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The Effects of Ivacaftor on CF Fatty Acid Metabolism: An Analysis from the GOAL Study

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Keywords

Fatty acids; Cystic Fibrosis; Ivacaftor; Prostaglandin E

Introduction

Ivacaftor offers tremendous clinical benefit to individuals with cystic fibrosis (CF) who have at least one G551D mutation (1). This orally administered drug is thought to increase CFTR channel opening, thus improving chloride ion flow and acting on the primary defect that leads to the clinical manifestations of CF (1, 2). However, despite the significant clinical observations, little is known about the drug's metabolic actions, including its effects on fatty acid (FA) metabolism and related inflammation in CF patients.

Individuals with CF exhibit abnormalities in the metabolism of unsaturated fatty acids reflected in blood and tissue levels (3, 4). These abnormalities include increased metabolism of linoleic acid (18: 2 n-6; LA) to arachidonic acid (20:4 n-6; AA), due to increased expression and activity of Δ5- and Δ6-desaturase enzymes, which leads to low LA levels in the plasma and tissue (5, 6). In addition, there is a decrease in docosahexaenate (22:6 n-3; DHA), for which the mechanism is not fully understood. A prior study showed that the plasma LA × DHA product can be used to distinguish individuals with CF from healthy controls with good sensitivity and specificity, indicating that these observations are consistently observed in all individuals with CF (7).

There is evidence that the levels of specific fatty acids may correlate with clinical outcomes in CF (8, 9). This may be due to an imbalance of increased pro-inflammatory AA and decreased anti-inflammatory DHA and their metabolites in tissue contributing to more

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severe CF-related inflammation (10, 11). Arachidonic acid is metabolized to many downstream products, including prostaglandins and leukotrienes, and it may be possible to quantify some of the impact of fatty acid metabolism on inflammation by measurement of these products (12).

It is possible that at least some of the clinical improvement observed with ivacaftor is due to reduction in inflammation. The fatty acid metabolism abnormalities of CF, described above, predispose individuals to increased inflammatory eicosanoid production (3, 12–14). Thus, an improvement in FA metabolism could explain part of the clinical improvement observed with ivacaftor. To further explore this idea, it is necessary to not only analyze the plasma FA profile, but also its downstream inflammatory products. Urine prostaglandin E metabolite is a product of arachidonic acid and is therefore a marker of inflammation that directly relates to FA metabolism. Urine PGE-M has previously been shown to be elevated in the CF population in comparison to healthy controls as well as positively correlated to more severe CF genotypes, and thus is a reasonable biomarker for such an investigation (12).

This study tests the hypothesis that ivacaftor improves fatty acid metabolism in individuals with CF who have a G551D mutation. Using samples from a prospective observational trial (GOAL study) (15), plasma FA profiles and urine prostaglandin E metabolites (PGE-M) were analyzed before and after 6 months of ivacaftor therapy.

Methods

Study design

The GOAL study was a prospective, observational trial of the drug ivacaftor (VX-770, Vertex pharmaceuticals) orally administered to individuals with CF who had at least one G551D CFTR mutation. The study enrolled participants from February 2012 until January 2013 (15). Study visits were completed at baseline, 1 month, 3 months, and 6 months and at each of these visits biological samples (blood, sputum, and urine) were collected in addition to other clinical measures such as spirometry. After completion of the primary study analysis, remaining biological samples were stored in the CF Foundation Therapeutics Biorepository, and later these samples were made available to other researchers.

After report of the primary study outcomes, plasma and urine samples were requested from 40 individual participants in the GOAL study in order to measure the effect of ivacaftor on metabolism of fatty acids and their downstream inflammatory metabolites. We focused our analysis on the changes in the plasma fatty acid profile as well as changes in prostaglandin E, measured as its metabolite in the urine (PGE-M). We chose to evaluate samples at baseline and 6 month study visits to give the greatest length of time for potential impact of ivacaftor on fatty acid metabolism.

This analysis was approved by the CF Therapeutic Development Network (TDN) and a waiver for sample analysis was obtained from the Vanderbilt University Institutional Review Board.

Study Participants

Eligibility criteria for the GOAL study (15) included a minimum age of 6 years and a confirmed diagnosis of CF with at least one G551D CFTR mutation. Based on the power calculation (described below), we requested samples from 40 participants who were started on ivacaftor and had completed the 6-month follow-up visit. To sample a wide age range, we requested 20 samples from participants less than 18 years of age (pediatric) and 20 samples from participants greater than or equal to 18 years of age (adult). We also requested that the 40 samples come from participants with the greatest decrease in their sweat Cl as a marker of a good response to ivacaftor.

Study Assessments

Frozen plasma aliquots were shipped from the CF Therapeutics Biorepository and stored at −80°C until time of analysis. Each analysis used 50μL of plasma combined with 450μL of phosphate buffered saline (PBS) in addition to 10μg of heptadecanoic acid (17:0) as an internal standard. Fatty acids were extracted, methylated, identified and quantified by gas chromatography/mass spectroscopy (GC/MS) as previously described (6). Fatty acid levels were reported as the mole percent of each individual fatty acid. Frozen urine aliquots were also received and stored at −80°C until time of analysis. Urine PGE-M levels were quantified in the Vanderbilt Eicosanoid Core laboratory by methods previously described and all samples were run by the core at the same time (12).

Statistical Analysis

A power analysis, using previously published data (7)**,** showed that an analysis of 35 samples was predicted to be adequate to demonstrate a 25% increase in the plasma LA × DHA product with 80% power at a significance level of p= 0.05. The plasma LA × DHA product has previously been shown to have good sensitivity and specificity in predicting CF(7). To account for potential technical failures, 40 samples were requested from the CF Foundation.

Statistical analysis was completed using GraphPad Prism 6 (La Jolla, CA). Individual plasma fatty acid levels at baseline and 6 months were evaluated using the non-parametric Wilcoxon signed rank test. Further statistical analysis by age was completed for all fatty acids that had a p-value ≤ 0.05 in the overall cohort. Because they have been previously reported as abnormal in individuals with CF, LA and DHA were also a major focus in this analysis. For the age-based analysis, the Wilcoxon signed rank test was used to compare fatty acid levels before and after ivacaftor treatment. To compare fatty acid levels between pediatric and adult participants at baseline and at the after ivacaftor time-point, a Mann-Whitney test was used. The Wilcoxon signed rank test was also used for the evaluation of urine PGE-M levels before and after ivacaftor. Statistical significance was set at a p-value of ≤ 0.05 for all testing.

Results

Participants

The demographics for the 40 GOAL participants in this study are displayed in table 1. The median age for the pediatric cohort was 9.6 years [7.7, 11.3], and the median age for the adult cohort was 26.3 years [23.4, 32.3]. A majority of individuals in both age cohorts had a ΔF508 CFTR mutation on the allele other than G551D. The adult cohort had a slight female predominance (80%). Consistent with the results observed in the primary analysis of the GOAL study (15), this subset of participants displayed a statistically significant increase in forced expiratory volume in one second (FEV1 % predicted) and body mass index (BMI) as well as a statistically significant decrease in sweat Cl measurements. However, when divided by age, the pediatric cohort showed a trend towards improvement in the median FEV1% predicted, that was not statistically significant.

Urine PGE-M Analysis

Urine PGE-M levels were significantly decreased after treatment with ivacaftor (Figure 1). In total, 29 of the 40 participants displayed a decrease in urine PGE-M level with ivacaftor treatment. Large ivacaftor-associated decreases (median decrease of 47 ng/mg Cr) in PGE-M levels were observed in 8 subjects who had markedly elevated PGE-M levels at baseline (> 44 ng/mg Cr). When a sensitivity analysis was performed excluding these 8 subjects from the cohort, the observed ivacaftor-associated decrease in PGE-M remained statistically significant.

In comparison to adult participants, pediatric participants had higher urine PGE-M values at baseline and also exhibited the greatest decrease in urine PGE-M with ivacaftor treatment (Figure 3). There was no significant correlation between the change in urine PGE-M levels and FEV1% predicted or BMI (data not shown).

Fatty acid analysis

Twenty different fatty acids were measured in the plasma from each participant before and after 6 months of treatment with ivacaftor (Table 2). When analyzed as mole percent, the following fatty acids were significantly decreased after treatment with ivacaftor: palmitoleic acid (16:1), mead acid (20:3n-9), arachidonic acid (20:4n-6), and docosapentaenoic acid (22:5n-3). However, when fatty acids were analyzed by their absolute values (μM/L), the statistical significance was lost (Supplement Table 1). Eicosadienoic acid (20:2n-6) showed a small statistically significant increase by mole percent with treatment with ivacaftor, but also no statistically significant change by μM/L. There was no change in relative levels of LA (18:2n-6), DHA (22:6n-3), the LA × DHA product, or the triene/tetraene (T:T) ratio with ivacaftor treatment. Specifically, at baseline, 33 of 40 participants had an abnormally elevated T:T ratio (>0.4) and after ivacaftor treatment 36 participants had an elevated ratio. Reference ranges, obtained from previously reported data, for absolute values were also reported (supplement Table 1 & 2). Of note, in comparison to reference values, participants displayed elevated levels of palmitoleic acid (16:1), linoleic acid (18:2n-6), mead acid (20:3n-9), and arachidonic acid (20:4n-6); DHA (22:6n-3) levels were within the reference range (16).

An additional analysis of fatty acid levels by age group (pediatric vs. adult) was completed for fatty acids of clinical interest and fatty acids that showed a statistical change in the overall cohort. The analysis is displayed by mole percent in Table 3 and by μM/L in supplement table 2. Reference ranges are also provided in supplement Table 2. Palmitoleic acid (16:1) levels were significantly elevated in adults at baseline (by both mole percent and μM/L) and with ivacaftor treatment they displayed a significant decrease by mole percent, but not by μM/L. Pediatric participants had a higher LA levels in comparison to the adult participants at baseline, but this was only significant when analyzing by mole percent. There was no difference between age groups at either time point for arachidonic acid, but the pediatric participants did show a decrease with ivacaftor treatment when analyzed by mole percent. No differences were observed within age groups with treatment or between age groups at either time point for DHA. Statistically significant decreases in eicosadienoic acid, mead acid, and docosapentaenoic acid were seen with ivacaftor treatment in the pediatric group by mole percent, but when analyzed by μM/L no changes were observed. Eicosadienoic acid levels were statistically lower in pediatric participants at baseline (mole percent), but again the difference was not observed by μM/L.

The changes in fatty acid levels were compared to changes in measured clinical parameters. There was a weak positive correlation ($r=0.47$, [0.18, 0.69]; $p<0.01$) between the change in FEV1% predicted and the change in arachidonic acid levels with ivacaftor treatment in the overall cohort (supplement figure 1). No other significant correlations between change in fatty acid levels and change in either FEV1 or BMI were noted.

Discussion

In this pilot study, we analyzed biological samples from 40 participants in the GOAL study to investigate the effects of the drug ivacaftor on fatty acid metabolism and subsequent downstream inflammatory metabolites. There was a significant decrease in urine PGE-M levels with ivacaftor treatment. While some changes in fatty acid levels were noted with ivacaftor therapy, especially when analyzed by age and in units of mole percent, the fatty acid profile was not corrected to levels consistent with healthy controls, specifically in regards to clinically relevant fatty acids such as LA and DHA (3).

There are now multiple documented reports of the clinical benefits of ivacaftor. This drug has not only been shown to improve FEV1, but also improve nutritional status as measured by BMI as well as improvement in other CF disease manifestations such as sinus disease(1, 15, 17–19). However, despite these demonstrations of significant clinical improvement, relatively little is known about the mechanism of action. Ivacaftor is thought to induce CFTR channel opening through a nonconventional ATP-independent mechanism (2, 20) and consequently ivacaftor may fail to resolve downstream signaling of defective CFTR. There is evidence that CF fatty acid abnormalities are related to defective signaling from CFTR (5, 21) and thus the lack of clinically significant fatty acid changes observed in this study may be a reflection of ivacaftor's mechanism. However, the robust decrease in urine PGE-M may be representative of improvement in the airway surface layer and subsequent improvement in airway clearance (15) that leads to decreased inflammation. Urine PGE-M is unique in that there have not been many other inflammatory markers that have shown a decrease with

ivacaftor treatment (15). While it is possible that some of the change in urine PGE-M could be attributed to other treatments or increased inflammation at baseline, the uniqueness of this marker warrants further investigation for future CF therapeutic studies.

To our knowledge, urine PGE-M values have not been previously reported in the pediatric CF population. In our cohort, pediatric participants had the highest baseline urine PGE-M levels and with ivacaftor treatment exhibited the greatest decrease. Despite having higher PGE-M levels, the pediatric participants had a higher FEV1% predicted at baseline in comparison to the adult participants. In addition, while the adult participants observed a significant increase in FEV1% predicted, the pediatric cohort only observed a trend towards an increase in FEV1% predicted. Taking these observations together, it may be interesting to consider a potential role for urine PGE-M as a biomarker for CF therapeutic studies, especially when more traditional efficacy measures such as FEV1 are sometimes less helpful in the pediatric population.

At baseline, we observed fatty acid levels that were similar to what has been previously reported, including low levels of DHA as well as elevated levels of mead acid and palmitoleic acid (3, 21, 22). Additionally, despite a decrease in mead acid levels in the overall cohort, we did not observe a significant decrease in the triene: tetraene (T:T) ratio because there was also a decrease in arachidonic acid levels. An elevated T:T ratio is used clinically as a marker of essential fatty acid deficiency and it has previously been reported as being elevated in individuals with CF (22, 23); though, the etiology for fatty acid changes in individuals with CF is likely different than that of individuals with dietary essential fatty acid deficiency as for individuals with CF the fatty acid changes are likely related to up-regulation of enzymes of fatty acid metabolism by dysfunctional CFTR (5).

Considering the overall fatty acid profiles, we did not observe statistically significant changes when the fatty acids were analyzed in units of μM/L as we did when fatty acids were analyzed in units of mole percent. This observation raises questions regarding the best units to report fatty acid levels and it also questions the overall significance of the observed fatty acid changes when analyzed by mole percent. It also gives further evidence that ivacaftor is likely not causing robust changes in the fatty acid profile of these participants. However, ivacaftor decreases inflammation in individuals with CF, as demonstrated by the urine PGE-M results, and this decrease in inflammation could have some effect on fatty acid levels and account for some of the observations, including mead acid and arachidonic acid, though further research is needed in this regard.

We also observed linoleic acid levels that were intermediate between what has been previously reported for individuals with CF and healthy controls, when analyzed by mole percent (3). In particular, we observed that at baseline pediatric participants had significantly greater levels of linoleic acid than the adult participants. Several recent studies have also reported higher levels of plasma LA levels in pediatric patients with CF than were originally reported for adults with CF (9, 22, 24). In addition, when analyzed by μMol/L, elevated levels of LA were observed for both pediatric and adult participants in comparison to a healthy control reference range (16). There could be several factors that influence this observation, including trends in diet modification and a clinical practice that seeks a higher

BMI for pediatric patients with CF as it has been associated with better lung function (25). In any case, the observation of higher baseline plasma LA levels in CF patients in this GOAL subset is interesting and warrants further follow-up.

There were several limitations to this study. First, this study investigated biological samples from a small subset of participants from a previous prospective observational trial. Fatty acid levels can be affected by diet and by the fasted state of the participant at time of measurement, but due to the observational design of the GOAL study we were not able to control for this in our analysis. Our investigation was well powered to detect a change in the LA × DHA product, but this change was not observed. In exploratory analyses, we split the cohort by 18 years of age to investigate the widest age range as possible and we found some interesting differences in fatty acid levels and urine PGE-M levels between the two age populations. However, this study was not powered to detect age related changes in fatty acid metabolism. Due to the pilot nature of this study, we were only able to investigate one inflammatory metabolite related to fatty acid metabolism. We chose urine PGE-M because it has previously shown to be elevated in the CF population and to be correlated with severity of CF genotype (12). Finally, measuring fatty acids in the plasma alone, as opposed to also measuring in the tissue, may not reflect the true changes in overall fatty acid levels (26–28).

In summary, the purpose of this study was to investigate the effects of ivacaftor on fatty acid metabolism in individuals with CF who have a G551D mutation. While in this cohort, ivacaftor failed to demonstrate a robust improvement in the plasma fatty acid profile, we did observe a significant decrease in a prostaglandin E metabolite. After further investigation, this metabolite could be useful as a CF biomarker, especially in the pediatric population where there is such a need for alternative measures of therapeutic efficacy. Finally, this study also observed age differences in the plasma fatty acid profile that may be explained by several clinical factors including diet. It will be important to determine if these age differences are seen in larger cohorts and if they have any long-term clinical significance.

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Highlights

- Ivacaftor decreases urine prostaglandin-E metabolite (PGE-M) in CF participants.
- Pediatric CF participants had higher baseline urine PGE-M in comparison to adults.
- Ivacaftor failed to correct plasma fatty acid levels to that of healthy controls.
- Differences in plasma fatty acid levels were observed by participant age.
- After further investigation, urine PGE-M may be a useful CF biomarker.

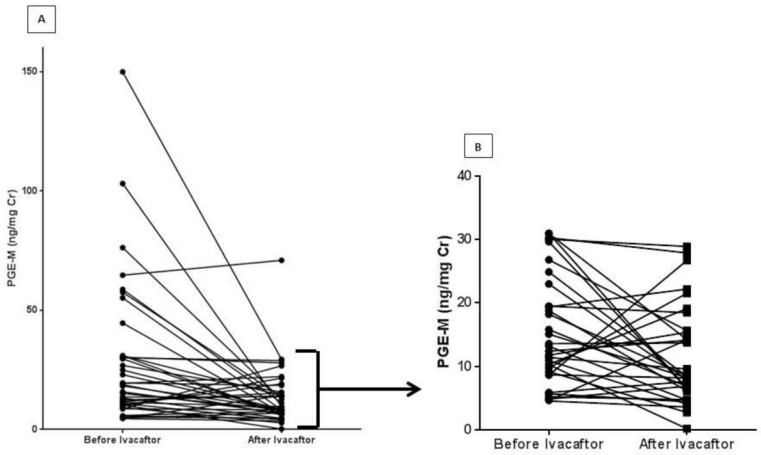

Figure 1. Urine Prostaglandin E Metabolite (PGE-M) Analysis

(A) The change in urine PGE-M for all 40 participants before and after treatment with ivacaftor; $p < 0.001$ by Wilcoxon signed rank test. (B) The change in urine PGE-M before and after ivacaftor with the elevated outliers (n=8) removed; $p<0.05$ by Wilcoxon signed rank test.

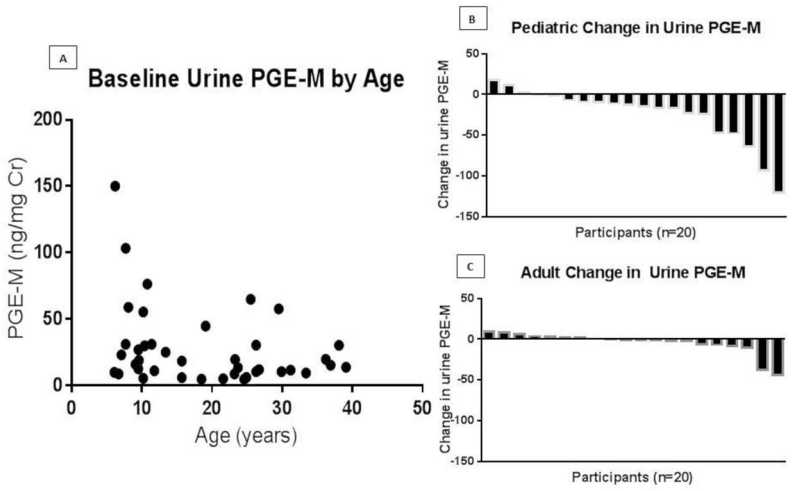

Figure 2. Urine Prostaglandin E Metabolite (PGE-M) Levels by Age

(A) Baseline urine PGE-M by age. (B) The individual participant change in urine PGE-M after 6 months of ivacaftor treatment in the pediatric population (age < 18 years). (C) Displays the individual participant change in urine PGE-M after 6 months of ivacaftor treatment in the adult population (age ≥ 18 years).

Table 1

Participant Demographics

Participant Demographics (n=40)		Pediatric (< 18 years) n=20	Adult (≥ 18 years) n=20
Age (years)		9.6 [7.7, 11.3]	26.3 [23.4, 32.3]
Sex (female)		50%, n=10	80%, n=16
Allele other than G551D that is ΔF508		95%, n=19	75%, n=15
FEV1 % predicted	Before Ivacaftor *	104.8 [99.6, 120.5]	57.4 [49, 90.6]
	After Ivacaftor *	112.4 [101.4, 121.7]	78.9 [56.2, 91.8]†
BMI	Before Ivacaftor *	17.2 [15.9, 19.2] 57.24% [38.01, 75.03] 0.27 [−0.68, 0.85]	22.0 [19.3, 23]
	After Ivacaftor *	17.7 [16.1, 20.7]†† 61.14% [50.39, 86.10]† 0.26 [−0.21, 1.05]†	22.9 [19.9, 24.4]†
Sweat Cl (mEq/L)	Before Ivacaftor	106.3 [101.3, 110]	105.3 [102.4, 109.8]
	After Ivacaftor	28.8 [22.5, 32.9]††	29.0 [26.8, 38.8]††

Data expressed as median [IQR] where appropriate. For pediatric participants, BMI is expressed as raw value, as percentile (%), and z-score.

*Statistical significance between age groups by Mann-Whitney ($p<0.001$).

†Statistical significance before and after ivacaftor treatment within age groups by Wilcoxon test, † $p=0.01$,

††$p<0.001$.

FEV1 = forced expiratory volume in one second; BMI = body mass index; Cl = chloride

Table 2

Plasma Fatty Acid Levels Before and After Ivacaftor

Fatty Acid	Before Ivacaftor	After Ivacaftor	p-value
Tetradecanoic acid (14:0)	1.10 [0.80, 0.67]	1.26 [0.67, 1.72]	0.40
Hexadecanoic acid (16:0)	32.84 [30.96, 35.20]	33.58 [30.69, 35.85]	0.18
Palmitoleic acid (16:1)	2.29 [1.47, 3.04]	1.74 [1.44, 2.69]	0.02
Octadecanoic acid (18:0)	10.73 [9.02, 11.56]	10.88 [9.76, 12.10]	0.22
Oleic acid (18:1 n-9)	11.10 [9.34, 12.59]	10.05 [8.69, 11.55]	0.20
Vaccenic acid (18:1 n-7)	11.48 [10.62, 12.57]	11.44 [10.14, 12.93]	0.95
Linoleic acid (18:2 n-6; LA)	21.37 [18.71, 24.80]	21.61 [18.31, 25.23]	0.62
α-linoleic acid (18:3 n-3)	0.21 [0.15, 0.28]	0.18 [0.13, 0.31]	0.29
Gamma-linoleic acid (18:3 n-6)	0.36 [0.24, 0.42]	0.40 [0.20, 0.60]	0.17
Eicosanoic acid (20:0)	0.04 [0.03, 0.06]	0.04 [0.03, 0.07]	0.84
Eicosenoic acid (20:1 n-9)	0.12 [0.08, 0.15]	0.12 [0.10, 0.17]	0.48
Eicosadienoic acid (20:2 n-6)	0.12 [0.1, 0.15]	0.14 [0.11, 0.17]	0.004
Mead acid (20:3 n-9)	0.31 [0.23, 0.39]	0.25 [0.20, 0.34]	0.006
Dihomo-gamma-linoleic acid (20:3 n-6)	1.09 [0.97, 1.34]	1.13 [0.94, 1.22]	0.66
Arachidonic Acid (20:4 n-6; AA)	4.90 [4.30, 5.68]	4.62 [3.56, 5.96]	0.04
Eicosapentaenoic acid (20:5 n-3)	0.18 [0.12, 0.25]	0.17 [0.11, 0.28]	0.55
Adrenic acid (22:4 n-6)	0.12 [0.10, 0.16]	0.11 [0.08, 0.14]	0.19
Docosapentaenoic acid (22:5 n-6)	0.07 [0.05, 0.10]	0.08 [0.04, 0.10]	0.85
Docosapentaenoic acid (22:5 n-3)	0.20 [0.16, 0.25]	0.18 [0.13, 0.23]	0.004
Docosahexaenoic acid (22:6 n-3; DHA)	0.37 [0.29, 0.51]	0.38 [0.3, 0.47]	0.87
LA × DHA	8.32 [5.93, 12.53]	7.95 [6.04, 10.8]	0.55
Triene/Tetraene (20:3n-9/20:4n-6)	0.06 [0.05, 0.07]	0.06 [0.05, 0.06]	0.16

Data in units of mole percent and expressed as median [IQR]. Statistical testing by Wilcoxon signed rank test with significance set at $p < 0.05$.

Table 3

Plasma Fatty Acid Levels Before and After Ivacaftor by Participant Age

Fatty Acid		Before Ivacaftor	After Ivacaftor
Palmitoleic acid (16:1)	Pediatric	1.64 [1.03, 2.50]	1.53 [1.12, 2.03]
	Adult	2.83 [1.78, 3.86]**	2.41 [1.67, 3.42]**†
Linoleic acid (18:2 n-6; LA)	Pediatric	24.41 [19.72, 26.4]	22.8 [18.53, 26.78]
	Adult	20.46 [18.23, 22.88]**	21.13 [18.31, 23.73]
Eicosadienoic acid (20:2 n-6)	Pediatric	0.11 [0.09, 0.13]	0.14 [0.11, 0.16]††
	Adult	0.14 [0.11, 0.18]*	0.15 [0.13, 0.18]
Mead acid (20:3 n-9)	Pediatric	0.30 [0.24, 0.35]	0.24 [0.21, 0.31]†
	Adult	0.32 [0.21, 0.41]	0.26 [0.2, 0.36]
Arachidonic acid (20:4 n-6)	Pediatric	4.97 [4.44, 6.47]	4.62 [3.56, 6]††
	Adult	4.82 [4.05, 5.49]	4.59 [3.3, 5.94]
Docosapentaenoic acid (22:5 n-3)	Pediatric	0.23 [0.2, 0.27]	0.18 [0.14, 0.23]††
	Adult	0.18 [0.13, 0.23]	0.17 [0.12, 0.23]
Docosahexaenoic acid (22:6 n-3; DHA)	Pediatric	0.34 [0.29, 0.5]	0.36 [0.26, 0.43]
	Adult	0.39 [0.3, 0.51]	0.44 [0.31, 0.57]
LA × DHA	Pediatric	8.17 [5.37, 12.59]	7.72 [5.78, 9.34]
	Adult	8.32 [6.03, 12.2]	9.44 [6.04, 10.86]
Triene/Tetraene (T:T)	Pediatric	0.06 [0.05, 0.06]	0.05 [0.05, 0.06]
	Adult	0.07 [0.04, 0.08]	0.06 [0.04, 0.07]

Data in units of mole percent and expressed as median [IQR]. Statistical testing by Wilcoxon signed rank test with significance set at $p < 0.05$.