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Drug treatment and adherence of subjects <40 years with diagnosis of heterozygous familial hypercholesterolemia

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ABSTRACT

Background and aims: We aimed at describing the therapeutic approach in young adult patients diagnosed with heterozygous familial hypercholesterolemia (HeFH) and their adherence and persistence to treatment.

Methods: From regional administrative databases, individuals aged ≤40 years, who received exemption for HeFH between January 1, 2003 and December 31, 2011, and concomitantly started statin treatment, were identified. Within the first year of treatment, we evaluated therapeutic changes, adherence as MPR (medication possession ratio), persistence as continuous drug coverage without gaps ≥60 days, and influencing factors using log binomial models.

Results: Of 1404 patients, 42.4% were initially treated with a high-efficacy statin. 23.4% of patients showed at least one treatment change. Mean MPR was 68.7% (29.9), and patients showing continued statin use were 47.0%. Therapy modification was significantly associated with a past cardiovascular event (relative risk, RR [95% confidential interval] 2.28 [1.69–3.09]) and at least one lipid test (RR 1.82 [1.31–2.53]). MPR ≥80% was significantly associated with the first statin prescribed (atorvastatin RR 1.28 [1.09–1.51] and rosuvastatin RR 1.21 [1.01–1.44], *vs.* simvastatin), a past cardiovascular event (RR 1.33 [1.12–1.59]), at least one therapy change (RR 1.28 [1.15–1.43]), at least a lipid test (RR 1.26 [1.07–1.49]). A similar pattern was observed for persistence.

Conclusions: This analysis of young adult HeFH patients showed that therapy change was quite frequent, and probably reflected adjustments according to individual response. Adherence and persistence were inadequate, even in this population at high cardiovascular risk, and they need to be improved through proper patient education and shared treatment decision-making approach.

1. Introduction

Familial hypercholesterolemia (FH) is the most common genetic disorder associated with the development of premature coronary heart disease (CHD), due to lifelong elevated plasma low-density lipoprotein (LDL) cholesterol levels [1]. The heterozygous form (HeFH) has recently been shown to be more common than previously thought, present in 1 per 200–250 of the general population [2–4], that means potentially 4.5 million individuals in Europe and probably 35 million worldwide.

Statins are the first-line therapy in all lipid disorders, including familial forms [3,5]. Once diagnosed, HeFH patients should be immediately treated to attenuate development of atherosclerosis and to prevent CHD. It was indeed shown that statin treated adult patients had a risk of myocardial infarction approaching that of the general population [6]. Nevertheless, FH is underdiagnosed and undertreated worldwide [3,7]. Without treatment, the risk of CHD increases 20-fold among HeFH individuals [8], and they typically develop CHD before age 60 years. Furthermore, the corresponding

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increase in risk for CHD among individuals with FH on statin was 10-fold, suggesting a failure in maximizing the effectiveness of treatment, possibly because a delay in starting therapy or for inadequate adherence levels. Statins, as many other drugs for chronic therapy, have a poor level of adherence in primary and secondary prevention [9]. To obtain the maximum treatment effectiveness, it is essential that the patient adheres properly and continuously to therapy, and this is critical especially for patients at high or very high cardiovascular risk, such as patients with FH [10–12]. The other fundamental aspect for the proper control of serum cholesterol is the achievement of the therapeutic target, and this is accomplished through the appropriate choice of the statin; therefore the active ingredient or the dose are to be varied as a function of possible signs of intolerance or lack of efficacy [5,13].

The aim of this study was to analyse the treatment patterns of young adult patients with newly diagnosed heterozygous familial hypercholesterolemia, to assess therapy changes, and to describe short-term adherence and persistence and their predictors.

2. Materials and methods

2.1. Healthcare utilization database of Lombardy

The data used for the present study were retrieved from the healthcare utilization databases of the Italian Lombardy region, which accounts for about 16% (almost 10 million) of national population.

In Italy, the population is covered by the National Health Service (NHS), and Lombardy provides an automated system of databases to collect a variety of information, including: (1) an archive of residents who receive NHS assistance, reporting demographic and administrative data; (2) a disease exemptions database, with the information about the exemptions to payment of the healthcare services (diagnostic tests, drugs, and specialist visits) needed by subjects with a specific chronic condition; (3) a database of the outpatient drug prescriptions reimbursable by the NHS; (4) a database on outpatient services, including lipid profile lab test in ambulatories accredited by the NHS; (5) a database on diagnosis at discharge from public or private hospitals of the region.

For each patient, we linked the aforementioned databases via a single identification code. In order to preserve privacy, each identification code was automatically converted into an anonymous code, the inverse process being prevented by deletion of the conversion table. Full details of the databases and the merging procedure have been reported elsewhere [14].

2.2. Cohort selection and follow-up

The target population consists of all beneficiaries of the NHS <40 years old, resident in Lombardy, who have been assigned the exemption code for heterozygous familial hypercholesterolemia in the period 1/1/2003–31/12/2011 and who concomitantly started statin treatment (first prescription between two months before and six months after the date of the exemption). The first prescription was defined as the index prescription. Since in our study the detection of HeFH patients is based on exemptions and some of them may be erroneously assigned to subjects with non-genetic dyslipidaemia, affecting mainly older patients, we selected only young subjects.

Patients were excluded from data analysis if: (i) they received any lipid-lowering drugs within the 3 years before the index prescription; (ii) they had less than one year of follow-up.

Each member of the cohort was followed from the date of the index prescription until one year afterwards.

2.3. Statins exposure

We stratified statin prescriptions at index date as well as during follow-up according to the active ingredient of first prescription and according to the efficacy, as: (a) low efficacy (≤30% LDL reduction): daily dose of fluvastatin ≤40 mg, pravastatin ≤40 mg, simvastatin ≤10 mg, or lovastatin ≤40 mg; (b) moderate efficacy (31%–40% LDL reduction): daily dose of rosuvastatin 5 mg, simvastatin 20 mg or 40 mg, atorvastatin 10 mg; (c) high efficacy (≥40% LDL reduction): daily dose of simvastatin ≥10 mg + ezetimibe, atorvastatin ≥20 mg, or rosuvastatin ≥10 mg [5,15].

2.4. Covariates assessment

Some patients' characteristics were assessed at cohort entry such as age, gender, and history of cardiovascular events or during follow-up, as the lipid profile lab tests.

2.5. Outcome assessment

Modification of therapy was defined as the first change of treatment dose or drug - from one statin to another one. The date of the prescription defining therapy modification was considered the date of change. For each prescription, we estimated days covered as the number of tablets available in each prescribed box. In the case of a prescription dispensed before the end of the coverage of the previous one, we assumed that the patient ended the available tablets before starting new pack.

Assuming a treatment schedule of one tablet per day [16], adherence was measured by the Medication Possession Ratio (MPR) [17], that is the ratio between the number of days covered by the drug and the length of the observation period [365 days] x 100. MPR values above 100% were truncated at 100% [18].

Treatment discontinuation was defined as a gap of at least 60 days between the end of prescription coverage and the beginning of the following one. The date of the end of the coverage of the last prescription before interruption was taken as the date of discontinuation. Persistence was intended as the lack of any discontinuation during follow-up.

2.6. Data analysis

Descriptive statistics were calculated to describe the patient characteristics, treatment characteristics, and medication adherence. Anova and Chi-square tests were used to evaluate potential differences in age and sex for presence of previously cardiovascular events, type and efficacy of first statin.

The differences in covariate distribution and type and efficacy of first statin between patients with only one prescription and those with more than one prescription were tested using chi-square and t tests for categorical and continuous variables, respectively.

Since the outcome under study is not rare, to examine the relationship between several covariates and adherence, a log binomial regression model was fitted to estimate relative risks (RR) and 95% confidence intervals (95%CI) for optimal adherence levels (MPR ≥80%); covariates included gender, first statin, efficacy of first statin, post cardiovascular events, treatment change, and lipid lab test, controlling for age. Similarly, we estimate the relationship between several covariates and persistence. In both cases, outcome (adherence and persistence) were assessed at one year and all patients were followed-up for 365 days.

An a priori threshold for statistical significance was set at $p < 0.05$.