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 pathway\(^1\). 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\(^1\). 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 atherosclerosis\(^3\).

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 liver\(^6\). 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 treatment\(^7\). However, the feasibility of a long-term low-fat diet has become a growing concern as the fat intake of the Japanese population is rising\(^8\). 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 nutritional 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 elsewhere\(^5\). Briefly, the study consisted of three phases: a pre-treatment run-in phase (Weeks −6 to 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
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 (Ken-paku-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
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 study. 5

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 $\geq 10$ g of lipids/100 g) was almost the same as that of “Fatty meat and poultry” (containing $\geq 10$ 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 $\geq 10$ 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
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 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)   | Efficacy phase (g) | Safety phase (g)  | P value           |
|                  | (Weeks 6–26)       | (Weeks 0–26)       | (Weeks 26–56)     |                   |
| 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 visera | 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) | 0.678             |
| 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 visera | 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) | 0.039 |
| 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)   | 0.456             |
| 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.
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

| Nutrient                        | Run-in phase (Weeks −6−0) | Efficacy phase (Weeks 0−26) | Safety phase (Weeks 26−56) | P 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 (%)                      | 44.0 (21.9, 132.5)        | 39.0 (20.0, 46.3)           | 39.0 (25.7, 58.3)         | 0.882   |
| SFA (g) (%)                    | 21.4 (12.7, 36.5)         | 19.2 (5.7, 23.0)            | 17.9 (14.6, 21.8)         | 0.417   |
| MUFA (g) (%)                   | 10.44 (4.60, 47.64)       | 10.84 (5.87, 11.57)         | 9.96 (6.56, 21.12)        | 0.223   |
| n-3 PUFA (g) (%)               | 5.4 (3.0, 13.0)           | 5.2 (1.7, 6.3)              | 4.6 (3.4, 6.0)            | 0.417   |
| n-6 PUFA (g) (%)               | 15.18 (6.99, 56.15)       | 11.62 (5.68, 16.99)         | 12.36 (8.54, 20.47)       | 0.882   |
| n-3 PUFA (%E)                  | 1.63 (0.99, 4.37)         | 1.87 (0.54, 2.81)           | 2.16 (1.27, 3.60)         | 0.417   |
| n-6 PUFA (%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   |
| Linoleic acid (g) (%)          | 8.77 (5.68, 14.03)        | 8.10 (4.05, 10.03)          | 8.04 (4.38, 12.04)        | 0.417   |
| Arachidonic acid (g)           | 4.3 (3.4, 5.7)            | 4.1 (1.1, 5.1)              | 4.2 (1.9, 5.6)            | 0.882   |
| 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   |
| Carbohydrate (g)               | 271.5 (206.1, 299.0)      | 278.7 (225.5, 539.9)        | 288.3 (229.5, 538.9)      | 0.687   |
| 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 (µg 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 (µg)    | 2947 (1137, 3802)         | 2495 (1090, 5011)           | 3074 (1282, 5252)         | 0.325   |
| Vitamin D (µg)                 | 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 (µg)                 | 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, RA E: 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);

1Significant 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.

*Significantly different at the P<0.05 level. *P* values were calculated using the Wilcoxon signed-ranks test, with the Bonferroni correction for pair-wise comparison between the phases.

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 intake 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
significant 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 $\beta$-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 $\alpha$-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/m$^2$ at Week 0 experienced weight losses during the 56 weeks and had a BMI $<18.5$ kg/m$^2$.

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...
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 $370 \mu$mol/L regardless of their “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 did not correlate with the fish intake during the safety phase (Fig. 3). The serum DHA concentrations did not correlate with the fish intake dur-

### 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           | $P$ value |
|------------------|-------------------|-------------------|-------------------|-----------|
| **Body weight (kg)** | 57.7 ± 13.6       | 55.6 ± 12.4       | 55.2 ± 12.4       | 0.039     |
| * (45.4, 82.5)   | * (42.8, 80.8)    | * (41.2, 78.5)    |                   |           |
| **BMI (kg/m²)**  | 21.9 ± 4.4        | 21.0 ± 4.0        | 20.9 ± 3.9        | 0.028     |
| * (18.5, 30.6)   | * (17.7, 30.0)    | * (17.1, 29.1)    |                   |           |
| **α-linolenic acid (µmol/L)** | 49.8 ± 21.0 | 25.3 ± 12.2* | 33.4 ± 16.4 | 0.002     |
| * (26.4, 84.7)   | * (12.9, 49.8)    | * (12.9, 69.9)    |                   |           |
| **EPA (µmol/L)** | 1027.3 ± 669.7    | 468.4 ± 399.1*    | 377.6 ± 336.9*    | <0.001    |
| * (423.5, 2522.1)| * (81.6, 1235.7)  | * (105.6, 1181.8) |                   |           |
| **DHA (µmol/L)** | 374.0 ± 62.0      | 177.3 ± 49.9*     | 315.8 ± 107.0*    | <0.001    |
| * (286.6, 462.4) | * (107.7, 236.3)  | * (195.2, 495.3)  |                   |           |
| **Linoleic acid (µmol/L)** | 2246.4 ± 467.5 | 1417.1 ± 392.8* | 1690.9 ± 421.2 | 0.001     |
| * (1646.8, 3056.6)| * (890.2, 1829.4)| * (1255.9, 2531.2)| |           |
| **Arachidonic acid (µmol/L)** | 726.2 ± 201.0 | 289.8 ± 162.6* | 416.4 ± 222.7* | <0.001    |
| * (437.3, 967.8) | * (146.9, 637.3) | * (233.8, 937.3) | |           |
| **Vitamin A (µg/dL)** | 38 ± 9       | 40 ± 6           | 41 ± 7           | 0.546     |
| * (25, 52)       | * (33, 51)       | * (32, 49)       |                   |           |
| **Vitamin D (nmol/L)** | 39 ± 18      | 33 ± 14          | 51 ± 24*         | 0.014     |
| * (15, 65)       | * (12, 57)       | * (22, 102)      |                   |           |
| **Vitamin E (mg/dL)** | 2.81 ± 0.42   | 1.34 ± 0.44*     | 1.41 ± 0.30*     | <0.001    |
| * (2.13, 3.39)   | * (0.68, 2.20)   | * (0.77, 1.67)   |                   |           |
| **Vitamin E / Total lipids (mg/g)** | 8.05 ± 1.32  | 5.96 ± 1.90*    | 5.94 ± 1.77*     | 0.001     |
| * (6.38, 10.12)  | * (3.15, 8.94)   | * (3.36, 8.62)   |                   |           |
| **Uncarboxylated osteocalcin (ng/mL)** | 3.75 ± 1.99  | 3.56 ± 1.57     | 3.69 ± 1.07      | 0.945     |
| * (1.60, 6.94)   | * (1.86, 6.16)   | * (1.61, 5.00)   |                   |           |
| **Albumin (g/dL)** | 4.1 ± 0.3      | 4.2 ± 0.3        | 4.3 ± 0.2        | 0.292     |
| * (3.7, 4.6)     | * (3.6, 4.7)     | * (4.0, 4.6)     |                   |           |
| **Protein (g/dL)** | 6.6 ± 0.6      | 6.5 ± 0.6        | 6.6 ± 0.5        | 0.545     |
| * (5.8, 7.5)     | * (5.7, 7.6)     | * (6.3, 7.6)     |                   |           |

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).
The mean serum vitamin E concentration at Week 0 was $2.81 \pm 0.42$ 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. 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%). 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 $17.2 \pm 3.3$ kg/m$^2$. 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 Italy. 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 concern. Fig. 3 shows the relationships between serum eicosapentaenoic acid (EPA) concentration and fish intake during lomitapide treatment in Japanese patients with HoFH. The correlation coefficients were analyzed by Spearman’s correlation analysis.
concern during lomitapide treatment. 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 deficiency. 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 lomitapide; 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.

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 study. 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 treatment, 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 slightly, 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 regulation. Low-fat diets and lipid-lowering therapy 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 ± 128.0 µmol/L), 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 VLDL, its concentration was assumed to decrease during lomitapide treatment. In the present study, the serum vitamin E concentration at Week 0 was 59.8 µmol/L, which was not 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 lomitapide; 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.

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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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References

1) Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjaerg-Hansen A, Watts GF, Averna M, Boileau C, Borén J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O and Chapman MJ; European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia: Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J, 2014; 35: 2146-2157
2) Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS,Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averna M, Borén J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR and Tybjaerg-Hansen A; European Atherosclerosis Society Consensus Panel: Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J, 2013; 34: 3478-3490a
3) Makino H and Harada-Shiba M: Long-term effect of low-density lipoprotein apheresis in patients with homozygous familial hypercholesterolaemia. Ther Apher Dial, 2003; 7: 397-401
4) Cuchel M, Meagher EA, du Toit Theron H, Blom DJ, Marais AD, Hegele RA, Averna MR, Siritori CR, Shah PK, Gaudet D, Stefanutti C, Vigna GB, Du Plessis AME, Probert KJ, Sasiela WJ, Bluedon LT and Rader DJ; Phase 3 HoFH Lomitapide Study investigators: Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet, 2013; 381: 40-46
5) Harada-Shiba M, Ikewaki K, Nohara A, Otsubo Y, Yanagi K, Yoshida M, Chang Q and Foulds P: Efficacy and Safety of Lomitapide in Japanese Patients with Homozygous Familial Hypercholesterolemia. J Atheroscler Thromb, 2017; 24: 402-411
6) Wetterau JR, Lin MC and Jamil H: Microsomal triglyceride transfer protein. Biochim Biophys Acta, 1997; 1345: 136-150
7) Roeters van Lennep J, Averna M and Alonso R: Treating homozygous familial hypercholesterolemia in a real-world setting: Experiences with lomitapide. J Clin Lipidol, 2015; 9: 607-617
8) Ministry of Health, Labor and Welfare: The National Health and Nutrition Survey in Japan, 2015. http://www.mhlw.go.jp/bunya/kenkou/eiyou/dl/h27-houkoku.pdf
9) Mekawama K, Pendergast DR, Leddy JJ, Mason M, Horvath PJ and Awad AB: Effect of low and high fat diets on nutrient intakes and selected cardiovascular risk factors in sedentary men and women. J Am Coll Nutr, 2004; 23: 131-140
10) Winbauer AN, Pingree SS and Nuttall KL: Evaluating serum alpha-tocopherol (vitamin E) in terms of a lipid ratio. Ann Clin Lab Sci, 1999; 29: 185-191
11) Thurnham DI, Davies JA, Crump BJ, Situnayake RD and Davis M: The use of different lipids to express serum tocopherol: lipid ratios for the measurement of vitamin E status. Ann Clin Biochem, 1986; 23 : 514-520
12) Bujo H, Takahashi K, Saito Y, Maruyama T, Yamashita S, Matsuzawa Y, Ishibashi S, Shionoiri F, Yamada N and Kita T; Research Committee on Primary Hyperlipidemia of the Ministry of Health, Labour and Welfare of Japan: Clinical features of familial hypercholesterolemia in Japan in a database from 1996-1998 by the research committee of the ministry of health, labour and welfare of Japan. J Atheroscler Thromb, 2004; 11: 146-151
13) Hooper AJ, Burnett JR and Watts GF: Contemporary aspects of the biology and therapeutic regulation of the microsomal triglyceride transfer protein. Circ Res, 2015; 116: 193-205
14) Ministry of Health, Labor and Welfare: Dietary Reference Intakes for Japanese (2015). 2014 http://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka/0000114399.pdf
15) Papanikolaou Y, Brooks J, Reider C and Fulgoni VL 3rd: U.S. adults are not meeting recommended levels for fish and omega-3 fatty acid intake: results of an analysis using observational data from NHANES 2003-2008. Nutrition Journal, 2014; 13: 31
16) Gebauer SK, Psota TL, Harris WS and Kris-Etherton PM: n-3 fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits. Am J Clin Nutr, 2006; 83: 1526S-1535S
17) Wang TY, Liu M, Portincasa P and Wang DQ: New insights into the molecular mechanism of intestinal fatty acid absorption. Eur J Clin Invest, 2013; 43: 1203-1223
18) Raatz SK, Bibus D, Thomas W and Kris-Etherton P: Total fat intake modifies plasma fatty acid composition in humans. J Nutr, 2001; 131: 231-234
19) Jula A, Marniemi J, Ronnemaa T, Virtanen A and Huupponen R: Effects of diet and simvastatin on fatty acid composition in hypercholesterolemic men: a randomized controlled trial. Arterioscler Thromb Vasc Biol, 2005; 25: 1952-1959
20) Kayden HJ and Traber MG: Absorption, lipoprotein transport, and regulation of plasma concentrations of vitamin E in humans. J Lipid Res, 1993; 34: 343-358
21) Nagao M, Moriyama Y, Yamagishi K, Iso H and Tamakoshi A; JACC Study Group: Relation of Serum Ј and ѓ-Tocopherol Levels to Cardiovascular Disease-Related Mortality Among Japanese Men and Women. J Epidemiol, 2012; 22:402-410
22) Tanumihardjo SA: Vitamin A: biomarkers of nutrition for development. Am J Clin Nutr, 2011; 94: 658S-665S
23) Panel on micronutrients Food and Nutrition Board, Institute of Medicine: Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. 2001
24) Shearer MJ: Vitamin K. Lancet, 1995; 345: 229-234
25) Furusyo N, Ihara T, Hayashi T, Toyoda K, Ogawa E, Okada K, Kainuma M, Murata M and Hayashi J: The serum undercarboxylated osteocalcin level and the diet of a Japanese population: results from the Kyushu and Okinawa Population Study (KOPS). Endocrine, 2013; 43: 635-642
26) Brustad M, Alsaker E, Engelsen O, Aksnes L and Lund E: Vitamin D status of middle-aged women at 65-71 degrees N in relation to dietary intake and exposure to ultraviolet radiation. Public Health Nutr, 2004; 7: 327-335
27) Nakamura K, Kitamura K, Takachi R, Saito T, Kobayashi R, Oshiki R, Watanabe Y, Tsugane S, Sasaki A and Yamazaki O: Impact of demographic, environmental, and lifestyle factors on vitamin D sufficiency in 9084 Japanese adults. Bone, 2015; 74:10-17