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Statin reduces mortality and morbidity in systemic lupus erythematosus patients with hyperlipidemia: A nationwide population-based cohort study

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ABSTRACT

Objective: The anti-inflammatory and cardiovascular protective effects of statin for patients with systemic lupus erythematosus (SLE) are not clear. We tested the hypothesis that statin use is associated with reduced mortality and morbidity in SLE patients with hyperlipidemia.
Methods: We included 4095 patients with SLE and hyperlipidemia from the entire population using the Taiwan National Health Insurance Research Database between 1997 and 2008. A total of 935 matching sets (1:2) of patients who had never used lipid-lowering medications and statin users were included in the nested matched cohort. Cox proportional hazards regression was used to calculate the hazard ratios (HR) and 95% confidence intervals (CI) for the association between statin and all-cause mortality, coronary artery disease (CAD), cerebrovascular disease (CVD) and end-stage renal disease (ESRD), conditional for matching sets in the matched cohort.
Results: The multivariate adjusted hazard ratios (HR) for statin users, as compared with patients had never used lipid-lowering medications, were 0.67 (95% CI, 0.54 to 0.83) for death from any cause. High-dose statins (>365 cumulative defined daily dose) significantly reduced risk of all-cause mortality (HR 0.44, 95% CI 0.32 to 0.60); CAD (HR 0.20, 95% CI 0.13 to 0.31); CVD (HR 0.14, 95% CI 0.08 to 0.25); and ESRD (HR 0.22, 95% CI, 0.16 to 0.29), with similar results in the nested matched study.
Conclusion: Statin therapy in SLE patients with hyperlipidemia may reduce the risk of mortality, cardiovascular disease and ESRD. The effect of statins needs to be demonstrated in large prospective studies with long-term follow-up.

1. Introduction

Cardiovascular disease has emerged as a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE) [1,2]. Estimates of cardiovascular diseases prevalence vary from 6% to 40% among patients with SLE [1]. When compared to the general population, women with SLE have a 5-fold increased risk of cardiovascular disease, and the risk in women aged 35–44 years old is increased 50-fold [3]. Atherosclerosis is the main etiology for most cases of the cardiovascular disease including coronary artery disease (CAD) and cerebrovascular disease (CVD). Atherosclerosis is considered to be a chronic inflammation affecting the arterial intima that is the outcome of uncontrolled activation of the immune system [4].

Clinical studies have revealed that traditional atherosclerotic risk factors (e.g. age, male gender, smoking, hyperlipidemia, hypertension, and diabetes) do not fully account for the level of cardiovascular disease susceptibility in patients with SLE [5]. Several lines of evidence support that additional factors, such as autoantibodies, systemic inflammation, endothelial injury due to the autoimmune disease itself, and impaired renal function or end-stage renal disease (ESRD), have been suggested to play an important role in the pathogenesis of premature atherosclerosis in SLE

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[4,6–8].

Dyslipidemia is common in SLE and it contributes to lupus-enhanced atherogenesis [9]. The prevalence of hypercholesterolemia increased from 40% at the study entry to 73% after a mean follow-up of 6.7 years in a large prospective cohort study of SLE. This study showed that the levels of cholesterol varied in a dynamic course because of changes in disease activity and treatment [10]. The complex relationships between SLE disease activity, cytokines, inflammation, glucocorticoids and immunosuppressive agents, diet, renal disease, body mass index, physical activity, and dyslipidemia remains poorly understood [11].

Statins, the 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitor, have been widely prescribed for hyperlipidemia, which could slow the atherosclerosis progression and reduce cardiovascular disease events [12,13]. To date, there have been no large-scale studies proving that statins are effective when used for primary or secondary cardiovascular prevention in patients with SLE. Randomized controlled trials using different statins (atorvastatin or rosuvastatin) on adult or pediatric lupus patients for 1–3 years have shown a decrease in serum lipids and C-reactive proteins, but also controversial effects on markers for atherosclerotic diseases [14–17]. We hypothesized that statin therapy would be associated with reduced mortality and morbidity in patients with SLE and hyperlipidemia. To test this hypothesis, we compared the risk of all-cause mortality, CAD, CVD and ESRD among SLE patients who used statins or non-statin lipid-lowering medications, with patients who never used lipid-lowering medications.

2. Material and methods

2.1. Study population and data collection

The sampling cohort dataset of this nationwide population-based cohort study was obtained from the Taiwan National Health Insurance Research Database (NHIRD). The National Health Insurance Program of the Bureau of National Healthy Insurance (BHNI) covers more than 98% of the population in Taiwan. It maintains a comprehensive database comprising all medical claims for all forms of health care services. There were 22,808,324 beneficiaries in the sampling cohort from year 1997–2008 (Fig. 1). We retrieved inpatient and ambulatory care order records, which included information on patient characteristics and diagnoses using the International Classification of Diseases, Ninth Revision (ICD-9) codes. These databases have been used for epidemiologic research of SLE and other diseases and information on prescription use, diagnoses, and hospitalizations is of high quality [18,19]. High accuracy of the diagnosis of CVD, acute myocardial infarction or diabetes mellitus (DM) using NHIRD has been validated [20–22].

The National Health Research Institute Ethics Review Committee approved this study. The review board waived the requirement for written informed consent from the patients because the secondary data were de-identified and stropped of personal information prior to use according to personal electronic data protection regulations and confidentiality guidelines.

2.2. Identification of study cohort

Patients with SLE (ICD-9 codes 710.0) diagnosed between January 1, 1997 and December 31, 2008 were identified from NHIRD. A registry system for catastrophic illness, a category to which SLE belongs, has been established. The BNHI performs validation of the diagnosis of SLE by reviewing the original medical charts of patients who apply for a catastrophic illness certificate. The diagnosis of SLE was made on the basis of the presence of 4 of the 11 American College of Rheumatology 1997 criteria for the classification of SLE by rheumatologists in Taiwan [23]. The date of application for the status of catastrophic illness was used as the diagnosis date of SLE. We allowed for at least 1 year of follow-up for all patients. Patients who never received blood tests for lipid levels were excluded.

Hyperlipidemia was defined as patient who had three or more ambulatory claims in a year or one claim on hospitalization with principle diagnoses of hyperlipidemia (ICD-9 codes 272). A total of 4095 patients with SLE and hyperlipidemia were eligible for inclusion in the analysis. Follow-up ended on the date of death or on December 31, 2008 (Fig. 1).

We also conducted a nested 1:2 matched study (i.e., a study that matched one patient who never used lipid-lowering medications with 2 statin users), with matching for sex, age at SLE diagnosis (in categories of every 10 years), hypertension (HTN), DM and chronic kidney disease (CKD). A total of 935 matching sets (1:2) of patients without lipid-lowering medications and statin users were included in the nested matched cohort.

We modified System Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index [24] to evaluate cumulative organ damage at the end of the study (Supplementary Table S1). Due to limitation of the database, the repeated episodes of damage could not be confirmed and was defined as a score of 1. The individual score form each item (0 or 1 point) was summed to calculate a patient's total modified SLICC/ACR damage index score. The maximum score was 39.

2.3. Statins and non-statin lipid-lowering drugs exposure

Using inpatient and ambulatory care order records, we identified patients who filled prescriptions for statins or non-statin lipid-lowering drugs between 180 days before the date of the diagnosis of SLE and 180 days before death, or 28 days before morbidity outcomes. Data on drug name, the date of dispensing, daily dose prescribed, number of days supplied, and the total amount of pills per prescription were obtained. In accordance with the Anatomic Therapeutic Chemical Classification of the drugs, simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, and rosuvastatin were selected as the major statin of interest.

Statins and non-statin lipid-lowering drugs (including cholestyramine, colestipol, colextran, niceritrol, nicofuranose, acipimox, probucol, or ezetimibe) were prescribed under the indication of hyperlipidemia: low-density lipoproteins cholesterol (LDL) $\geq$ 190 mg/dL for subjects without cardiovascular disease risk factors; total cholesterol (TC) $\geq$ 240 mg/dL or LDL $\geq$ 160 mg/dL for subjects with 1 risk factor; TC $\geq$ 200 mg/dL or LDL $\geq$ 130 mg/dL for subjects with more than 2 risk factors; or TC $\geq$ 160 mg/dL or LDL $\geq$ 100 mg/dL for subjects with cardiovascular disease or diabetes. Triglyceride (TG)-lowering medications (including bezafibrate, clofibrate, etofibrate, fenofibrate, gemifibrozil, or simfibrate) were prescribed under the indication of hypertriglyceridemia: TG $\geq$ 500 mg/dL for subjects without risk factors: TG $\geq$ 200 mg/dL and high-density lipoprotein <40 mg/dL for subjects with cardiovascular disease or diabetes. The prescription of any kind of lipid-lowering drugs was strictly evaluated by BNHI every three months.

Statin or non-statin lipid-lowering drugs users were defined by using medications more than 28 cumulative defined daily dose (DDD). The DDD (i.e., the assumed average maintenance dose per day) recommended by the World Health Organization is a method of standardizing drug dose across multiple drug types so that they can be compared. Cumulative DDD (cDDD) was estimated as the sum of the dispensed DDD of any statin. Average statin dose (DDD per day) was calculated as cDDD divided by total drug prescription days. Atorvastatin 20 mg, simvastatin 30 mg, lovastatin 45 mg, pravastatin 30 mg, fluvastatin 60 mg, or rosuvastatin 10 mg will be calculated as 1 DDD.