

Dietary Intake during 56 Weeks of a Low-Fat Diet for Lomitapide Treatment in Japanese Patients with Homozygous Familial Hypercholesterolemia

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Aim: Lomitapide is an oral inhibitor of the microsomal triglyceride transfer protein used to treat homozygous familial hypercholesterolemia (HoFH); patients require a low-fat diet to minimize gastrointestinal adverse effects and dietary supplements to prevent nutrient deficiencies. We investigated the diet and nutritional status during lomitapide treatment.

Methods: Japanese patients with HoFH, who were in a phase 3 trial of lomitapide, were instructed to start low-fat diets with supplements of vitamin E and essential fatty acids 6 weeks before starting lomitapide treatment. Dietary education was conducted by registered dietitians 16 times during the study period, which included a pre-treatment run-in phase (Weeks -6-0), a lomitapide treatment efficacy phase (Weeks 0-26) and a safety phase (Weeks 26-56). Two-day dietary records were collected at each dietary counseling session. Anthropometric and biochemical parameters were measured at Weeks 0, 26 and 56.

Results: Eight patients completed the 56 weeks of lomitapide treatment. Their median energy intakes derived from lipids were 19.2% and 17.9% during the efficacy and safety phases, respectively. "Fats and oils" intakes, and "Fatty meat and poultry" intakes in two patients, were successfully reduced to achieve low-fat diets. Although intakes of energy, fatty acids and fat-soluble vitamins did not differ significantly among phases, body weight, serum fatty acid levels and vitamin E concentrations were decreased at Week 26 as compared with Week 0.

Conclusion: HoFH patients can adhere to low-fat diets with ongoing dietary counseling. Instructions about intakes of energy, fatty acids and fat-soluble vitamins, as well as periodic evaluations of nutritional status, are necessary.

Key words: Homozygous familial hypercholesterolemia, Lomitapide, Diet therapy, Low-fat diet

Introduction

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disease characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) levels, generally more than 500 mg/dL in untreated individuals, which is commonly caused by mutations in the genes related to the LDL receptor pathway¹). The cumulative LDL-C burden from birth causes premature atherosclerotic cardiovascular disease, and if left untreated, patients generally do not survive past the age of 30 years^{1, 2}). Therefore, early and intensive lipid-lowering therapy for patients with HoFH is critical.

Lipid-lowering drugs that rely on upregulation of LDL receptors have limited results in achieving the recommended LDL-C target in most patients with HoFH. Lipoprotein apheresis is recommended and is an effective treatment producing large but transient reductions in LDL-C. However, frequent treatments are essential because LDL-C accumulates rapidly after apheresis. Even with regular lipoprotein apheresis, many patients with HoFH still develop atherosclerosis³).

Lomitapide (Juxtapid, Aegerion Pharmaceuticals Inc., Cambridge, MA, USA; Lojuxta, Aegerion Pharmaceuticals Ltd., Uxbridge, UK) is an oral inhibitor of the microsomal triglyceride transfer protein (MTP) and is approved as an adjunctive therapy for adults with HoFH in several countries^{4, 5}). MTP transfers triglycerides onto apolipoprotein B during chylomicron assembly in the intestine and very-low-density lipoprotein (VLDL) assembly in the liver⁶). Lomitapide inhibits MTP activity and reduces production and secretion of chylomicrons and VLDL, thus reducing LDL-C.

As lomitapide is known to cause gastrointestinal adverse effects such as diarrhea and nausea, a very low-fat diet is required to minimize these effects during lomitapide treatment^{4, 5, 7}). Adherence to a low-fat diet is an important factor for maintaining lomitapide treatment⁷). However, the feasibility of a long-term low-fat diet has become a growing concern as the fat intake of the Japanese population is rising⁸). Deficiencies of energy and some nutrients due to low-fat diets and decreased absorption caused by lomitapide are also concerns^{6, 9}). Patients who take lomitapide are recommended to consume dietary supplements of vitamin E and essential fatty acids to prevent these nutri-

tional deficiency side effects^{4, 5}).

To our knowledge, this is the first investigation of nutritional status and dietary intake during lomitapide treatment.

Aim

We investigated dietary intakes and nutritional status to identify problems with clinical low-fat diets in Japanese patients with HoFH on lomitapide therapy.

Methods

Study Design and Subjects

We recruited Japanese patients who had been diagnosed with functional HoFH. The study design of the phase 3, single-arm, open-label, multicenter clinical trial of lomitapide in Japanese patients with HoFH has been reported elsewhere⁵). Briefly, the study consisted of three phases: a pre-treatment run-in phase (Weeks -6-0), an efficacy phase (Weeks 0-26) and a safety phase (Weeks 26-56; **Fig. 1**). During the run-in phase, the low-fat diet and other lipid-lowering therapies were stabilized and patients started to take daily dietary supplements. During the efficacy phase, lomitapide was initiated and doses were escalated up to an individual maximum tolerated dose, defined as the highest lomitapide dose that did not result in unacceptable adverse events. The maximum tolerated lomitapide dose was continued during the safety phase. In the safety phase, the lomitapide dose could be decreased according to the modification rules but could not be raised above the maximum tolerated dose established in the efficacy phase.

The study was conducted in accordance with the International Council for Harmonization Guidance for Industry E6, Guideline for Good Clinical Practice, which is consistent with the ethical principles that have their origins in the Declaration of Helsinki. The protocol and patient informed consent form were reviewed and approved by an Institutional Review Board and/or Independent Ethics Committee that covered each participating facility before the study began.

Dietary Counseling and Supplement Prescriptions

At the start of the run-in phase (Week -6), all patients were counseled by a registered dietitian in

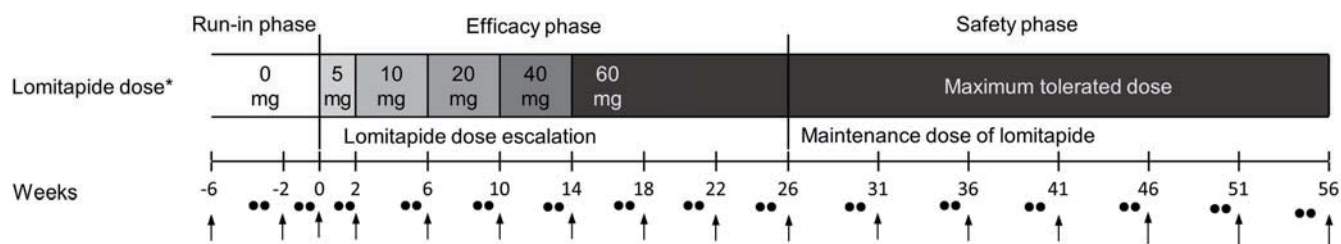


Fig. 1. Study design

The study period was divided into three phases: pre-treatment run-in phase (Weeks -6–0), efficacy phase (Weeks 0–26) and safety phase (Weeks 26–56).

*This is a protocol dose. Lomitapide doses were initiated at 5 mg/day and escalated to each patient's maximum tolerated dose (up to 60 mg/day), defined as the highest dose of lomitapide that did not result in unacceptable adverse events during the efficacy phase. During the safety phase, the maximum tolerated dose of lomitapide (as determined for each patient) was continued.

↑ Dietary counseling from registered dietitian.

●● Two-day dietary records were kept and collected at each dietary counseling session.

each center on adhering to a low-fat diet, and a low-fat diet was prescribed with daily intake of supplements; vitamin E (400 IU: equivalent to 268 mg of α -tocopherol), fatty acids (200 mg linoleic acid [LA], 210 mg α -linolenic acid [ALA], 110 mg eicosapentaenoic acid [EPA], and 80 mg docosahexaenoic acid [DHA]). At Week -2, during the run-in phase, the patients were reviewed for compliance with the low-fat diet and were instructed on diet modification by the dietitians. Following the run-in phase, dietary counseling sessions were held at Weeks 0 and 2, and then once every 4 weeks during the efficacy phase and once every 5 weeks during the safety phase, 16 times in total (Fig. 1).

The primary goal of the dietary counseling was to limit the energy intake derived from lipids to <20% of the total caloric intake. Learning materials pertaining to the low-fat diet during lomitapide treatment were provided to the patients. Pamphlets were distributed, informing participants of how to reduce fat intake, to switch fatty foods to lean foods including fat-free and low-fat alternatives, to cook with smaller quantities of fats and oils, and to check nutrition facts in commercial food products to monitor fat content. Patients were advised regarding the recommended energy intake to maintain healthy weights and a balanced diet to prevent nutrient deficiencies. Patients who had lost more than 1.5 kg since the previous visit were further advised on practical ways to increase energy intake to maintain a normal body weight (body mass index [BMI] 18.5–25.0 kg/m²). In addition, patients were advised to completely avoid alcohol, or at least limit themselves to one alcoholic drink per day if avoidance was not feasible. The registered dietitian reviewed current food intake and provided additional dietary instructions relevant to each patient's needs

and problems in meeting their dietary targets.

Dietary Data Collection

At their first dietary counseling session during Week -6, patients were instructed on how to keep their dietary records. On and after the study visit of Week -2, 2-day dietary records that had been kept by patients were confirmed and collected by a registered dietitian at each dietary counseling session. Thirty days of dietary records were collected from each patient.

Energy and nutrient intakes were calculated employing Excel-Eiyokun Version 6 software (Kenpaku-sha Co., Ltd., Tokyo, Japan) based on the Standard Table of Food Composition in Japan 2010 (Ministry of Education, Culture, Sports, Science and Technology, Japan). The food group intakes were calculated. The alcoholic beverage intake values were calculated as pure ethanol amount. The lipid contributions of each food group were calculated as percentages of total lipid intake. The average intakes of foods and nutrients were each calculated during the run-in, efficacy and safety phases.

Measurements

Body height and weight were measured, and BMI was calculated as weight (kg) divided by the square of height (m). A BMI of 22 was regarded as corresponding to the standard body weight (SBW).

Fasting blood samples were obtained during each visit and concentration measurements were conducted as follows: Fatty acids (ALA, EPA, DHA, LA and arachidonic acid [AA]; LC/MS/MS method) were measured at PPD Central Labs (Zaventem, Belgium). Protein and albumin were measured at PPD Central Labs (Singapore). Vitamins A and E (α -tocopherol; HPLC

Table 1. Baseline patient characteristics and anthropometric measurements

Patient	Age (years)	Gender (M/F)	Height (cm)	Weight (kg)	BMI (kg/m ²)
A	35	F	162.0	48.5	18.5
B	52	F	155.4	45.5	18.8
C	63	F	157.2	46.9	19.0
D	40	F	154.9	46.0	19.2
E	43	M	174.0	59.2	19.6
F	75	M	162.8	63.0	23.8
G	66	M	166.7	70.3	25.3
H	46	M	164.2	82.5	30.6

method) and 25-OH vitamin D (chemiluminescence immunoassay method) were measured at PPD Central Labs (KY, USA). Uncarboxylated osteocalcin (chemiluminescence immunoassay method) as a parameter indicative of vitamin K deficiency was measured at Bioclinica Labs (Lyon, France). The vitamin E to total lipids ratio was calculated as vitamin E (mg/dL) divided by the sum of total cholesterol (g/dL) and triglyceride (g/dL) concentrations^{10,11}.

Statistical Analysis

Statistical analyses were carried out using IBM SPSS Statistics (Version 22; IBM Japan, Ltd., Tokyo, Japan). The statistical significance of differences in energy, nutrients and food intakes during each phase were assessed using the nonparametric Friedman's test followed by the Wilcoxon signed-rank test for pairwise comparisons with the Bonferroni correction. Differences in anthropometric and biochemical parameters obtained at Weeks 0, 26 and 56 were analyzed by repeated measures analysis of variance, following multiple pair comparison based on the Bonferroni's method. Spearman's correlation analysis was used to identify correlations between food and nutrient intakes and biochemical parameters. $P < 0.05$ was considered significant.

Results

This study included four men and four women, aged 35 to 75 years, who completed a 56-week course of lomitapide treatment (Table 1). Five of the eight patients tended to be lean (BMI range: 18.5–20.0 kg/m²) at Week 0. The efficacy of lomitapide on blood lipid parameters was demonstrated in a previous study⁵.

Food Intakes

The median daily food intake during each phase is shown in Table 2. The median intake of “Fats and oils” was only 7.4 g during the run-in phase but

tended to decrease to 5.7 g ($P = 0.075$) during the efficacy phase, with a significant decrease in “Vegetable oils” intake ($P = 0.036$), and then an increase to 8.4 g in the safety phase ($P = 0.036$). Consumption of “Animal fats and margarines” was minimal during the study period.

“Meat and poultry”, “Eggs”, “Milk and dairy products”, “Fish” and “Soybeans and soy products” are rich in protein and lipids, and their intakes did not vary significantly among the phases. During the run-in phase, the median intake of “Lean meat and poultry” (i.e., containing < 10 g of lipids/100 g) was almost the same as that of “Fatty meat and poultry” (containing ≥ 10 g of lipids/100 g). During the safety phase, the median intake of “Lean meat and poultry” was larger than that of “Fatty meat and poultry” ($P = 0.036$). Patients H and A consumed large amounts of “Fatty meat and poultry” during the run-in phase (350.5 and 105.8 g, respectively), but their intakes were reduced during the efficacy and safety phases (65.0 and 45.2 g, respectively). The egg intake tended to gradually rise from the run-in phase to the safety phase; the maximum amount in the safety phase was 51 g, which is roughly equivalent to one egg a day. “Milk and dairy products” intakes varied among subjects from none to 900 g. The median intake of total “Fish” including “Fatty fish” (containing ≥ 10 g of lipids/100 g) was small during the run-in phase, whereas the median intakes during the safety phase were 63.0 and 25.8 g, respectively. The median intake of “Low-fat seafood” such as “shellfish, squid, octopus, fish eggs and viscera” was low in the run-in phase, but consumption rose during the subsequent phases ($P < 0.05$).

Among plant foods, almost 100 g of “Soybeans and soy products” was the median amount consumed during the study. “Vegetables” intake tended to increase to 239.0 g during the safety phase as compared with only 177.8 g during the efficacy phase ($P = 0.075$). “Green and yellow vegetables” intakes tended to differ among the three phases ($P = 0.093$), and the

Table 2. Average daily intakes of foods during the run-in, efficacy and safety phases of lomitapide treatment in Japanese patients ($n = 8$) with homozygous familial hypercholesterolemia

	Run-in phase (g) (Weeks -6-0)	Efficacy phase (g) (Weeks 0-26)	Safety phase (g) (Weeks 26-56)	<i>P</i> value
Fats and oils	7.4 (2.4, 14.7)	5.7 (0.0, 13.2)	8.4 [†] (4.3, 14.6)	0.010
Vegetable oils	7.4 (2.4, 13.5)	4.8*(0.0, 11.5)	8.3 (4.0, 14.6)	0.010
Animal fats and margarines	0.0 (0.0, 2.8)	0.8 (0.0, 1.9)	0.4 (0.0, 1.5)	0.401
Meat and poultry	35.4 (0.0, 452.3)	37.4 (16.0, 318.6)	51.2 (11.8, 333.8)	0.687
Lean meat and poultry (Lipids <10g/100g)	12.5 (0.0, 40.0)	18.6 (0.0, 287.1)	26.1 (9.4, 255.3)	0.508
Fatty meat and poultry (Lipids ≥10g/100g)	12.8 (0.0, 350.5)	13.9 (0.0, 48.1)	15.0 (0.0, 65.0)	0.542
Processed meat products and viscera	6.6 (0.0, 84.0)	2.5 (0.7, 31.4)	4.6 (0.4, 19.0)	1.000
Eggs	5.5 (0.0, 39.8)	16.4 (0.0, 54.9)	24.4 (0.0, 51.7)	0.102
Milk and dairy products	65.6 (0.0, 325.0)	77.3 (0.0, 995.7)	77.3 (0.0, 868.4)	0.156
Fish	28.6 (7.5, 218.9)	43.2 (17.9, 114.9)	63.0 (23.4, 201.5)	0.687
Lean fish (Lipids <10g/100g)	25.0 (4.5, 55.0)	25.1 (10.1, 53.2)	22.0 (0.4, 121.9)	0.687
Fatty fish (Lipids ≥10g/100g)	7.9 (0.0, 97.5)	15.4 (0.0, 40.0)	25.8 (3.5, 32.5)	0.368
Fish processed food	10.6 (0.0, 86.4)	6.6 (2.7, 37.0)	8.6 (0.0, 53.3)	0.748
Shellfish, prawns, shrimp, crab, squid, octopus, fish eggs and viscera	0.0 (0.0, 41.3)	15.1 (3.1, 67.6)	14.8 (0.4, 67.9)	0.034
Soybeans and soy products	94.7 (0.0, 201.8)	95.5 (18.6, 160.1)	119.6 (3.9, 216.2)	0.607
Other beans	0.0 (0.0, 9.5)	2.1 (0.0, 6.1)	0.0 (0.0, 4.2)	0.084
Nuts	0.4 (0.0, 4.6)	2.3 (0.0, 7.5)	0.3 (0.0, 2.8)	0.565
Cereals and cereal products	466.0 (335.8, 606.3)	465.5 (286.2, 1037.9)	466.6 (327.3, 1046.0)	0.325
Potatoes and other starches	28.2 (0.0, 142.5)	43.9 (0.7, 65.5)	36.1 (24.5, 58.5)	0.882
Total vegetables	202.1 (113.0, 287.0)	177.8 (106.0, 288.0)	239.0 (140.0, 361.0)	0.093
Green and yellow vegetables	71.6 (51.8, 137.5)	66.9 (19.2, 90.2)	126.3 (19.5, 142.6)	0.093
Other vegetables	109.6 (60.0, 162.2)	124.3 (51.2, 197.4)	115.9 (88.3, 197.8)	0.325
Vegetable juice	0.0 (0.0, 50.0)	0.0 (0.0, 35.7)	4.2 (0.0, 32.5)	0.465
Seaweed, mushrooms and konjac	16.8 (1.8, 97.2)	21.4 (5.5, 39.8)	33.5 (2.6, 44.3)	0.417
Fruits and fruit juices	83.4 (0.0, 276.8)	86.3 (31.4, 203.6)	80.6 (0.0, 289.2)	0.882
Sweets, desserts and snacks	34.5 (0.0, 67.9)	34.0 (15.6, 118.2)	36.3 (5.8, 105.0)	0.223
Sugars, sweeteners and jam	10.9 (2.6, 22.1)	10.4 (4.7, 33.3)	12.0 (6.4, 18.6)	0.687
Alcoholic beverages [§]	0.0 (0.0, 6.5)	0.0 (0.0, 3.2)	0.3 (0.0, 1.2)	0.282

Values are expressed as median (range).

P values were calculated using the nonparametric Friedman's test for comparisons among the phases.

*Significant difference ($P < 0.05$) from run-in phase (Weeks -6-0);

[†]Significant difference ($P < 0.05$) from efficacy phase (Weeks 0-26). *P* values were calculated using the Wilcoxon signed-ranks test, with the Bonferroni correction for pair-wise comparison between the phases.

[§]Values are calculated as pure ethanol amount in grams.

intake during the safety phase was 126.3 g. However, the "Vegetables" intake was small during the study period. "Seaweed, mushrooms, and konjac" were consumed throughout the entire study period.

"Fruits and fruit juices" and "Sweets, desserts and snacks" intakes varied among the patients during all phases. "Alcoholic beverages" intake was limited. The highest pure ethanol amount consumed was only 3.2 g while taking lomitapide.

Energy and Nutrient Intakes

The average energy and nutrient intakes during each phase are shown in **Table 3**. The median energy intake did not change among phases, and was about

30 kcal/SBW kg, but the minimum was less than 25 kcal/SBW kg.

The median energy intake derived from lipids was more than 20% during the run-in phase because five of the eight patients exceeded the expected 20% lipid intake volume. However, the median energy intake derived from lipids was kept below 20% during the efficacy and safety phases, within a narrow range of 14.6%–21.8%. No relationships were observed between the average lipid intakes and the frequencies of gastrointestinal adverse events during lomitapide treatment.

The median energy intake derived from saturated fatty acids (SFA) was low during all phases. One

Table 3. Average daily energy and nutrient intakes during the run-in, efficacy and safety phases of lomitapide treatment in Japanese patients ($n=8$) with homozygous familial hypercholesterolemia

	Run-in phase (Weeks -6-0)	Efficacy phase (Weeks 0-26)	Safety phase (Weeks 26-56)	<i>P</i> value
Energy (kcal/SBW kg)	29.7 (23.4, 47.2)	30.3 (23.7, 52.3)	31.4 (23.8, 59.3)	0.135
Lipid (g)	44.0 (21.9, 132.5)	39.0 (20.0, 46.3)	39.0 (25.7, 58.3)	0.882
(%E)	21.4 (12.7, 36.5)	19.2 (5.7, 23.0)	17.9 (14.6, 21.8)	0.417
SFA (g)	10.44 (4.60, 47.64)	10.84 (5.87, 11.57)	9.96 (6.56, 21.12)	0.223
(%E)	5.4 (3.0, 13.0)	5.2 (1.7, 6.3)	4.6 (3.4, 6.0)	0.417
MUFA (g)	15.18 (6.99, 56.15)	11.62 (5.68, 16.99)	12.36 (8.54, 20.47)	0.882
n-3 PUFA (g) [§]	1.63 (0.99, 4.37)	1.87 (0.54, 2.81)	2.16 (1.27, 3.60)	0.417
(%E) [§]	0.9 (0.3, 2.0)	0.9 (0.1, 1.4)	1.0 (0.3, 1.6)	0.607
α -linolenic acid (g) [§]	1.098 (0.827, 1.309)	1.084 (0.411, 1.360)	1.031 (0.439, 1.661)	0.687
EPA (g) [§]	0.110 (0.015, 0.825)	0.187 (0.046, 0.527)	0.301 (0.095, 0.640)	0.417
DHA (g) [§]	0.242 (0.064, 1.444)	0.330 (0.080, 0.929)	0.479 (0.208, 1.215)	0.417
n-6 PUFA (g) [§]	8.77 (5.68, 14.03)	8.10 (4.05, 10.03)	8.04 (4.38, 12.04)	0.417
(%E) [§]	4.3 (3.4, 5.7)	4.1 (1.1, 5.1)	4.2 (1.9, 5.6)	0.882
Linoleic acid (g) [§]	8.468 (5.638, 13.321)	7.901 (3.911, 9.853)	7.864 (4.305, 11.848)	0.325
Arachidonic acid (g)	0.101 (0.028, 0.283)	0.096 (0.072, 0.138)	0.109 (0.056, 0.181)	0.093
Cholesterol (mg)	204 (67, 495)	181 (100, 350)	221 (83, 358)	0.325
Protein (g)	67.4 (47.2, 115.8)	66.9 (46.2, 174.6)	72.3 [†] (53.3, 193.8)	0.044
(%E)	15.7 (12.6, 18.1)	15.6 (13.6, 22.5)	16.9 (14.5, 22.6)	0.030
(g/SBW kg)	1.1 (0.9, 2.0)	1.3 (0.8, 2.9)	1.3 [†] (0.9, 3.3)	0.044
Carbohydrate (g)	271.5 (206.1, 299.0)	278.7 (225.5, 539.9)	288.3 (229.5, 538.9)	0.687
(%E)	62.5 (47.3, 74.7)	64.8 (62.0, 71.8)	64.1 (62.8, 69.5)	0.417
Total dietary fiber (g/1000kcal)	8.5 (6.1, 10.6)	8.1 (4.5, 12.1)	7.7 (4.7, 11.4)	0.417
Vitamin A (μ g RAE/SBW kg)	6.9 (2.9, 10.1)	5.7 (3.8, 9.9)	6.5 (2.8, 10.9)	0.687
β -Carotene equivalents (μ g)	2947 (1137, 3802)	2495 (1090, 5011)	3074 (1282, 5252)	0.325
Vitamin D (μ g)	7.4 (1.4, 26.9)	8.4 (2.6, 13.1)	6.2 (3.9, 16.6)	0.417
α -Tocopherol (mg) [§]	5.7 (3.9, 10.5)	6.3 (3.5, 7.5)	6.8 (5.3, 8.0)	0.197
Vitamin K (μ g)	160 (107, 519)	152 (127, 535)	189 (73, 570)	0.607
Ascorbic acid (mg)	69 (35, 113)	102 [*] (59, 181)	98 (43, 246)	0.034

Values are expressed as the median (range).

DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, MUFA: monounsaturated fatty acids, PUFA: polyunsaturated fatty acids, RAE: retinol activity equivalents, SBW: standard body weight, SFA: saturated fatty acids.

P values were calculated using the nonparametric Friedman's test for comparisons among the phases.

*Significant difference ($P<0.05$) from run-in phase (Weeks -6-0);

[†]Significant difference ($P<0.05$) from efficacy phase (Weeks 0-26). *P* values were calculated using the Wilcoxon signed-ranks test, with the Bonferroni correction for pair-wise comparison between the phases.

[§]The values do not include daily dietary supplements of vitamin E (400 IU: equivalent to 268 mg of α -Tocopherol) and fatty acids (200 mg linoleic acid, 210 mg α -linolenic acid, 110 mg EPA, and 80 mg DHA), which were provided with lomitapide treatment

patient who had an extremely high run-in-phase SFA intake at 13.0% decreased his SFA intake, and all patients limited their SFA intake to <7% during the efficacy and safety phases.

The median n-3 polyunsaturated fatty acids (PUFA) intake was 1.63 g (including 0.110 g of EPA and 0.242 g of DHA) during the run-in phase but increased by up to threefold for EPA and doubled for DHA during the safety phase, though these differences did not reach statistical significance. During the safety phase, total n-3 PUFA intakes ranged from 1.27

to 3.60 g. The fish intake correlated positively with the total n-3 PUFA, EPA and DHA intakes during all phases (safety phase correlation coefficients—n-3 PUFA: $r=0.786$, $P=0.021$; EPA: $r=0.833$, $P=0.010$; DHA: $r=0.952$, $P<0.001$). ALA comprised about half the total n-3 PUFA intake, and LA comprised most of total n-6 PUFA intake, with no differences among the phases. The median cholesterol intake was about 200 mg during the study period.

The protein intake decreased from the run-in phase to the efficacy phase in half of the patients, but

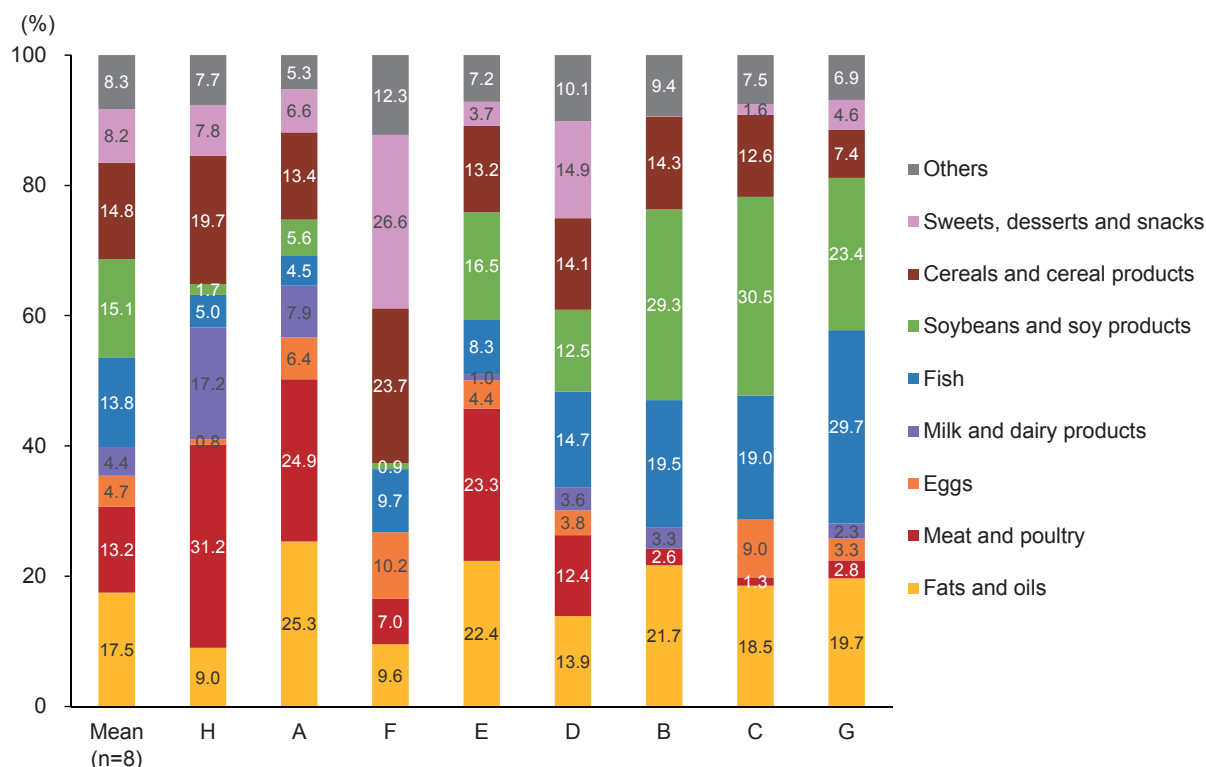


Fig. 2. Contributions of food groups to lipid intake during the safety phase of lomitapide treatment in Japanese patients with HoFH

The values are average contributions to lipid intake through the safety phase (Weeks 26–56) and were calculated as the amounts of lipid intake from certain food groups divided by total lipid intake.

significantly increased during the safety phase as compared with the efficacy phase ($P=0.036$).

Vitamin A intake was low throughout the entire study period, only 6.5 μg retinol activity equivalent (RAE)/SBW (kg) as the median and 2.8 μg RAE/SBW (kg) as the minimum intake during the safety phase. The β -carotene and “Green and yellow vegetables” intakes correlated positively with the vitamin A intake during the safety phase ($r=0.905$, $P=0.002$ and $r=0.738$, $P=0.037$, respectively).

The median intakes of dietary vitamin E as α -tocopherol were similar during the run-in, efficacy and safety phases at 5.7, 6.3, and 6.8 mg, respectively.

The vitamins D and K intakes varied widely among patients (safety phase ranges—vitamin D: 3.9–16.6 μg ; vitamin K: 73–570 μg), but the median intakes did not differ among the phases. The largest vitamin K intake was observed in a patient who consumed *natto* (fermented soybeans) habitually.

Contributions of Food Groups to Lipid Intakes

The contributions of food groups to lipid intakes during the safety phase are shown in Fig. 2. The major food sources for lipids were “Fats and oils” (17.5%),

“Soybeans and soy products” (15.1%), “Cereals and cereal products” (14.8%), “Fish” (13.8%) and “Meat and poultry” (13.2%; mean percentage for all eight patients); cumulatively, these foods accounted for >70% of the total lipid intake. The major food sources for lipids varied markedly among patients: these sources were “Fish” and “Soybeans and soy products” in patients B, C and G, animal foods such as “Meat and poultry” and “Milk and dairy products” in patients H and A, and a variety of foods in patients E and D.

Anthropometric and Biochemical Parameters

Body weights of seven of the eight patients, including the patients who increased their energy intakes, decreased during the 56 weeks of lomitapide treatment (Table 4). Three of the five patients with a BMI < 20 kg/m² at Week 0 experienced weight losses during the 56 weeks and had a BMI < 18.5 kg/m².

All measured serum fatty acid concentrations at Week 26 were significantly decreased by nearly half at Week 0 ($P<0.05$). At Week 56, ALA and LA concentrations returned to their prior levels, while DHA and AA concentrations were increased from Week 26 onward ($P=0.004$ and $P=0.021$, respectively), though

Table 4. Anthropometric and serum biochemical parameters at Weeks 0, 26 and 56 in lomitapide treatment in Japanese patients ($n=8$) with homozygous familial hypercholesterolemia

	Week 0	Week 26	Week 56	<i>P</i> value
Body weight (kg)	57.7 ± 13.6 (45.4, 82.5)	55.6 ± 12.4 (42.8, 80.8)	55.2 ± 12.4 (41.2, 78.5)	0.039
BMI (kg/m ²)	21.9 ± 4.4 (18.5, 30.6)	21.0 ± 4.0 (17.7, 30.0)	20.9 ± 3.9 (17.1, 29.1)	0.028
α-linolenic acid (μmol/L)	49.8 ± 21.0 (26.4, 84.7)	25.3 ± 12.2* (12.9, 49.8)	33.4 ± 16.4 (12.9, 69.9)	0.002
EPA (μmol/L)	1027.3 ± 669.7 (423.5, 2522.1)	468.4 ± 399.1* (81.6, 1235.7)	377.6 ± 336.9* (105.6, 1181.8)	<0.001
DHA (μmol/L)	374.0 ± 62.0 (286.6, 462.4)	177.3 ± 49.9* (107.7, 236.3)	315.8 ± 107.0 [†] (195.2, 495.3)	<0.001
Linoleic acid (μmol/L)	2246.4 ± 467.5 (1646.8, 3056.6)	1417.1 ± 392.8* (890.2, 1829.4)	1690.9 ± 421.2 (1255.9, 2531.2)	0.001
Arachidonic acid (μmol/L)	726.2 ± 201.0 (437.3, 967.8)	289.8 ± 162.6* (146.9, 637.3)	416.4 ± 222.7* [†] (233.8, 937.3)	<0.001
Vitamin A (μg/dL)	38 ± 9 (25, 52)	40 ± 6 (33, 51)	41 ± 7 (32, 49)	0.546
Vitamin D (nmol/L)	39 ± 18 (15, 65)	33 ± 14 (12, 57)	51 ± 24 [†] (22, 102)	0.014
Vitamin E (mg/dL)	2.81 ± 0.42 (2.13, 3.39)	1.34 ± 0.44* (0.68, 2.20)	1.41 ± 0.30* (0.77, 1.67)	<0.001
Vitamin E / Total lipids (mg/g) [§]	8.05 ± 1.32 (6.38, 10.12)	5.96 ± 1.90* (3.15, 8.94)	5.94 ± 1.77* (3.36, 8.62)	0.001
Uncarboxylated osteocalcin (ng/mL)	3.75 ± 1.99 (1.60, 6.94)	3.56 ± 1.57 (1.86, 6.16)	3.69 ± 1.07 (1.61, 5.00)	0.945
Albumin (g/dL)	4.1 ± 0.3 (3.7, 4.6)	4.2 ± 0.3 (3.6, 4.7)	4.3 ± 0.2 (4.0, 4.6)	0.292
Protein (g/dL)	6.6 ± 0.6 (5.8, 7.5)	6.5 ± 0.6 (5.7, 7.6)	6.6 ± 0.5 (6.3, 7.6)	0.545

Values are expressed as mean ± SD (range).

BMI: body mass index, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid.

P values were calculated using repeated measures analysis of variance.

*Significant difference from Week 0 ($P<0.05$); [†]significant difference from Week 26 ($P<0.05$). *P* values were calculated using Bonferroni's method.

[§]The values are calculated as vitamin E (mg/dL) divided by the sum of total cholesterol (g/dL) and triglyceride (g/dL).

AA was still lower than it had been at Week 0 ($P=0.009$). However, the EPA concentration at Week 56 was still lower than that at Week 0 ($P=0.006$). The mean EPA concentrations of the seven patients (excluding the patient who took a prescribed EPA ethyl ester) were as follows: Week 0, 813.8 ± 312.4 μmol/L; Week 26, 358.8 ± 271.4 μmol/L; and Week 56, 262.7 ± 96.1 μmol/L. The serum EPA concentration at Week 0 correlated positively with the fish

intake during the run-in phase ($r=0.821$, $P=0.023$) in these seven patients, but no correlation was observed between the EPA concentration and the fish intake at Week 26 (end of the efficacy phase), or at Week 56 (end of the safety phase). The serum EPA concentrations in seven patients at Week 56 were below 370 μmol/L regardless of their "Fish" intake during the safety phase (Fig. 3). The serum DHA concentrations did not correlate with the fish intake dur-

ing Week 0, 26 or 56.

The mean serum vitamin E concentration at Week 0 was 2.81 ± 0.42 mg/dL, which then decreased by almost half at Week 26 ($P < 0.001$) and was still low at Week 56. The ratio of vitamin E to total lipids was also decreased by about 70% at Weeks 26 and 56. Vitamin D concentrations were low at Weeks 0 and 26, then increased at Week 56 (vs Week 26, $P = 0.024$). The serum concentrations of vitamin A and vitamin K (measured as uncarboxylated osteocalcin) did not change during the study period. The serum albumin and protein concentrations remained within their standard concentration ranges.

Discussion

A low-fat diet is essential during lomitapide treatment because of gastrointestinal adverse effects such as diarrhea, which usually occurs if fat ingestion is more than 20% of the daily energy intake^{4,7}. In the HoFH patients participating in the present study, the primary dietary goal of keeping lipid intake below 20% of the total energy intake was achieved by repeated dietary counseling sessions that continued for more than 6 months.

According to a report on the National Health and Nutrition Survey, the Japanese consume lipids from the following food groups (from highest to lowest percentages): “Meat and poultry” (24.0% contribution to lipid intake), “Fats and oils” (21.6%), “Milk and dairy products” (8.8%) and “Fish” (8.7%)⁸. Our patients limited their “Fats and oils” intake to a very small amount about 10 g during the safety phase, and intake of “Fatty meat and poultry” was switched to “Lean meat and poultry”, “Fish” and “Low-fat seafood”. Decreasing intakes of “Fats and oils” and “Fatty meat and poultry” appeared to be an appropriate strategy for maintaining a low-fat diet.

The mean BMI of Japanese patients with HoFH is reportedly low, at 17.2 ± 3.3 kg/m²¹². More than half of the patients in the present study were lean at baseline. Body weight reduction was demonstrated in a global phase 3 study of lomitapide conducted in the USA, Canada, South Africa, and Italy⁴. In the present study, despite unchanged median energy intake during the study period, the body weight decreased even in patients whose energy intakes increased during lomitapide treatment. Energy restriction associated with lowering dietary fat consumption and reduced fat absorption is considered to be the cause of weight loss. Dietary guidance on sufficient energy intake from carbohydrates is necessary to prevent weight loss.

Possible deficiency due to reduced absorption of essential fatty acids and fat-soluble vitamins is also a

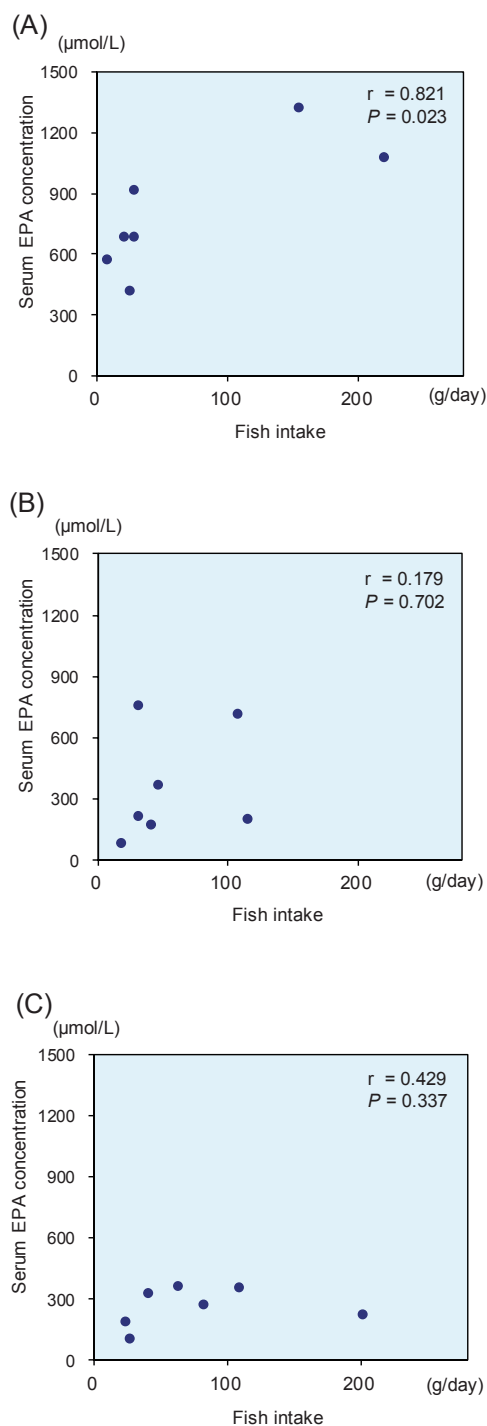


Fig. 3. Relationship between serum eicosapentaenoic acid (EPA) concentration and fish intake during lomitapide treatment in Japanese patients with HoFH

Relationships between serum EPA concentration and fish intakes in each phase; (A) at Week 0 and in the run-in phase (Weeks -6-0), (B) at Week 26 and in the efficacy phase (Weeks 0-26) and (C) at Week 56 and in the safety phase (Weeks 26-56) for seven patients (i.e., excluding the EPA ethyl ester-treated patient). The correlation coefficients were analyzed by Spearman's correlation analysis.

concern during lomitapide treatment^{6, 13}). To prevent essential fatty acid deficiencies, patients received fatty acid supplements during the study. The median intakes of n-3 and n-6 PUFA during the run-in phase were maintained at nearly the Japanese “adequate intake” recommended dietary levels, amounts that should minimize risks of deficiency¹⁴). In the present study, the mean serum fatty acid concentrations were markedly higher for EPA, but lower for LA, AA and ALA, and almost the same for DHA at Week 0 as compared to the values in the global phase 3 study of lomitapide⁴); the differences in fatty acid concentrations were apparently related to Japanese patients consuming more dietary EPA and DHA from fish, but less LA and ALA from fats and oils, than western populations^{15, 16}).

In the present study, despite no significant changes in dietary fatty acid intake, all measured serum fatty acid concentrations were decreased at Week 26, observations consistent with the results of the global phase 3 lomitapide study⁴). The decreases in serum fatty acid concentrations at Week 26 are presumably due to the approximately 40% decrease in serum lipids in response to lomitapide treatment⁵), that is, the fatty acid concentration would presumably, at least in theory, be decreased. Thereafter, during the period from Week 26 to Week 56, serum lipids increased slightly⁵), with increases in DHA and AA, whereas EPA remained low. The serum fatty acid concentrations are affected by many factors including metabolic demands and biosynthesis regulation¹⁷). Low-fat diets¹⁸) and lipid-lowering therapy¹⁹) reportedly alter serum PUFA compositions, possibly due to elongase and desaturase becoming more highly activated. However, it is not clear whether reductions in serum lipids produced by MTP inhibition (lomitapide) affect PUFA metabolism. Further investigation is needed focusing on changes in serum fatty acid concentrations during long-term lomitapide treatment and the metabolism of individual fatty acids in patients with HoFH. However, the EPA concentration at Week 56 was still higher than that at Week 0 in the global phase 3 study ($209.8 \pm 128.0 \mu\text{mol/L}$)⁴), a state in which fatty acids are not considered to be deficient. Thus, supplementation of essential fatty acids is necessary during continuous lomitapide treatment on a long-term basis.

As vitamin E is transported via chylomicrons and VLDL²⁰), its concentration was assumed to decrease during lomitapide treatment⁴). In the present study, the serum vitamin E concentration at Week 0 was high enough to correspond to the highest quintile of Japanese serum vitamin E concentrations²¹) with large supplemental vitamin E amounts. Thereafter, although

the vitamin E concentrations were decreased at Weeks 26 and 56, the levels did not fall below the lower limit of the reference value for vitamin E deficiency (0.5 mg/dL) nor did the ratios of vitamin E to total lipids (1.4 mg/g) in any of the patients¹⁰). Thus, vitamin E deficiency can be avoided with supplements that contain much larger amounts of vitamin E than would normally be obtained by dietary intake. These findings confirm that taking vitamin E supplements is indispensable during lomitapide treatment.

No other fat-soluble vitamins (A, D and K) were provided as supplements. The serum vitamin A concentration is considered to not decrease until hepatic retinol storage is $< 20 \mu\text{g/g}$ ^{22, 23}). In the present study, potential vitamin A deficiency was a concern because the intake of vitamin A was lower than the estimated average requirement¹⁴). Patients on low-fat diets should reduce the intake of retinol derived from animal foods. This can be achieved, for example, by increasing the intake of β -carotene, a precursor of retinol, from green and yellow vegetables. Such an approach is necessary to supply adequate quantities of vitamin A.

If vitamin K absorption is reduced by taking lomitapide, the risk of bleeding becomes a concern because vitamin K affects blood coagulation²⁴). In the present study, the concentration of uncarboxylated osteocalcin as a proxy for vitamin K deficiency did not change during the study period and was maintained at levels comparable to those in healthy Japanese people²⁵).

Blood vitamin D concentrations reflect the total amount of vitamin D from dietary sources and that produced in the skin via ultraviolet light²⁶) with seasonal variation²⁷). No association was observed between increased serum vitamin D concentration and vitamin D intake. Therefore, the increased vitamin D concentrations in the present study have yet to be explained.

Our present study has several limitations. First, we could not investigate the relationships between the daily dietary lipid intakes with gastrointestinal side effects. Gastrointestinal symptoms are thought to be strongly influenced by the last meal consumed. However, lack of information on the daily dietary intake in this study did not allow us to evaluate the relationship between the daily lipid intake and gastrointestinal adverse events. Further study focusing on how diet can minimize side effects is required. Second, the lack of dietary records before the run-in phase did not allow us to discuss initial changes in food and nutrient intakes on the low-fat diet. Third, since information about the required amounts of nutrients for patients with HoFH is not available, we cannot evaluate

whether their nutrient levels were clinically deficient. Therefore, a future study on the recommended dietary intakes for patients with HoFH is necessary to evaluate their dietary intake needs. Fourth, genetic backgrounds, as well as lomitapide doses and apheresis as background therapies, varied among subjects. These heterogeneous background factors, together with the small sample size due to HoFH being a rare disease, resulted in an incomplete analysis of the relationships of dietary intake and nutritional status with these factors.

While we acknowledge these limitations, a strength of this report is that it is the first to focus on dietary intake and nutritional status in Japanese HoFH patients who follow low-fat diets as part of a lomitapide treatment regimen. Moreover, few studies have investigated dietary intake based on 30-day dietary records kept for longer than a year. Therefore, our findings provide potentially useful information for implementing dietary therapy during lomitapide treatment. Monitoring nutritional status is necessary during long-term lomitapide treatment.

Conclusion

Dietary counseling with a registered dietitian facilitates compliance with a low-fat diet by patients who receive lomitapide treatment. Decreasing intakes of “fats and oils” and “fatty meat and poultry” are recommended strategies for maintaining a low-fat diet. Education on sufficient energy intake is needed to prevent excessive weight reduction, especially in underweight patients. Consumption of fish may improve essential fatty acid intakes. However, vitamin E and fatty acid dietary supplements prescribed for deficiency prevention are indispensable. As differences were observed in food and nutrient intakes among individuals, periodic monitoring of nutritional status is required for long-term lomitapide treatment.

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