
Vitamin E (alfa tocoferol mg/dL)	23	990 (702–1060)	1030 (810–1343)	0.015	8	883.5 (746–1185)	880 (776–958)	0.484	17	818.3 (660–1160)	900 (800–1061)	0.320
Elexecafator/tezacaftor/ivacaftor												
Vitamin A (Retinol mcg/dL)	110	44.5 (32–56)	50.5 (39–60)	<0.001	41	51 (46–68)	51 (45–63)	0.529	88	42 (32–50)	49.2 (41–59)	<0.001
Vitamin D (calcidiol ng/mL)	124	25 (20–34)	31 (25–38)	<0.001	56	31.5 (25–40)	31.5 (23–42)	0.571	105	27 (19–35)	32 (23–41)	<0.001
Vitamin E (alfa tocoferol mg/dL)	101	1050 (792–1338)	1038 (820–1286)	0.974	38	1034 (820–1274)	1155 (790–1392)	0.097	81	950 (780–1239)	993.5 (197–1252)	0.996

Note: Values were expressed as median and IQR.

Abbreviation: IQR, interquartile range.

*Wilcoxon signed-rank test *p* value.

Deficiencies in fat-soluble vitamins in CF are often attributed to fat malabsorption, particularly in patients with poorly controlled EPI.[5] However, in current clinical practice, deficiencies in vitamins A and E are rare, and vitamin D deficiency is the most common.[5,13] For these reasons, monitoring the serum levels of fat-soluble vitamins and adjusting their doses accordingly should be a regular part of CF management.[8,14] Despite the advent of CFTRm, their effect on fat-soluble vitamin levels remains unclear, as different studies have shown inconsistent results.

In our study, the baseline clinical and demographic characteristics of the two groups analyzed—dual or triple therapy—were similar except for age, genotype, and isolation of *P. aeruginosa*. This variation is likely due to the approval of different modulating drugs for different age groups and genotypes. *P. aeruginosa* colonization is more prevalent in the older age groups, given that colonization tends to increase with age.

Vitamin D plays several roles in bone health, immunity, the microbiome, inflammation, and pulmonary health.[5] As previously mentioned, vitamin D deficiency is common in CF patients.[13] Our study found that treatment with ETI results in a significant increase in vitamin D and A levels within the first 6 months, with these improvements maintained at 12 months. These findings align with previous studies that also observed increases in vitamins A and D in patients treated with ETI,[6,9,15] although these were retrospective studies.

Despite routine vitamin D supplementation, serum levels remain insufficient in many individuals with CF.[10,13] In our study, patients treated with ETI showed early improvement in vitamin D levels, which was sustained over time. This led to a substantial decrease in the proportion of patients with insufficient or deficient levels. If these results are confirmed, the recommendations for vitamin D supplementation may need to be revised.

Vitamin A involves various physiological functions, including vision, bone health, cellular proliferation and differentiation, immunity, and antioxidant function.[5] In our study, we observed a significant increase in vitamin A levels in patients treated with ETI, while in the dual therapy group, the initial increase at 6 months was not sustained at 12 months. These findings are consistent with those of other previous studies.[6,9,15] Schembri et al.[16] also reported an increase in vitamin A levels after starting ETI, but they were surprised by the lack of changes in vitamin D, because their impression was that there was an improvement. This discrepancy may be due to the retrospective nature of their study.

It is also important to note the increase in the proportion of patients with retinol levels in the toxic range after starting ETI treatment. Adverse effects related to hypervitaminosis A have been described in the literature,[17] although the patients in our study with elevated levels did not show symptoms. Therefore, the importance of monitoring vitamin A levels early after starting ETI should be highlighted, and using vitamin supplements with vitamin A in the form of beta-carotene (rather than retinol) is recommended to avoid toxicity.

Our study has several limitations. One of them is that serum 25-hydroxyvitamin D levels can be influenced by seasonality, as sun exposure increases vitamin D, but this factor was not accounted for. Despite this, the observed improvement is large enough to be considered significant. Another limitation is that only the dose of vitamin D supplementation was recorded, not that of other vitamins. Additionally, although our study lacked a control group to compare outcomes before the CFTRm treatment, previous studies from our group show that nearly half of CF patients do not reach sufficient serum vitamin D levels.[13] This supports the conclusion that the improvement seen in this cohort is likely due to CFTRm.

The high dropout rate for vitamin measurements occurred mainly at the 6-month mark, as some patients were reluctant to undergo multiple blood draws. However, the loss to follow-up was lower for the 12-month measurements.

Despite these limitations, our study has several strengths: it includes a large sample of patients, mostly children, followed prospectively across multiple centers, and is very well documented.

In summary, treatment with dual therapy does not appear to significantly affect serum vitamin levels, whereas ETI treatment leads to a significant increase in both vitamin D and A levels. Further studies are needed to confirm these findings. If corroborated, it may be necesary a review of current vitamin supplementation recommendations for patients treated with ETI, particularly regarding potential toxicities.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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How to cite this article: Crehuá-Gaudiza E, Vicente Santamaría S, Álvarez Beltrán M, et al. Effect of cystic fibrosis modulator therapies on serum levels of fat-soluble vitamins. *JPGN Rep*. 2025;1-7. doi:10.1002/jpr3.70007