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Transition from LDL apheresis to evolocumab in heterozygous FH is equally effective in lowering LDL, without lowering HDL cholesterol

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ABSTRACT

Background and aims: LDL apheresis is effective in reducing low-density lipoprotein (LDL) cholesterol (LDL-C) and clinical endpoints, however, the treatment is invasive and time consuming. In the present study, we explored lipid profiles and quality of life in patients with heterozygous familial hypercholesterolemia (FH) when altering the treatment regimen from weekly LDL apheresis to bi-weekly evolocumab treatment.

Methods: Three patients with FH and coronary artery disease, established in LDL apheresis for 135 ± 13(SD) months, participated. The patients were examined with blood sampling before and after LDL apheresis (week 0), and before evolocumab administration (week 1–7), quality of life was assessed (week 1, 3, 7).

Results: The historically highest, untreated LDL-C was 10.3 ± 0.8 mmol/L, during weekly LDL apheresis, 5.5 ± 0.9 mmol/L pre-apheresis and 1.2 ± 0.2 mmol/L post-apheresis ($p = 0.02$). One week after apheresis, LDL-C was 6.1 ± 0.7 mmol/L, after three (bi-weekly) injections of evolocumab, LDL-C was 5.0 ± 0.7 ($p < 0.001$). High-density lipoprotein cholesterol (HDL-C) was reduced from 1.0 ± 0.2 mmol/L pre- to 0.5 ± 0.1 mmol/L post-apheresis ($p = 0.03$), it increased after apheresis and remained constant during evolocumab treatment. Lipoprotein(a) (Lp(a)) decreased from 484 ± 76 mg/L pre- to 142 ± 15 mg/L post-apheresis ($p = 0.02$), but increased during evolocumab treatment, with a small increase from week one to week seven ($p < 0.01$). There was a non-significant trend towards an increase in perceived health status (week 0; 57 ± 21, week three; 65 ± 9 and week seven; 77 ± 10).

Conclusions: In the current study, we demonstrate reductions in LDL-C, HDL-C, triglycerides and Lp(a) during apheresis. Switching from LDL apheresis to evolocumab maintained the LDL-lowering effect but did not decrease HDL levels.

1. Introduction

Heterozygous familial hypercholesterolemia (FH) is an autosomal dominant disease with a prevalence of 0.2–0.5% that, due to high levels of low-density lipoprotein (LDL) cholesterol, carries a high risk of premature atherosclerosis [1]. Statins have been a game changer in treating patients with elevated levels of LDL cholesterol [2]. Some patients, however, experience side effects from statins, most commonly muscle pain, and hence must stop the medication [3].

When FH is not adequately controlled with medication, extracorporeal treatment by means of LDL apheresis has been the preferred treatment. This treatment is highly effective in reducing both LDL cholesterol and clinical endpoints [4]. In addition to lowering LDL cholesterol, LDL apheresis also effectively lowers Lp(a) [5], a lipoprotein increasing the risk of cardiovascular endpoints in FH patients [6]. An unwanted lipoprotein effect of LDL apheresis is the lowering of high density lipoprotein (HDL) cholesterol [4]. As the treatment is invasive and time consuming, some patients report side effects and reduced quality of life [7,8].

The new proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are effective in reducing LDL cholesterol (50–60%) and Lp(a) (20%) [9]. PCSK9 inhibitors exert their effect by increasing the LDL receptor function due to decreased degradation, however more

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complex interactions between PCSK9, LDL receptors and levels of lipoproteins exist [10], and all of PCSK9's physiological properties are yet to be discovered [11]. Clinical endpoints studies are being performed, possibly with results in 2016 or 2017. Currently, among PCSK9 inhibitors, the monoclonal antibodies evolocumab and alirocumab are available for clinical use, they are both effective and well tolerated [12,13].

In the present study, we explored lipid profiles and quality of life in patients with heterozygous FH established in long term LDL apheresis when altering the treatment regimen from weekly LDL apheresis to bi-weekly subcutaneous evolocumab treatment.

2. Materials and methods

The study was designed as an observational study with three FH patients established in long-term LDL apheresis. Treatment was converted to a PCSK9 inhibitor (evolocumab), and the patients were examined immediately before and after their last apheresis treatment (week 0), after one week (immediately before the first evolocumab injection (week 1)), then biweekly before administration of evolocumab (weeks 3, 5 and 7) (Fig. 1).

2.1. Patients and ethics

Three patients with genetically confirmed FH (C210G-mutation in the LDL receptor gene, a common FH mutation affecting the binding domain of the LDL receptor) were included in the study. There were two women and one man (53 ± 3 years of age), and they all had angiographically verified coronary artery disease. They were intolerant to statins due to myalgia, and they did not take any type of lipid lowering medication. The three patients had been in LDL apheresis for 135 ± 13 months. All three patients signed informed consent and the local ethics committee approved the study.

2.2. LDL apheresis

The patients were in weekly LDL apheresis, and then the last LDL apheresis in week 0 was performed with LDL column Cascadeflo-EC-50W (Asahi Kasei Medical Europe) after previous plasma separation with Plasmaflo OP-50 (Asahi Kasei Medical Europe), using the Infomed HF440 apheresis machine (Infomed SA, Geneva, Switzerland). Anticoagulation was obtained by heparin.

2.3. Evolocumab treatment

Evolocumab was administered according to the manufacturers' instructions in week one, three, five and seven with the recommended dose of 140 mg subcutaneously (autoinjector). The injection was performed by the patients in the hospital, supervised by experienced nurses, after demonstrations with dummy autoinjectors. There was no change in lifestyle or dietary pattern after changing the treatment to evolocumab.

2.4. Blood samples and analyses

Fasting blood samples – both for effect and for safety - were analyzed by standardized laboratory kits in the hospital laboratory immediately after collection. Serum LDL and HDL cholesterol, Lp(a) and triglycerides were analyzed on ADVIA 1800 from Siemens Healthcare Diagnostics (Deerfield, IL). The historically highest, untreated lipid profile was retrieved from the digital laboratory system.

2.5. Quality of life

Quality of Life (QoL) was obtained by means of the standardized EQ-5D-3L questionnaire at weeks zero, three and seven. The Norwegian version was used with permission [14]. QoL was reported as the patients' perception of own health (visual analogue scale) where 0 is the worst and 100 is the best health condition imaginable.

2.6. Statistics

Numerical data are presented with mean and standard deviation (SD). A repeated measures one-way analysis of variance (RM one-way ANOVA) was used to calculate the longitudinally effect of the evolocumab treatment (week one to week seven) on the lipid profile (LDL cholesterol, HDL cholesterol, triglycerides and Lp(a)). Historically highest (untreated) lipid profile was then compared with pre-apheresis (week 0), post-apheresis (week 0) and finally after six weeks of evolocumab (week seven) by means of paired *t*-tests. Lipid levels before and after LDL apheresis treatment (week 0) was compared by paired *t*-tests. All tests were two-tailed and results with a $p < 0.05$ were considered statistically significant.

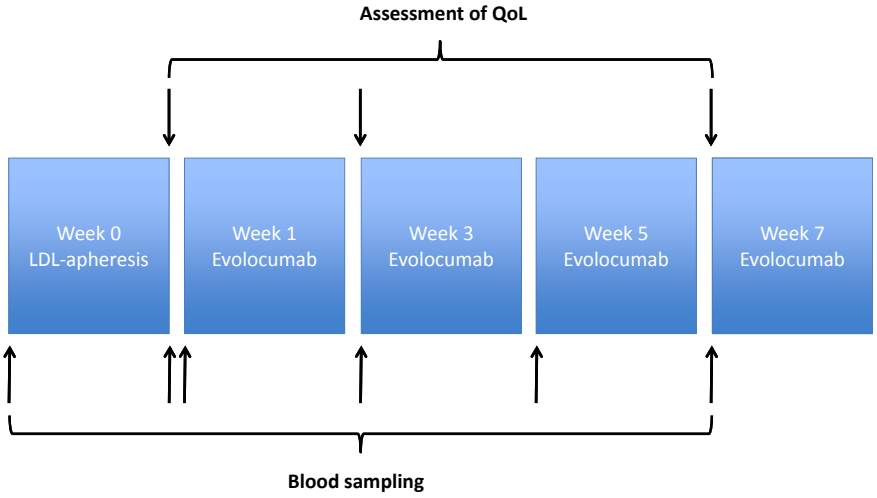

Fig. 1. Study design. Blood sampling was performed immediately before and after apheresis (week 0), and before evolocumab (week, 1, 3, 5, 7), while quality of life was assessed after apheresis (week 0) and before evolocumab (week 3 and 7). LDL, low density lipoprotein.