Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Effect of statin use on the risk of medically attended acute respiratory illness among influenza vaccinated elderly

Hsien-Tsung Chiu [a,1], Li-Jiuan Shen [a,b,c,1], Yee-Chun Chen [d], Jung-Hsin Lin [b,e], Chi-Chuan Wang [a,b,c,*]

[a] Graduate Institute of Clinical Pharmacy, School of Pharmacy, College of Medicine, National Taiwan University, No. 33, Linsen S. Rd., Zhongzheng Dist., Taipei City 10050, Taiwan, ROC
[b] School of Pharmacy, College of Medicine, National Taiwan University, No. 33, Linsen S. Rd., Zhongzheng Dist., Taipei City 10050, Taiwan, ROC
[c] Department of Pharmacy, National Taiwan University Hospital, No. 7, Chung Shan S. Rd. (Zhongshan S. Rd.), Zhongzheng Dist., Taipei City 10002, Taiwan, ROC
[d] Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung Shan S. Rd. (Zhongshan S. Rd.), Zhongzheng Dist., Taipei City 10002, Taiwan, ROC
[e] Research Center for Applied Sciences, Academia Sinica, No. 128, Academia Rd. Sec. 2, Nankang Dist., Taipei City 11529, Taiwan, ROC

ARTICLE INFO

Article history:
Received 17 November 2017
Received in revised form 9 August 2018
Accepted 27 August 2018
Available online xxxx

Keywords:
Statin
Seasonal influenza vaccine
Medically attended acute respiratory illness
Vaccine effectiveness
Elderly

ABSTRACT

Objectives: The immunomodulatory effects of statins may reduce the immune response induced by influenza vaccines. However, evidence regarding the effect of statin use on the effectiveness of seasonal influenza vaccines against medically attended acute respiratory illness (MAARI) in the elderly remains scarce.
Methods: We conducted a retrospective cohort study using data from Taiwan's National Health Insurance Research Database. Elderly adults aged ≧ 66 years who were vaccinated with seasonal influenza vaccines during the 2007–2008 to 2012–2013 influenza seasons were enrolled for this analysis. We compared the risk of MAARI between statin and non-statin users. Propensity score matching and conditional logistic regression models were used to analyze the data.
Results: A total of 440,180 elderly were included in this study. In general, the risk of MAARI was higher in statin users than non-statin users (odds ratio [OR]: 1.03, 95% confidence interval [CI]: 1.02–1.05). Statin exposure after vaccination was associated with a higher risk of MAARI (OR: 1.05, 95% CI: 1.02–1.07). Among different statin agents, simvastatin and lovastatin use was associated with a significant increase in the risk of MAARI ($OR_{simvastatin}$: 1.14, 95% CI: 1.10–1.18; $OR_{lovastatin}$: 1.18, 95% CI: 1.12–1.25).
Conclusions: Statin exposure, especially simvastatin and lovastatin, was associated with a higher risk of MAARI in the seasonal influenza vaccinated elderly. Future studies exploring the differences between individual statins and mechanisms of their immunomodulatory effects are necessary.

1. Introduction

In addition to their lipid-lowering properties, statins are known to have immunomodulatory effects. Through the inhibition of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, statins inhibit the isoprenylation of the GTPase protein, which affects T-cell maturation and migration [1,2]. In addition, statins also down-regulate the expression of major histocompatibility complex (MHC) molecules and interfere with the co-stimulatory pathway between T-cells and antigen-presenting cells [1,3,4]. Since antigen presentation to T cells and the cascade of events leading to T cell activation are central to the immune response elicited by influenza vaccines [5], statins could potentially reduce the immune responses induced by influenza vaccines.

Much is known about the immunomodulatory effect of statins; however, whether statin therapy modifies the association between seasonal influenza vaccination and the incidence of medically attended acute respiratory illness (MAARI) in the elderly remains unclear. Prior research has shown that statin use was associated with reduced vaccine effectiveness against laboratory confirmed influenza A (H3N2) [6]; and people who received statins had higher rates of MAARI during the period of widespread influenza

Abbreviations: CD40, clusters of differentiation 40; CI, confidence interval; CM, Clinical Modification; HAI, hemagglutination-inhibition; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; ICAM-1, intercellular adhesion molecule-1; ICM, International Classification of Diseases; IFN, interferon; LFA, lymphocyte function-associated antigen.

* Corresponding author at: No. 33, Linsen S. Rd., Zhongzheng Dist., Taipei City 10050, Taiwan, ROC.
E-mail addresses: r04451001@ntu.edu.tw (H.-T. Chiu), ljshen@ntu.edu.tw (L.-J. Shen), jlin@ntu.edu.tw (J.-H. Lin), chicwang@ntu.edu.tw (C.-C. Wang).
[1] Hsien-Tsung Chiu and Li-Jiuan Shen contributed equally to this study as the first authors.

https://doi.org/10.1016/j.vaccine.2018.08.067
0264-410X/

circulation [7]. However, the majority of subjects in these two studies were younger than 65 years [6,7]. Another study conducted in adults aged >65 years showed that statins were associated with reduced serum hemagglutination-inhibition (HAI) antibody responses in the elderly [8]; yet, the reduced serum antibody response may not necessarily predispose to an increased risk of the development of influenza illness [9]. Given that influenza vaccine effectiveness in the elderly is much lower than in young adults [10,11], and that statins are one of the most commonly prescribed medications among the elderly [12], it is important to investigate how statin use might affect the effectiveness of influenza vaccines. The objectives of our study were to investigate the association between statin use and MAARI in seasonal influenza vaccinated elderly, and to determine whether the association varied by timing of statin exposure, statin potency, or individual statin agents.

2. Methods

2.1. Data source

We conducted a retrospective cohort study using the 2006–2013 claims data of the elderly, from Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD contains de-identified information of beneficiaries' enrollment, inpatient, and outpatient service utilization, and prescription drug utilization records under the National Health Insurance (NHI) program. The database used in this study was a subset of the NHIRD which consisted of a randomly selected 20% sample of adults who were at least age 65 years between 2004 and 2008. All inpatient and outpatient prescriptions and dispensing claims of the elderly from 2006 to 2013 were then retrieved from the NHIRD as our data source. Since the trivalent seasonal influenza vaccination of the elderly aged ≥65 years was funded by the government in Taiwan throughout the entire study period, all vaccination records were expected to have been fully captured in this database.

2.2. Study design and sample

All the elderly who were vaccinated with the seasonal influenza vaccines during an influenza season (defined as October 1 in a given year until May 31 in the following year) were enrolled for our analysis, namely influenza season 2007–2008 through 2012–2013. All the seasonal influenza vaccines were provided by the government in Taiwan, and were unadjuvanted trivalent vaccines. The influenza vaccine strains in Taiwan were selected based on the WHO recommendation on the composition of influenza virus vaccines for northern hemisphere. The date of vaccination was defined as the index date, while 14 days before and after the index date was the exposure period (Fig. 1). Individuals were excluded, if they were younger than 66 years on the index date, switched statins in the exposure period, were diagnosed with AIDS/HIV within one year before the index date, received the seasonal influenza vaccines more than once in the influenza season, or received the H1N1 influenza vaccine (*A/California/7/2009 (H1N1)v-like virus)* in the 2009–2010 influenza season. Individuals who were younger than 66 years were excluded to ensure that all study subjects had at least one year of pre-index data for the assessment of baseline characteristics.

People with any statin use (reported either in the outpatient or the dispensing claims), in the exposure period, were defined as statin users, or conversely, non-statin users. The observational period was defined from 14 days after vaccination to the end of the influenza season. Influenza season year was also included as a covariate in the analyses that pooled more than one influenza seasons.

2.3. Statistical analysis

We compared the risk of MAARI between statin and non-statin users stratified by influenza match and mismatch seasons (ICD-9-CM codes of MAARI: see web-only Supplementary Table S1). An influenza season was defined as a vaccine match season if the influenza vaccine strains matched the circulated virus strains reported by the Taiwan Center for Disease Control. On the other hand, in the vaccine mismatch seasons, the influenza vaccine strains did not completely match the circulated strains (see web-only Supplementary Table S2). The vaccine match seasons included 2008–2009, 2010–2011, and 2012–2013, while the vaccine mismatch seasons included 2007–2008, 2009–2010, and 2011–2012 [13].

Furthermore, we also conducted subgroup analyses, stratifying by age, timing of statin exposure (before or after the influenza vaccination), statin potency (see web-only Supplementary Table S3), and different statin agents. We generated the propensity score of each individual by logistic regression, and used 1:4 matching within a maximum radius within each influenza season to make statin and non-statin users comparable. Covariates included age, gender, influenza vaccination in the prior year, number of outpatient visits in the previous year, emergency room visits or inpatient admissions in the previous year, medical resource allocation areas (high versus low), comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, hemiplegia or paraplegia, diabetes, liver disease, renal disease, any malignancy, and tuberculosis), and prescriptions of immunosuppressant drugs or long-term use of high dose corticosteroids. Comorbidities were identified by the International Classification of Disease (ICD)-9- Clinical Modification (CM) codes (see web-only Supplementary Table S4), and long-term use of high dose corticosteroids was defined as the use of systematic corticosteroids with a prednisone or equivalent dose >10 mg/day for at least 90 days. An absolute value of a standardized difference above 0.1 was considered a significant difference [14,15]. Conditional logistic regression models were used to estimate the odds ratios (OR) for MAARI. The confidence interval (CI) was set at 95% and $\alpha = 0.05$. This study was reviewed and approved by the Research Ethics Committee of the National Taiwan University Hospital (NTUH-REC No. 201607002W), and the informed consent was waived.

Sensitivity analyses were also conducted in our study. First, the beginning of the observational period was changed from 14 days after the index date, to the index date. Second, the beginning of the observational period was also changed from 14 days after the index date, to 28 days after the index date. Lastly, we expanded the definition of the exposure period from 14 to 28 days, before and after the index date.

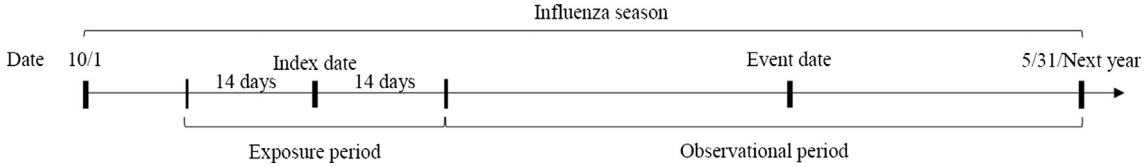

Fig. 1. Schematic diagram of the study design.

Please cite this article in press as: Chiu H-T et al. Effect of statin use on the risk of medically attended acute respiratory illness among influenza vaccinated elderly. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.08.067