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Impact of elexacaftor/tezacaftor/ivacaftor on fat-soluble vitamin levels in children with cystic fibrosis

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ABSTRACT

Background: Children with cystic fibrosis are at risk of fat-soluble vitamin deficiency. CFTR modulators positively effect nutritional status. This study aimed to assess changes in serum vitamins A, D & E after starting ETI therapy to ensure levels were not abnormally high. *Methods*. Retrospective review of annual assessment data over 3½ years, before and after starting ETI in a specialist paediatric CF centre, including vitamin levels. *Results*: 54 eligible patients were included, aged 5–15 yrs (median age 11.5). Median time to post measurements was 171 days. Median vitamin A was increased (1.38 to 1.63 μmol/L, $p<0.001$). Three patients (6%) had high vitamin A post-ETI, compared with none at baseline; and 2 (4%) had low levels compared to 4 (8%) at baseline. No changes in vitamins D&E. *Conclusions*: This study found increased vitamin A, sometimes to high levels. We recommend testing levels within 3 months of starting ETI.

1. Introduction

Children with cystic fibrosis (CF) have an increased risk of fat-soluble vitamin deficiencies principally due to fat malabsorption, but it is not limited to those who are pancreatic insufficient [1]. There are several clinical issues associated with both deficiencies and high levels [2,3], so supplementation and monitoring of these vitamins are recommended [1]. CFTR modulator (CFTRm) therapy has a positive effect on nutritional status due to improved nutrient absorption, reduced energy requirement, decreased gut inflammation and changes to the microbiome [4]. There have been reports of changes in vitamin status in those taking lumacaftor/ivacaftor [5,6]. We aimed to look at the effect on fat soluble vitamin levels of starting elexacaftor/tezacaftor/ivacaftor (ETI) in children with CF.

2. Methods

We studied children in our specialist paediatric CF unit who had started ETI between 1.1.19 and 24.6.22. We used data entered into the UK CF Registry and our hospital's electronic patient records, looking at results from the annual review prior to starting ETI, and the first annual review after starting. We collected patient demographics, pancreatic status, timing of starting ETI, Body Mass Index (BMI), vitamin doses prescribed, and results of vitamin assessments (serum vitamin A, vitamin E, vitamin E:cholesterol ratio, and total 25 hydroxy (OH) vitamin D levels). If fat-soluble vitamins levels were missing from the annual review, levels taken within 3 months were used. Vitamin K was not included as it was not routinely measured. In our hospital biochemistry laboratory, serum vitamins A and E were measured by high-performance liquid chromatography with ultraviolet detection, and vitamin D by liquid-chromatography-tandem-mass-spectrometry. Reference ranges for vitamins A & E were provided by our laboratory [7]; vitamin D levels were taken from the National Institute for Health & Care Excellence [8].

Statistical analyses were performed using Stata version 17 (StataCorp LLC, Texas USA). Variables were not normally distributed so data are presented as median (interquartile range) unless otherwise indicated. The Wilcoxon signed rank test was used to compare the difference in BMI, lipase intake, serum vitamins and doses of fat-soluble vitamins pre and post ETI. The Mann-Whitney U test was used to assess differences between unmatched groups (pancreatic insufficient *vs* sufficient patients, homozygous *vs* heterozygous Phe508del gene variant). Statistical significance was set at $p<0.05$.

The hospital's Quality & Safety team classified the work as a clinical service review rather than research hence ethics approval

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Table 1
Characteristics of patients at baseline and after starting ETI.

	Pre ETI	Post ETI	
All patients	$n = 54$	$n = 54$	
Age (yrs) median (range)	11.5 (5 - 15)	12.5 (6 - 16)	
Lipase (u/kg/day)	10,000 (8100 - 12,000)	7857 (4907 - 10,271)	$p = 0.002$
(Pancreatic insufficient pts.)	($n = 40/49$)	($n = 48/49$)	
BMI (kg/m^2)	18.2 (17.1 - 20.1)	19.0 (18.0 - 21.7)	$p < 0.001$
(Z score)	0.37 (−0.42 to −1.1)	0.30 (−0.21 to −1.06)	$p = 0.64$
FEV_1 (%)	91 (85 - 98)	95 (86 - 102)	$p = 0.005$
	($n = 45$)	($n = 44$)	

Values are median (IQR) unless otherwise indicated. Where a dataset for a specific parameter was incomplete, the number of patients is stated. ETI=elexacaftor/tezacaftor/ivacaftor; BMI=body mass index; FEV_1=forced expiratory volume in 1 s.

Table 2
Fat-soluble vitamin levels at baseline and after starting ETI.

	Reference ranges	Pre ETI	Post ETI	
All patients		$n = 54$	$n = 54$	
Time post ETI (days)			171 (74 - 270)	
Serum vitamin A	0.92 - 2.76 (M)	1.38 (1.15 - 1.65)	1.63 (1.33 - 2.00)	$p<0.001$
(μmol/L)	0.88 - 2.64 (F)	($n = 52$)	($n = 52$)	
Low		4 (8%)	2 (4%)	
High		0 (0%)	3 (6%)	
Serum vitamin E	13 - 36.2 (M)	27.1 (20.9 - 30.2)	26.7 (20.1 - 31.7)	$p = 0.70$
(μmol/L)	11.6 - 36.7 (F)	($n = 52$)	($n = 53$)	
Low		3 (6%)	4 (8%)	
High		7 (13%)	5 (9%)	
Serum vitamin E:cholesterol ratio (mmol/mol)	4.3 - 6.8	7 (5.8 - 8.9) ($n = 48$)	6.85 (5.8 - 8.3) ($n = 50$)	$p = 0.10$
Low		1 (2%)	4 (8%)	
High		24 (50%)	25 (50%)	
Serum total 25(OH) vitamin D (nmol/L)		88 (64 - 107) ($n = 52$)	80 (71 - 103) ($n = 53$)	$p = 0.66$
Deficient	<25	0 (0%)	0 (0%)	
Insufficient	25–50	3 (6%)	3 (6%)	
Adequate	50–75	16 (31%)	18 (34%)	
Optimal	>75	33 (63%)	32 (60%)	

Values are median (IQR). Also shown are number (%) outside (above or below) the normal ranges. Where a dataset for a specific parameter was incomplete, the number of patients is stated. *M*=male, *F*=female; ETI=elexacaftor/tezacaftor/ivacaftor.

was not required. All data were anonymised. The project was registered on the hospital's audit database (Project ID no. 005412).

3. Results

Over 3½ years, 295 patients were under our care, 74 of whom were eligible for ETI. Ten patients were excluded as they had not yet had vitamin levels measured after starting ETI; 10 patients were excluded due to missing data; 54 patients were included (25 girls, 29 boys). There were no differences in the excluded patients in terms of age, lipase intake, BMI, FEV_1, nor genotype; there were more males in the excluded group (70% *vs* 54%), which is of no relevance.

Patient characteristics are summarised in Table 1. Median time to measurements after starting ETI was 171 days (interquartile range (IQR) 74–270 days).

Vitamin results for all 54 patients are shown in Table 2 (Fig. 1 and online supplement Figs. 1&2). Median vitamin A increased from 1.38 μmol/L to 1.63 μmol/L ($p<0.001$), and 3/54 (6%) patients had a high vitamin A level on ETI. There were no significant differences in median serum levels of vitamins D, E or E:cholesterol ratios. There were no differences in vitamin levels comparing those homozygous for Phe508 del variant ($n = 26$) *vs* those who were heterozygous ($n = 26$); 2 children had rarer variants.

There were 35 children in whom ETI was their first CFTRm; their median vitamin A levels increased significantly from 1.37 μmol/L to 1.63 μmol/L ($p = 0.001$), but other vitamin levels were unchanged. Two of them had high levels post ETI. For the 19 who had been on one of the other 3 modulators before ETI, the vitamin A levels increased (median 1.39 μmol/L to 1.60 μmol/L although there was no statistical significance; one child had high levels.

In the 49/54 patients (91%) who were pancreatic insufficient, median serum vitamin A increased from 1.37 μmol/L to 1.63 μmol/L ($p<0.001$). No significant changes were seen in any other fat-soluble vitamin levels. However, in the 5/54 (9%) children with pancreatic sufficiency there were no differences seen in any of the levels once on ETI. Lipase intake was significantly reduced on ETI in the pancreatic insufficient children, and BMI significantly increased for all children (Table 1).

Before starting ETI, 3/54 (6%) children were not prescribed any vitamin supplements, and post ETI 2/54 (4%) were not prescribed supplements. Our policy is to prescribe to all patients (not just those who are pancreatic insufficient); reasons for not prescribing were pancreatic sufficient patients who had high vitamin levels previously, or patients with poor adherence who had openly stopped taking vitamins. There were no significant differences however in any vitamin dosages prescribed after ETI commencement, apart from in those with high vitamin A levels.

4. Discussion

This study retrospectively reviewed the effect of starting ETI on levels of vitamins A, D and E in 54 children aged 6–16 years. It demonstrated a statistically significant increase in median vitamin A level, with 3 (6%) having a high vitamin A level compared to

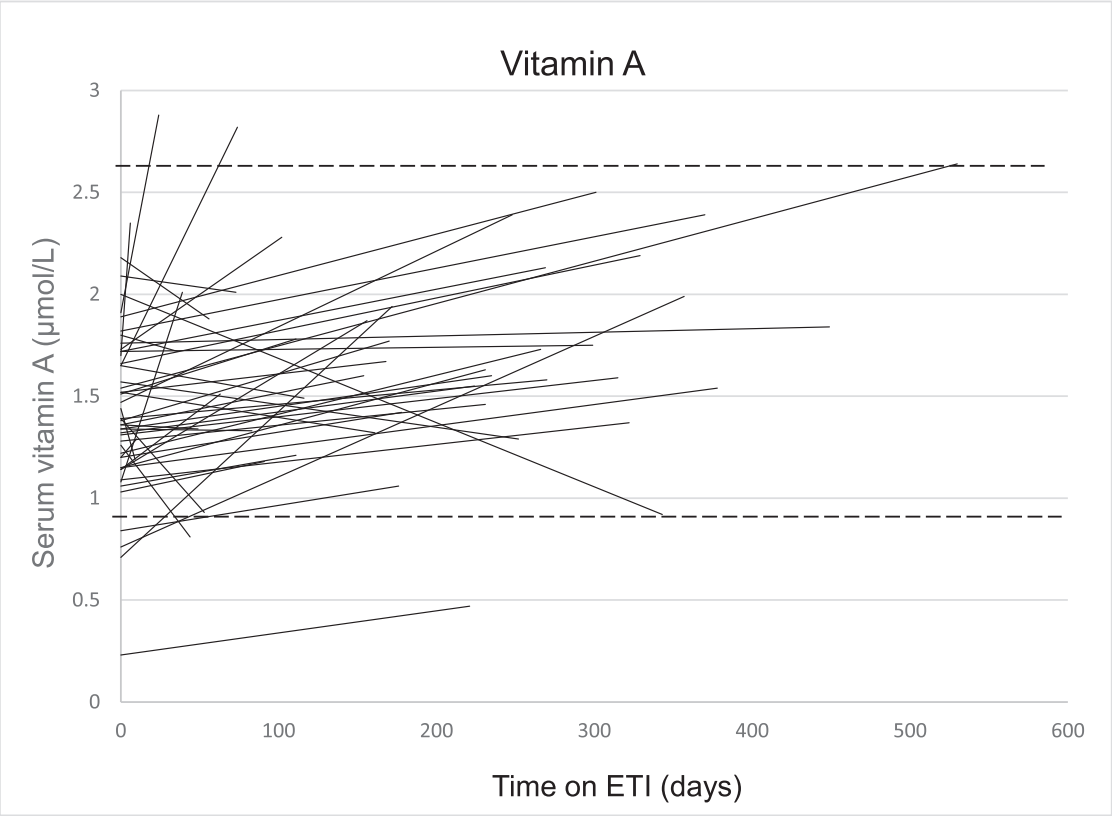

Fig. 1. Serum levels of vitamin A at baseline and after starting elexacaftor/tezacaftor/ivacaftor (ETI). Dashed lines indicate reference ranges (gender-specific ranges are not given for clarity).

none at baseline, and just 2 (4%) patients having a low level compared to 4 (8%) at baseline. There were no significant changes in levels of vitamins D, E or the vitamin E:cholesterol ratio. There was no influence from gender nor genotype. Lipase intake from pancreatic enzyme replacement therapy was significantly reduced (alongside a significant increase in BMI) but no one discontinued their enzymes.

Studies investigating effects of ivacaftor on children with CF gating gene variants have demonstrated improved pancreatic function [9]. One study on the effect of lumacaftor/ivacaftor in children and adults assessed vitamin levels over 2 years in 21 patients; they found significant increases in vitamin A (although none were above the upper limit of normal), with moderate decreases in vitamin E and vitamin E:cholesterol ratios [5]. A real world study of 845 adults and adolescents on lumacaftor/ivacaftor found any changes in vitamin A, D and E were not clinically significant, although the serum vitamin D was lower on treatment [6]. It would be expected that ETI would have similar or greater effects as it is a more effective CFTRm. To date there has been one publication in adults who were already on a CFTRm that reported a significant but small increase in vitamin D levels (median 12.5 nmol/L) after switching to ETI. [10]. A recent unpublished presentation at the ECFS 2021 reported significant increases in vitamins A and D in children after at least 3 months of ETI [11].

It is uncertain why we only saw a change in vitamin A levels. We were surprised not to see a change in vitamin D as our impression is that we see more patients with values high in the optimal range compared to the pre-CFTR era, but this is not backed up by the data. The adult study on ETI did find increased vitamin D levels [10]. We have not looked at seasonal effects on vitamin D in this small cohort. One possibility relates to adherence to taking vitamins, which is notoriously low, and is likely to take an even lower priority in patients who are feeling so well on ETI. Limitations of the study are that we cannot be certain about actual vitamin intake from supplementation due to adherence issues (we only know what was prescribed); nor do we have data on dietary intake.

High vitamin A levels may lead to toxicity, which can result in liver fibrosis, reduced bone mineral density and increased fracture risk [1]. There are case reports of three pre-teen girls with hypervitaminosis A resulting in papilloedema and fulminant secondary intracranial hypertension after starting ETI [12,13]. The majority of vitamin A supplementation prescribed to our cohort was in the form of β-carotene, a precursor to vitamin A [3]. Its metabolic conversion is regulated by vitamin A status therefore it may be a safer preparation than preformed vitamin A in patients on ETI [1]. Current guidelines recommend routine supplementation and annual monitoring of fat-soluble vitamins [1,14]. We would suggest that vitamin levels should be checked within a few months of starting ETI to ensure high levels are not reached. This could be done at the first liver function test (recommended at 3 months), although the exact timing is uncertain as one of our high vitamin A levels was detected at just 24 days after starting ETI. Adjusting vitamin intake after a high result of a single vitamin is challenging as people with CF routinely use multivitamin preparations [14].

Author contributions

All authors were involved in the conceptualisation, LS and SW collected the data; all authors analysed the data and contributed to writing the paper.

Declaration of Competing Interest

None of the authors have anything to declare.

CRediT authorship contribution statement

L Schembri: Conceptualization, Data curation, Formal analysis, Methodology, Investigation, Writing – original draft, Writing – review & editing. **S Warraich:** Data curation, Formal analysis, Investigation, Writing – original draft. **S Bentley:** Data curation, Investigation, Methodology, Writing – review & editing. **SB Carr:** Conceptualization, Methodology, Writing – review & editing. **IM Balfour-Lynn:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2023.04.019.

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