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Treatment pattern of familial hypercholesterolemia in Slovakia: Targets, treatment and obstacles in common practice

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ABSTRACT

Background and aims: Maximal doses of potent statins are the cornerstone of treatment of familial hypercholesterolemia (FH). Despite this, a substantial proportion of FH patients are either under-treated or not treated at all. The aim of this work was to evaluate, in a retrospective study, the treatment of FH patients, the proportion of FH patients reaching low-density lipoprotein cholesterol (LDL-C) goals, and reasons for not reaching LDL-C goals, in 8 lipid clinics in Slovakia dealing with FH patients.
Methods: 201 heterozygous FH patients (50.8 ± 14.9 years, 55% females) who attended the lipid clinics at least three times were included in the study.
Results: At the first visit, 31.3% of patients were treated with statins and the most common dose was 20 mg of atorvastatin, rosuvastatin and simvastatin. At the third visit, 78.1% of patients were treated with statins and 24.4% with ezetimibe. The majority of patients were treated with atorvastatin (75.8%) and rosuvastatin (18.5%) and 31.3% of all patients were treated with atorvastatin 80 mg or rosuvastatin 40 mg with/without ezetimibe. However, only 11.9% of patients with the LDL-C goal level <2.5 mmol/l and 6.9% with the goal <1.8 mmol/l reached the level. Reasons for not reaching the goal levels were evaluated by physicians in each patient. Insufficient LDL-C lowering effect of treatment, side-effects of therapy and non-compliance of patients were responsible for 46%, 18% and 30% of cases, respectively.
Conclusions: Referral of FH patients to lipid clinics in Slovakia leads to improvement in the treatment; however, almost 22% of the patients are still without statin treatment and the majority of patients do not reach the LDL-C goal level.

1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder that occurs in the heterozygous form in approximately 1 in 200–500 individuals, with more recent estimates of 1:250 from systematic review and meta-analysis of different studies [1,2]. The disease is characterised by strikingly elevated LDL-cholesterol, the presence of xanthoma, and premature atherosclerosis. Heterozygous FH show low-density lipoprotein cholesterol (LDL-C) levels in the range 5–10 mmol/l and, if left untreated, typically develop coronary heart disease (CHD) before the age of 55 in men and 60 years in women [1]. However, once diagnosed, they can readily be treated with cholesterol-lowering medication to attenuate development of atherosclerosis and to prevent coronary heart disease [3,4]. Despite the fact that cholesterol-lowering treatment with a maximal potent statin dose

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Table 1
Main characteristics of patients.

Age	50.8 ± 14.9 years
Sex (females/males)	55%/45%
Diabetes	10.5%
FH diagnosis	
Genetic	48.2%
Dutch Lipid Clinic Network criteria	32.7%
Simon Broome Register criteria	11.6%
US MED PED criteria	7.5%

Mean±SD.
FH diagnosis: proportion (%) of the FH patients confirmed genetically or with clinical diagnosis only (Dutch Lipid Clinic Network, Simon Broome or US MedPed criteria).

should be initiated immediately at the time of diagnosis, results of a few cohort studies suggest that many FH patients receive insufficient statin doses and many physicians do not up-titrate statin doses to reach the LDL-C goal levels [3–5].

Diagnosis and treatment of FH patients in the Slovak republic were first performed in 1999 as part of the MedPed FH Slovakia project [6,7]. A network of MedPed FH collaborating out-patient departments serve as referring departments for general practitioners and specialists not focused on lipid disorders. All three major clinical criteria (the Dutch Lipid Clinic Network (DLCN), the Simon Broome Register and US MED PED criteria) have been used to establish clinical diagnosis of FH; however, currently, the DLCN criteria are preferentially used [8–10]. Recently, genetic testing has become partially available due to scientific projects and health care insurance [11]. Lipid-lowering therapy and health care are available in Slovakia for free or with only marginal financial participation of the patients.

The aim of the current study was to evaluate everyday clinical practice in the management of FH patients and to identify obstacles related to proper treatment of FH in 8 busy out-patient departments involved in the MedPed FH project in Slovakia. In particular, we were interested in the proportion of patients reaching LDL-C goal levels according to the EAS/ESC 2011 treatment guidelines [12] and in the proportion of FH patients under maximal doses of potent statins.

2. Patients and methods

Patients with definite or probable diagnosis of FH (using all three major clinical criteria - DLCN, the Simon Broome Register and US MED PED criteria, according to preferences of the participating centres) were included in this retrospective observation in 8 MedPed FH centres (four Diabetes Clinics, three Internal Medicine Departments and one Cardiology Centre) geographically distributed throughout Slovakia. Other inclusion criteria were age ≥18 years, signed informed consent to participate in the MedPed FH project, and individual patients medical records from at least 3 clinical visits in a centre, of which at least one was performed in 2015. Data collection was performed between December 2015 and January 2016. A minimum of 3 clinical visits was required to ensure sufficient possibility to initiate and/or up-titrate statin therapy for optimal treatment. FH diagnosis was confirmed by the presence of mutations in the LDL receptor or APOB genes [11] in 48.2% of the patients; in the remaining patients, the diagnosis was based on clinical diagnosis only. Data from the first patients visit in the centre and from the last visit in 2015 were retrospectively collected using a structured questionnaire. The information collected included lipid levels, type and dose of lipid-lowering therapy, personal history of diabetes, myocardial infarction, stroke, peripheral artery disease, percutaneous coronary intervention and coronary artery bypass surgery. Emphasis was given to obtaining information as to whether LDL-C goal levels were reached at the last visit, and reasons for not reaching it were evaluated by physicians by choosing one or more predefined options (not sufficient lipid-lowering therapy effect, side effect of the therapy - e.g. myopathy or intolerance due to other reasons, bad compliance of a patient with therapy, cost of treatment paid by a patient or other reason). Serum LDL-C concentration was calculated using the Friedewald formula [13]. The MedPed FH Slovakia project was approved by the central ethics committee, and all subjects gave written informed consent.

Quantitative data were expressed as mean and standard deviation (SD) and qualitative data as absolute number and percentage. Comparisons of frequencies between qualitative variables were carried out using the chi-square test or Fisher exact test. Normal distributions of quantitative variables were examined by using the Shapiro-Wilk W test for normality. Differences between the measured quantitative parameters were compared by paired *t*-test or Wilcoxon signed-rank test based on distribution of data.

3. Results

Two hundred and one FH patients (mean age 50.8 ± 14.9 years, 111 females - 55% and 90 males - 45%) were included in the study (Table 1). Prevalence and mean time of occurrence (first occurrence in case of more events in the same patient) of myocardial infarction, stroke and peripheral artery disease were 13.4% (51.3 ± 11.7 years), 3% (60.0 ± 12.2% years) and 4% (51.2 ± 3.8 years), respectively. Percutaneous coronary intervention and coronary artery bypass surgery were done in 10.4% (51.9 ± 9.5 years) and 6.5% (60.2 ± 9.0 years) of FH patients. Prevalence of diabetes was 10.4%.

The main characteristics of lipid levels and statin treatment are listed in Table 2. At the first visit to centres, 31.3% of patients were treated with statins (37.3% on any lipid lowering therapy, e.g. statins, ezetimibe, fibrates, resins) and the most common dose was 20 mg of a potent statins (given to 59% of those patients receiving

Table 2
Main characteristics of lipids and treatment.

	Initial visit	Last visit
Total cholesterol [mmol/l]	8.3 ± 1.4	6.0 ± 1.6[a]
LDL-C [mmol/l]	6.0 ± 1.4	3.9 ± 1.5[a]
HDL-C [mmol/l]	1.4 ± 0.5	1.5 ± 0.6
Triglycerides [mmol/l]	1.6 ± 0.7	1.4 ± 0.7[a]
Statin treatment	31.3%	78.1%[a]
Any hypolipidemic treatment	37.3%	78.6%[a]
Atorvastatin [% of all statins, mean dose]	61.9%, 33.6 ± 21.8 mg	75.8%[a], 51.0 ± 26.7 mg[a]
Rosuvastatin [% of all statins, mean dose]	11.1%, 22.9 ± 12.5 mg	18.5%[a], 27.7 ± 13.1 mg[a]
Simvastatin [% of all statins, mean dose]	20.6%, 23.8 ± 9.6 mg	3.8%[a], 27.5 ± 14.7 mg
Fluvastatin [% of all statins, mean dose]	4.8%, 66.7 ± 23.1 mg	1.9%[a], 80 mg[a]

[a] $p < 0.05$, p for before *vs*. after management in the MedPed centres; mean ± SD.

atorvastatin, 43% for rosuvastatin and 69% for simvastatin). Only one patient was treated with pravastatin 20 mg at the first visit.

At the last visit, 78.1% of patients were treated with statins and 24.4% with ezetimibe. Most patients were treated with atorvastatin (75.8%) and rosuvastatin (18.5%); only one patient was treated with fluvastatin and no-one with pravastin. 31.3% of all patients were treated with atorvastatin 80 mg or rosuvastatin 40 mg with (14.9%)/ without (16.4%) ezetimibe, respectively. A 50% drop in LDL-C levels was noted in 27.9% of patients. However, only 11.9% of patients with LDL-C levels <2.5 mmol/l goal and 6.9% with the target <1.8 mmol/l reached the level. Even in patients treated with the maximal dose of atorvastatin 80 mg or rosuvastatin 40 mg, only 7.9% reached the LDL-C goal level. The most frequent reason for not reaching LDL-C goals (46%) was insufficient effect of the treatment. Side-effects of therapy (intolerance of statins) and non-compliance of patients were responsible for 18% and 30% of cases.

4. Discussion

FH patients have a significantly higher risk of CHD compared to other subjects in the general population. The challenge in patients with this disorder is to prevent the development of premature atherosclerosis. If diagnosed, heterozygous FH patients can be readily treated with cholesterol-lowering medication. However, evidence from all the reported FH studies document severe under-diagnosis and under-treatment of FH and failure to achieve recommended LDL cholesterol targets in a large proportion of individuals with FH [1]. In our current study, we were interested in whether clinical management of FH patients in specialised clinics can improve FH treatment. In Slovakia, a network of out-patient departments (currently 25 centres including 4 paediatric, by specialisation diabetologists, internists, cardiologists and paediatricians) involved in the MedPed FH project serves as referring departments for general practitioners and specialists not focused on lipid disorders. In the study, only 31.3% of FH patients referred to the MedPed FH centres had been treated with statins, which is even below the proportion of treated FH patients identified within the Copenhagen General Population Study [5]. When the patients were treated and followed up in the specialised centres, the proportion of FH patients on statins increased to 78% and the mean total and LDL cholesterol levels decreased significantly. The proportion is similar to the number of patients treated with statins in a French FH population (79.3%), but nearly all FH patients (96%) were on statin treatment in a Dutch cross-sectional study and the majority (89%) of adult subjects with molecularly defined FH were treated in a Norwegian study [14–16]. Almost 22% of our patients did not receive statin treatment and the majority of the patients were under-treated. Only one third of all patients were treated with atorvastatin 80 mg or rosuvastatin 40 mg and only 14.9% were on a combined treatment of atorvastatin 80 mg or rosuvastatin 40 mg plus ezetimibe, despite the fact that only less than 12% of all patients reached the LDL-C goal levels. Our proportion of FH patients achieving the LDL-C goal is similar to the proportions found in the Spanish SAFEHEART Registry (less than 10%), in French FH patients treated in academic centres (10.4%) and in the Norwegian FH population (12.2%) but lower compared to 21% observed in the Dutch cross-sectional study [14–17]. Several reasons can explain our outcome. According to participating clinicians, the most frequent reason (46%) was an insufficient effect of the treatment. A combined high-dose statin plus ezetimibe therapy can decrease LDL-C levels by 60–70%, which may be insufficient to reach the targeted levels in many FH patients. However, as only a small proportion of our FH patients were treated with the combination, other factors could contribute. Side-effects of therapy (intolerance of statins) and non-compliance of patients were responsible for 18% and 30% of cases. According to our empirical experience, a strong anti-statin campaign is present in Slovakia, and this can at least partially influence the perception of myopathy and can decrease compliance with statin treatment. Despite the limits in management identified in our study, we strongly believe that diagnosis and treatment of FH patients should be performed optimally in specialised clinics where a complex approach (clinical and genetic diagnosis, high dose statins, ezetimibe and potentially PCSK9 inhibition together with cascade screening) to FH patients is available. We can expect improvement in LDL-C goal attainability as PCSK9 inhibitors have been available and fully covered in Slovakia since 2017. Unfortunately, the LDL-C threshold for the treatment with PCSK9 inhibitors in Slovakia is higher than the threshold recommended by the ESC/EAS [18].

Our study has several limitations. First, a relatively small number of subjects included in the study in only 8 centres might not reflect the situation in all MedPed centres in Slovakia. The centres involved in the study, however, reflect well the geographical distribution of all centres in Slovakia and are responsible for clinical management of the majority of registered FH patients in Slovakia. We also cannot exclude selection bias due to the reporting of more treatment-resistant patients to the specialised centres. The prevalence of cardiovascular events in our study was lower than expected, which again can be partially explained by selection bias. Only one out of 8 participating centres was a cardiology centre, and we can speculate that many FH patients with overt cardiovascular disease are not recognised as FH patients and are in fact managed in regular cardiology departments with high dose statins according to recommendations for very high risk patients so that mainly FH patients without CHD are reported to the MedPed FH centres.

4.1. Conclusion

Referral of FH patients to specialised MedPed FH centres in Slovakia leads to improvement in the treatment; however, almost 22% of the patients are still without statin treatment and the majority of patients do not reach the LDL-C goal. Insufficient cholesterol-lowering effect of the currently available treatment, statin intolerance and non-compliance of patients are major obstacles in the proper management of FH patients. We believe that diagnosis and treatment of FH patients should optimally be performed in specialised centres with a complex approach to FH patients.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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