Two Patients with Familial Hypercholesterolemia Who Were Successfully Weaned from Low-density Lipoprotein Apheresis after Treatment with Evolocumab

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Abstract

Two elderly patients (a 76-year-old man and a 75-year-old woman), who had been previously diagnosed with familial hypercholesterolemia (at 58 and 48 years of age, respectively) underwent long-term treatment with oral therapy and low-density lipoprotein (LDL) apheresis. As their LDL cholesterol levels remained high (>150 mg/dL and >120 mg/dL, respectively) and their familial hypercholesterolemia was complicated with angina pectoris, we added evolocumab to their prescription. Thereafter, their LDL cholesterol levels decreased rapidly, and the patients were successfully weaned from LDL apheresis. Evolocumab therapy should thus be considered when LDL apheresis cannot achieve the target LDL cholesterol levels, though the prognosis of such treatment remains unclear.

Key words: familial hypercholesterolemia, low-density lipoprotein apheresis, evolocumab

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Introduction

Hypercholesterolemia is a known risk factor for cardiovascular disease (CVD), and reducing the levels of low-density lipoprotein (LDL) cholesterol is important for decreasing the risk for CVD (1, 2). Hence, several guidelines stated that lowering LDL cholesterol (LDL-C) represents a therapeutic target (3, 4). Among patients with hypercholesterolemia, those with familial hypercholesterolemia (FH) typically exhibit extremely high levels of LDL-C, the rapid progression of atherosclerotic diseases, and a high prevalence of CVD. Hence, to prevent CVD, the rigorous control of LDL-C is important in patients with FH. When LDL-C is not effectively controlled by oral therapy alone, LDL apheresis (LDL-A) is sometimes used, with relatively good results (5, 6). While LDL-A is indeed effective in reducing LDL-C, certain procedure-related aspects such as restraint time and vascular access remain matters of concern.

Evolocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, has recently become available. Evolocumab represents a promising drug, as it is reported to reduce the risk of CVD in patients with hypercholesterolemia, including those with FH (7). Furthermore, the efficacy of evolocumab in reducing LDL-C in FH patients has been reported (8, 9). However, these trials did not include FH patients receiving LDL-A. There are no reports on the effects of evolocumab therapy combined with LDL-A. We herein report 2 cases of FH in which evolocumab treatment enabled the patients to be successful weaned from LDL-A.

Case Reports

Case 1

A 76-year-old man was suspected of having FH at 58 years of age when he presented with angina pectoris and high levels of total cholesterol (>500 mg/dL). The patient also had Achilles tendon xanthoma and a family history of hypercholesterolemia (sister and son). At the time, the patient was diagnosed with FH according to the Simon Broome criteria (10), and LDL-A was added to his ongoing
oral therapy. Thereafter, he experienced angina pectoris 5 times, which was managed via percutaneous coronary intervention (4 times) and coronary artery bypass grafting (once). A further complication of bilateral carotid artery stenosis was treated via bilateral carotid endarterectomy.

In March 2016, when the patient was 76 years of age, he presented to our department with consistently high levels of LDL-C despite the ongoing treatment. At the time, the patient’s prescription for oral therapy included rosuvastatin (10 mg/day), indapamide (1 mg/day), lansoprazole (15 mg/day), ethyl-eicosapentaenoic acid (1,800 mg/day), ezetimibe (10 mg/day), and benidipine (8 mg/day). For this patient, the dosage of rosuvastatin represented the maximum tolerated dose, as he exhibited muscle pain that was associated with the administration of rosuvastatin. In addition to the oral therapy, the patient underwent LDL-A approximately once a month. LDL-A was performed with a system using dextran sulfate cellulose columns (Liposorber LA-15°, Kaneka Medix, Osaka, Japan). The amount of processed plasma was 4,000 mL/session; heparin was used as an anticoagulant. Because few good vessels for use in vascular access remained, an arteriovenous fistula was created in his left forearm to serve as vascular access (the same as for hemodialysis).

With the above-described treatment strategy, the levels of LDL-C before the LDL-A sessions were maintained at approximately 150 mg/dL. For the secondary prevention of CVD, we aimed to achieve a significant decrease in the levels of LDL-C. Our first suggestion was to increase the frequency of LDL-A, which was refused by the patient on account of the long restraint time during treatment and discomfort related to the urge to urinate. In May 2016, the patient was started on evolocumab (140 mg every 2 weeks). Thereafter, the levels of LDL-C rapidly decreased. Fig. 1 shows the evolution of the LDL-C levels, which remained below 100 mg/dL as soon as evolocumab therapy was initiated. Thereafter, the patient was successfully weaned from LDL-A. Table 1 shows the results of the laboratory investigations that were performed before the final LDL-A session and at 2 weeks after the final LDL-A session.

Case 2

A 75-year-old woman experienced myocardial infarction at 48 years of age, and exhibited high levels of total cholesterol (>500 mg/dL). The patient had a family history of cardiovascular events, as her mother had died from myocardial infarction in her 30s, and her daughter had hypercholesterolemia. The patient showed xanthoma on her Achilles tendon, cubital fossa, and her back. At the time, she was diagnosed with FH according to the Simon Broome criteria. At 55 years of age, the patient was started on LDL-A, in addition to her ongoing oral therapy. Thereafter, the patient experienced angina pectoris once.

In March 2016, when the patient was 75 years of age, she presented to our department with consistently high levels of LDL-C despite the ongoing treatment. At the time, the patient’s prescription for oral therapy included rosuvastatin (10 mg/day), aspirin (100 mg/day), lansoprazole (15 mg/day), ethyl-eicosapentaenoic acid (1,800 mg/day), ezetimibe (10 mg/day), and bisoprolol (1.25 mg/day), telmisartan (40 mg/day), sodium ferrous citrate (100 mg/day), minodronic acid hydrate (50 mg/month), and paroxetine (25 mg/day). The dose of rosvastatin represented the maximum tolerated dose, as the patient experienced muscular pain related to the administration of rosvastatin. In addition to oral therapy, the patient underwent LDL-A once a month. LDL-A was performed as described in case 1.

With the above-described treatment strategy, the levels of LDL-C were maintained at approximately 120 mg/dL. As in
but in which the LDL-C levels were successfully managed not be sufficiently controlled via oral therapy and LDL-A, may have the advantage of continuously maintaining low values within 1 or 2 weeks (13, 14). On the other hand, evolocumab when the target LDL-C levels cannot be achieved in FH patients receiving LDL-A.

Evolocumab, which is a type of PCSK9 inhibitor, is believed to decrease the levels of LDL-C by upregulating the recycling of the LDL receptor, which is responsible for removing LDL-C from the bloodstream by means of endocytosis (11, 12). Given this mechanism of action, the efficacy of PCSK9 inhibitors is expected to be low in patients with homozygous LDL receptor mutations that lead to the complete depletion of the LDL receptor. Based on the response of our patients’ LDL-C levels to evolocumab treatment, we assume that they represent cases of heterozygous FH; however, we did not perform any genetic testing to confirm the nature of their mutations. We believe that PCSK9 inhibitors represent a promising treatment when a residual LDL receptor is available.

The optimal choice of treatment (i.e., LDL-A or evolocumab) for improving the prognosis of FH patients remains an important topic for discussion. From the patient’s perspective, the major disadvantages of LDL-A are the long restraint time during treatment sessions, as well as the discomfort related to ensuring suitable vascular access. In one of our patients, vascular access for LDL-A was achieved in the same manner as in hemodialysis patients. However, while LDL-A is effective in reducing the levels of LDL-C, the effect is short-lived, and the LDL-C levels reach abnormal values within 1 or 2 weeks (13, 14). On the other hand, LDL-A has pleiotropic effects, which include the improvement of the vascular endothelial function by decreasing the oxidative stress responses and inhibiting nitric oxide synthesis (15), and the improvement of the rheological properties of the blood (16, 17). Hence, aside from its ability to lower the LDL-C levels, LDL-A may be more effective in alleviating arteriosclerotic disease. On the other hand, evolocumab may have the advantage of continuously maintaining low LDL-C levels, whereas these levels are expected to recover within 1 to 2 weeks after an LDL-A session (13, 14). Furthermore, as of 2016, the cost of evolocumab therapy (140 mg every 2 weeks) increased arteriosclerotic disease. On the other hand, evolocumab may have the advantage of continuously maintaining low LDL-C levels, whereas these levels are expected to recover within 1 to 2 weeks after an LDL-A session (13, 14). Furthermore, as of 2016, the cost of evolocumab therapy (140 mg every 2 weeks) increased.
The clinical course of the low-density lipoprotein cholesterol (LDL-C) levels of a 75-year-old woman with familial hypercholesterolemia (Case 2). The continuous line indicates the LDL-C values measured before and after each LDL apheresis session (LDL-A; full triangles). The patient was successfully weaned from LDL-A because her LDL-C levels remained low immediately after the initiation of evolocumab therapy (arrows).

Table 2. Before and after Evolocumab Administration in Case 2.

| Parameter | Before | 2 weeks later |
|-----------|--------|---------------|
| WBC (μL)  | 4,100  | 4,100         |
| Hb (g/dL) | 12.9   | 12.7          |
| Pt (10^3/μL) | 18.3 | 18.0          |
| TP (g/dL) | 6.67   | 6.68          |
| Alb (g/dL) | 4.27   | 4.23          |
| ALT (U/L) | 16     | 20            |
| ALP (U/L) | 185    | 215           |
| UA (mg/dL) | 4.26   | 4.29          |
| BUN (mg/dL) | 16.5 | 18.0          |
| Cr (mg/dL) | 0.61   | 0.66          |
| eGFR (mL/min/m²) | 71.3 | 65.4         |
| Na (mEq/L) | 142    | 143           |
| K (mEq/L) | 3.8    | 4.8           |
| Adjusted Ca (mg/dL) | 9.20  | 9.40          |
| P (mg/dL) | 3.2    | 3.4           |
| CRP (mg/dL) | 0.20   | 0.20         |
| HbA1c (%) | 5.8    |               |
| T-C (mg/dL) | 236  | 138           |
| LDL-C (mg/dL) | 133 | 46            |
| HDL-C (mg/dL) | 63  | 64            |
| TG (mg/dL) | 165    | 96            |
| Lp (a) (mg/dL) | 58   | 34            |
| Apo A-I (mg/dL) | 185  | 187           |
| Apo A-I (mg/dL) | 119  | 53            |
| Apo E (mg/dL) | 5.2    | 3.2           |
| PCSK9 (ng/mL) | 536  |               |

WBC: white blood cells, Hb: hemoglobin, Pt: platelet, TP: total protein, Alb: albumin, ALT: alanine transaminase, ALP: alkaline phosphatase, UA: uric acid, BUN: blood urea nitrogen, Cr: creatinine, eGFR: estimated glomerular filtration rate, Na: sodium, K: potassium, Ca: calcium, P: phosphate, CRP: C-reactive protein, HbA1c: hemoglobin A1c, T-C: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, Lp(a): lipoprotein (a), Apo A-I: apolipoprotein fraction A-I, Apo B: apolipoprotein fraction B, Apo E: apolipoprotein fraction E, PCSK9: proprotein convertase subtilisin/kexin type 9.

The authors state that they have no Conflict of Interest (COI).

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