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Apheresis in homozygous familial hypercholesterolemia: The results of a follow-up of all Norwegian patients with homozygous familial hypercholesterolemia

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BACKGROUND: Homozygous familial hypercholesterolemia (HoFH), which affects 1 in a million individuals, leads to extremely elevated levels of cholesterol and early-onset cardiovascular disease.

OBJECTIVE: The aim of this study was to assess all 7 HoFH patients treated with low-density lipoprotein (LDL) apheresis in Norway with respect to quality of life, clinical and laboratory assessments, and cardiovascular status.

METHODS: Apheresis treatment and assessment of cardiovascular status was performed at local hospitals but coordinated by the Lipid Clinic that has followed all patients since diagnosis. Quality of life was evaluated by a validated questionnaire.

RESULTS: Results are shown as median (min-max). LDL cholesterol at diagnosis (untreated) was 704 (592–1268) mg/dL (18.2 [15.3–32.8] mmol/L). Medication was initiated at age 9 (2–35) years, and apheresis treatment at age 10 (6–44) years. Regular once-weekly apheresis combined with the maximum-tolerable doses of a statin and ezetimibe reduced LDL cholesterol to 197 (170–282) mg/dL (5.1 [4.5–7.3] mmol/L) pre-apheresis and 85 (50–108) mg/dL (2.2 [1.3–2.8] mmol/L) post-apheresis. Calculated interval mean LDL cholesterol was 162 (135–220) mg/dL (4.2 [3.5–5.7] mmol/L). Duration of apheresis treatment was 11 (1–24) years. Cardiovascular manifestations progressed in most patients despite the apheresis treatment. The subjects' quality of life was comparable with that of a healthy population, with the exception of two patients, who were significantly affected by coronary disease.

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CONCLUSIONS: Well-tolerated, once-weekly LDL apheresis achieves lower interval mean LDL cholesterol levels between apheresis treatments than previously reported for apheresis every second week. However, progressions of cardiovascular manifestations still occurred, which highlights the importance of earlier and even more aggressive treatment and follow-up in HoFH.

Familial hypercholesterolemia (FH) is typically caused by a mutation in the gene that encodes the low-density lipoprotein (LDL) receptor. The heterozygous form of FH (HeFH) is among the most common monogenic diseases worldwide and has an approximate frequency in the population of 1 in 500 (~10 million persons affected).[1] Homozygous familial hypercholesterolemia (HoFH) is caused by homozygosity or compound heterozygosity mutations related to defects in the gene that encodes the LDL receptor. The exact prevalence of HoFH is unknown but is estimated to be 1 per 1 million individuals (on the basis of the heterozygous frequency of 1/500). The untreated total cholesterol levels of HoFH patients are typically between 580 and 1160 mg/dL (15–30 mmol/L). If HoFH remains untreated, proximal coronary disease or aortic valve disease frequently occurs during childhood. Myocardial infarction has been reported for patients 3 years of age and older, and most affected patients suffer from fatal coronary disease before the age of 30.[1–3]

Since the mid-1970s, LDL cholesterol has been removed from the blood of patients with a treatment called "plasma exchange",[4] and this treatment can significantly improve the life expectancy of HoFH patients.[5] In addition, the techniques for removing plasma cholesterol have been refined since the 1980s[6]; LDL apheresis selectively removes LDL cholesterol but not immunoglobulins and other beneficial proteins, thereby overcoming a potential drawback of the traditional plasma exchange method. LDL cholesterol is effectively reduced by more than 60% immediately after apheresis, although, following a hyperbolic curve, LDL levels rebound rapidly.[7] The apheresis efficacy is expressed as the interval mean LDL cholesterol concentration between apheresis treatments (calculated as the time-averaged area under the rebound curve) and can be estimated by determining the pre- and post-apheresis LDL cholesterol levels as well as the rebound coefficient.[7,8] In previous studies of patients with HoFH authors reported interval mean LDL cholesterol levels of 232 to 271 mg/dL (6–7 mmol/L) between apheresis treatments,[9–11] although early-onset cardiovascular manifestations remained common in these patients. Therefore, Thompson and coworkers[8] suggested that an interval mean LDL cholesterol level below 251 mg/dl (6.5 mmol/L) could serve as a treatment target for this patient group. The aim of the present study was to assess all of the HoFH patients treated with LDL apheresis in Norway with respect to quality of life, clinical and laboratory assessments, and cardiovascular status.

Patients and methods

Since genetic testing for HoFH began in 1998, eight patients in Norway have been diagnosed with this disease. The Department of Medical Genetics at Oslo University Hospital Rikshospitalet in Oslo, Norway, performs all genetic testing for FH in Norway. Each of these 8 patients with HoFH have been followed by the Lipid Clinic of Oslo University Hospital Rikshospitalet. One patient (who began plasma apheresis in 1976) has undergone liver transplantation,[12] and is currently being treated with only oral medication. The other seven patients are currently being treated with LDL apheresis. This study was considered a "quality assurance project" by the hospital and was therefore not registered as a clinical trial but was approved by The Regional Committee for Medical and Health Research Ethics. Written informed consent was obtained from all patients before their inclusion, and this study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki.

LDL apheresis was coordinated by the Lipid Clinic and performed at the patients' local hospitals. The medical histories of the patients were reviewed and updated, full clinical examinations were performed, and fasting pre- and post-apheresis blood samples were collected for routine laboratory analysis. The patients completed a validated questionnaire (the Short Form-36 [SF-36]) concerning their quality of life at present, and the results were compared with previously published results from a healthy, normal Norwegian population.[13] For two of the HoFH patients, the SF-36 score before apheresis treatment was also available. With respect to treatment, reported adverse events were collected from the patients' journals after the onset of apheresis treatment. The patients were considered on an individual basis for referrals to assess their cardiovascular status by carotid Doppler ultrasonography, echocardiography, exercise stress testing, nuclear stress testing, or 64-slice CT coronary angiography (CTCA) with calcium scoring. On the basis of the findings of these initial investigations, further referrals and individual treatment plans were provided for each patient. The overall results from the seven patients, in combination with previously published data, were used to propose a general follow-up strategy for the HoFH patients.

The interval mean LDL cholesterol level between apheresis treatments was calculated using the equation devised by Kroon et al[7] and the rebound coefficient of 0.64 reported by Thompson et al.[8]