HMG-CoA reductase inhibitors (statins) use and risk of non-Hodgkin lymphoma in HIV-positive persons

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Objective: Experimental studies suggested that HMG-CoA reductase inhibitors ('statins') may have antilymphoma properties. We investigated whether statin use is associated with reduced risk of non-Hodgkin lymphoma (NHL) in HIV-positive persons.

Design: A nested case–control study was conducted among HIV-positive members of Kaiser Permanente California, a large managed care organization.

Methods: Cases were incident HIV+ NHL diagnosed from 1996 to 2008. Controls were HIV-positive members without NHL matched 5 : 1 to cases by age, sex, race, index year and known duration of HIV infection. Data were collected from Kaiser Permanente's electronic medical records. Conditional logistic regression was used to examine the effect of statin use on HIV + NHL risk, adjusting for potential confounders (matching factors, prior clinical AIDS diagnosis, antiretroviral use, baseline CD4 cell count, and history of selected co-morbidity) and use of nonstatin lipid-lowering therapy (LLT).

Results: A total of 259 cases and 1295 controls were included. Eight percent of the cases and 14% of the controls had a history of statin use. Statin use was associated with lower risk of HIV + NHL; hazard ratio and 95% confidence intervals for ever use, less than 12, and at least 12 months cumulative use was 0.55 (0.31–0.95), 0.64 (0.31–1.28), and 0.50 (0.23–1.10), respectively. *P* value for trend for duration of statin use was 0.08. No association between nonstatin LLT use and risk of NHL was observed.

Conclusion: Our results suggested an inverse association between statin use and risk of NHL in HIV-positive persons. Potential limitations include the likelihood of residual confounding by indication and limited study power for some statin use subgroups.

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Keywords: AIDS, HIV, HMG-CoA reductase, inhibitors, lymphoma, non-Hodgkin lymphoma, statins

Introduction

HIV-related non-Hodgkin lymphoma (NHL) continues to be a significant source of morbidity and mortality in HIV-positive persons in the era of combined antiretroviral therapy (ART) [1]. Not only are HIV-positive persons at significantly elevated risk of NHL [2], they also tend to have a more aggressive course of disease [3–5]. Both immunosuppression and chronic inflammation associated with HIV infection are implicated in the pathogenesis of HIV-related NHL [6–8]. Studies have shown that levels of inflammatory cytokines such as interleukin-6 and interleukin-10 are elevated prior to the clinical diagnosis of NHL in HIV-positive individuals [9–11]. These findings suggest a role for alleviating systemic inflammation to reduce the risk of NHL in HIV-positive persons, in addition to preserving immune function.

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HMG-CoA reductase inhibitors, or statins, are known to have anti-inflammatory properties [12–15]. In addition, in-vitro and in-vivo studies suggest that statins may have a number of anticancer activities. Statins have been found to arrest cell cycle progression [16], induce apoptosis [17], and reverse v-myc myelocytomatosis viral oncogene homolog-induced lymphomagenesis [18]. Use of statins has been linked to reduced risk of lymphoma in the general populations in several epidemiologic studies [19–21]. Among these, a large population-based case–control study of 2362 lymphoma cases conducted in Europe reported a 40% reduced risk of lymphoma for ever use of statins [19]. Given these findings, the role of statin use in lymphoma prevention warrants further investigation. To our knowledge, the effect of statin use on NHL risk has not been much evaluated among HIV-positive individuals. Strategies are needed to further reduce the burden of HIV-related NHL in the ART era. We hypothesized that regular use of statins reduces risk of NHL in HIV-positive persons. We conducted a nested case–control study to examine this hypothesis among HIV-positive persons enrolled in the Kaiser Permanente California Health Plans, utilizing the health information prospectively collected at Kaiser Permanente.

Methods

Study population and case–control selection

Kaiser Permanente is the largest managed care organization in California, serving over 6 million ethnically and socioeconomically diverse members [22]. HIV-positive individuals were identified from Kaiser Permanente's HIV registries, which maintain an updated list of all known HIV-positive members since 1988 for Kaiser Permanente Northern California and 2000 for Kaiser Permanente Southern California. HIV-positive patients included in these HIV registries were initially identified using electronic databases, and confirmed as cases by chart review and/or consulting with clinical staff at the patient's medical centers. All confirmed HIV-positive members included in the HIV registries were considered the source cohort for this study. The study baseline for the cohort members was the time of entering the HIV registries.

We identified all incident NHL cases among HIV-positive persons diagnosed between 1996 and 2008 by record linkage with Kaiser Permanente's cancer registries using the patient's unique medical record number. The Kaiser Permanente cancer registries are contributing sites to the Surveillance, Epidemiology, and End Results (SEER) program registry and Kaiser Permanente registry's data are of comparable accuracy and completeness to that of SEER. Controls were HIV-positive members without NHL diagnosis matched to cases at 5 : 1 ratio by age (±5 years), sex, race (white or nonwhite), index year (year of case's NHL diagnosis), and known duration of HIV infection, using an incidence-density sampling approach. An index date (within the index year) was assigned to each case and control. For cases, index date was the date of their NHL diagnosis. For controls, the assigned index date allowed matching by index year and known duration of HIV infection to their corresponding cases. This study was approved by the responsible Institutional Review Boards.

Measurements of covariates

The primary exposure of interest was statin use prior to the index date (date of NHL diagnosis for cases and the assigned index date for controls), but after the earliest known date of HIV-positive status in Kaiser Permanente's system. Statin use was ascertained from Kaiser Permanente electronic pharmacy records, which include prescription medications dispensed at all Kaiser Permanente hospitals and medical offices. To help assess the degree of confounding by indication, use of other nonstatin lipid-lowering therapy (LLT), including fibrates, niacin, and resins, was also assessed. Potential confounding factors considered, in addition to the matching factors, included Kaiser Permanente region (Northern or Southern California), clinical AIDS diagnosis prior to index, duration of ART use, baseline CD4 cell count level, and history of selected co-morbidities, that is, history of hepatitis B and C, diabetes, and obesity. Information on age, sex, race, dates of known HIV, and AIDS diagnoses was available from the Kaiser Permanente HIV registries. Use of ART (determined by the published guideline [23]) by the case and control participants was also captured by the Kaiser Permanente pharmacy records. Measurements of CD4 cell count were obtained from Kaiser Permanente's laboratory records. Information on history of diabetes, obesity, and hepatitis B/C infection was assessed using a combination of ICD-9 diagnosis code, laboratory tests, and anthropometric measures recorded in both the outpatient and inpatient settings.

Statistical analysis

The distributions of demographics, HIV-related disease factors, co-morbidities, and history of statin and nonstatin LLT use were calculated for cases and controls. The distributions of these covariates were also calculated for statin users, nonstatin LLT users, and those who did not use these medications. Crude associations between covariates and NHL status were evaluated using bivariate conditional logistic regression. Multivariable conditional logistic regression adjusting for potential confounders and nonstatin LLT use was used to examine the independent association between history of statin use and risk of NHL. History of statin use was modeled in four ways: ever use vs. never use; regular use (defined as ever having a 12-month continuous use), nonregular use (defined as never having a 12-month continuous use) vs. never use; long-term use (defined as >12-month cumulative use, i.e., allowing discontinuation between use) and

short-term use (defined as ≤12-month cumulative use) vs. never use; and a continuous variable to assess linear trend by cumulative duration of use in months. History of nonstatin LLT use was modeled similarly. The effect of statins use was mutually adjusted with nonstatin LLT use in the model. Given that some studies suggested that lipophilic and hydrophilic statins may have varying degrees of anticancer activities [24–26], use of lipophilic (lovastatin, simvastatin, and atorvastatin) and hydrophilic (pravastatin) statins was also examined separately, as duration of use for each group of statins. Due to a substantial degree of missing value for CD4 cell count at baseline (27%), Rubin's multiple imputation method [27] was used to address the missing data issue in the covariates. All analyses were conducted using SAS statistical software version 9.2 (Statistical Analyses System Inc., Cary, North Carolina, USA).

Results

A total of 259 incident HIV + NHL cases diagnosed between 1996 and 2008 were identified, for whom 1295 matching controls were selected. Distributions of history of statin use and other covariates of interest by case–control status are presented in Table 1. Statin use was more common among controls than cases, with 14 and 8% of the controls and cases ever using statins, respectively (P value = 0.01). For nonstatin LLT, 7 and 5% of the cases and controls ever used this group of medication, respectively (P value = 0.17). CD4 cell count at baseline was significantly higher in controls than that in cases. The majority (64%) of these NHL cases were diffuse large B-cell lymphoma. Statin users and nonstatin LLT users in our HIV-positive cohort were similar in terms of demographics, HIV disease, and co-morbidity histories (Table 2). Thirty percent of the statin users had also used nonstatin LLT.

In multivariable analyses, ever statin use was significantly associated with lower risk of NHL (Table 3). Hazard ratios for ever statin use was 0.55 (95% confidence interval = 0.31–0.95). A reduced hazard ratio for all categories of statin use was suggested, although some were not statistically significant. A marginally significant linear trend for the duration of statin use on NHL risk was found (P value for trend = 0.08). On the contrary, no association between nonstatin LLT use and risk of NHL was observed (Table 3).

When use of lipophilic and hydrophilic statins was examined separately, hazard ratio was slightly lower for hydrophilic statins, although none of these reached statistical significance [hazard ratio for lipophilic statin use (per month) = 0.99 (0.97–1.01), and hazard ratio for hydrophilic statin use (per month) = 0.97 (0.93–1.02), Table 3, bottom].

Discussion

As hypothesized, we found an inverse association between statin use and risk of NHL in HIV-positive individuals. In cell line and animal models, statins showed anticancer effects for many types of cancer, including lymphoma, by inhibiting proliferation and metastasis as well as inducing apoptosis [28]. The underlying anticancer mechanisms of statins are still to be elucidated, although it is thought to involve the interaction with the Ras and Rho family GTPase and inhibition of certain cyclin-dependent kinases [28]. Statin use is also linked to reduced inflammation [29], which is a pathogenic mechanism of HIV-related NHL. A randomized controlled trial of 24 participants examining the effect of atorvastatin use on HIV RNA and cellular immune activation markers found reduction of immune activation markers among atorvastatin users (but no effect on HIV RNA), suggesting a protective role of atorvastatin for chronic inflammation [30]. In addition, laboratory studies have suggested that statins may inhibit HIV viral replication [31–33]. However, the effect of statin on HIV RNA level in humans has not been consistently demonstrated [30,34].

The associations between statins use and risk of lymphoma in the general population are mixed, although current evidence seems to be more consistent with a reduced risk in statin users [35]. However, a systemic review concluded that the quality of this evidence is weak at best [35]. Literature on the association between statin use and risk of NHL or other type of cancer in HIV-positive individuals is limited at present.

Due to the metabolic side-effects of antiretroviral drugs, particularly the class of protease inhibitor, management of risk factors such as dyslipidemia has become critical to prevent life-threatening cardiovascular events in HIV-positive persons. As such, statins has been used more widely in this group of patients, particularly among ART users. Preliminary guideline by the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group listed statin as the first choice medication treatment for HIV-positive patients with isolated high low-density lipoprotein cholesterol [36–38]. However, side-effects such as myalgia and rhabdomyolysis have been reported with the use of certain class of statins. Drug–drug interaction between statins, antiretroviral drugs and certain anti-infection treatments have also been documented [39]. As a result, the choice of statin therapy needs to be carefully evaluated for HIV-positive persons with dyslipidemia. Should an anticancer effect of statin be confirmed in HIV-positive persons, this information may be incorporated into the cost-benefit consideration for initiating statin therapy.

In our study, however, a considerable reduction of NHL risk was suggested by the hazard ratio estimates (though

Table 1. Distribution of demographics, HIV disease factors, history of statin and nonstatin lipid-lowering therapy use, and co-morbidity among non-Hodgkin lymphoma cases and controls.

	Controls ($N=1295$)	NHL cases ($N=259$)	
	Number (%) or mean (SD)		*P* value
Age[a] mean (SD, years)	43.1 (8.9)	43.2 (8.9)	–
Male sex[a]	1240 (95.8%)	248 (95.8%)	–
Race[a]			
White	775 (59.9%)	155 (59.9%)	–
Nonwhite	520 (40.2%)	104 (40.2%)	
History of statin use			
Ever use	177 (13.7%)	21 (8.1%)	0.01
Nonregular use (<12 mos continuous use)	154 (11.9%)	18 (7.0%)	0.05
Regular use (≥12 mos continuous use)	23 (1.8%)	3 (1.2%)	
Short-term use (<12 mos cumulative use)	75 (5.8%)	10 (3.9%)	0.05
Long-term use (≥12 mos cumulative use)	97 (7.5%)	11 (4.3%)	
Among those ever used statins			
Duration of use (mos), mean (SD)	22.4 (22.9)	19.7 (17.6)	–[b]
Duration of lipophilic statin use (mos)[b], mean (SD)	20.0 (21.8)	19.0 (19.1)	–[b]
Duration of hydrophilic statin use (mos)[b], mean (SD)	17.2 (18.5)	15.3 (12.2)	–[b]
Type of statin (% among dispensed statin prescriptions)			
Atorvastatin	37.4%	21.7%	–[b]
Lovastatin	14.4%	35.5%	–[b]
Simvastatin	20.7%	20.8%	–[b]
Pravastatin	27.5%	22.0%	–[b]
History of nonstatin lipid-lowering therapy use			
Ever use	96 (7.4%)	13 (5.0%)	0.17
Nonregular use (<12 mos continuous use)	88 (6.8%)	11 (4.3%)	0.30
Regular use (≥12 mos continuous use)	8 (0.6%)	2 (0.8%)	
Short-term use (<12 mos cumulative use)	64 (4.9%)	9 (3.5%)	0.38
Long-term use (≥12 mos cumulative use)	32 (2.5%)	4 (1.5%)	
Among those ever used nonstatin lipid-lowering therapy			
Duration of use[b] (mos), mean (SD)	15.0 (19.7)	11.8 (14.2)	–[b]
Baseline CD4 cell count			
Mean (SD)	376 (295)	246 (213)	<0.0001
≤200/μl	288 (22.2%)	96 (37.1%)	<0.0001
201–500/μl	397 (30.7%)	74 (28.6%)	
>500/μl	254 (19.6%)	19 (7.3%)	
Unknown	356 (27.5%)	70 (27.0%)	
Baseline HIV RNA level			
≤500 copies/ml	221 (17.11%)	14 (5.4%)	<0.0001
501–10 000 copies/ml	124 (9.6%)	25 (9.7%)	
>10 000 copies/ml	217 (16.8%)	74 (28.6%)	
Unknown	733 (56.6%)	146 (56.4%)	
Duration of ART use (years)	1.7 (2.3)	1.3 (2.0)	0.01
Clinical AIDS diagnosis prior to index	123 (9.5%)	33 (12.7%)	0.11
History of co-morbidity			
Hepatitis B	17 (1.3%)	5 (1.9%)	0.44
Hepatitis C	33 (2.6%)	7 (2.7%)	0.89
Diabetes	41 (3.2%)	8 (3.1%)	0.95
Obesity	36 (2.8%)	12 (4.6%)	0.12
NHL subtype			
Diffuse large B-cell lymphoma	–	167 (64.5%)	–
Burkitt's lymphoma	–	41 (15.8%)	
Follicular lymphoma	–	2 (0.8%)	
Other	–	49 (18.9%)	

ART, antiretroviral therapy; mos, months; NHL, non-Hodgkin lymphoma.
[a]Matching factors.
[b]*P* value not provided because measures were calculated for statin or nonstatin lipid-lowering therapy users only.

not significant) for a short duration of statin use, that is, less than 12 months of use, suggesting the likelihood of residual confounding by indication. As a result, we cannot exclude the likelihood that confounding by indication might explain the inverse association observed for statin use in this study. Despite adjusting for the history of several medical conditions associated with statin use that might also affect lymphoma risk, residual confounding remains a potential limitation of this study for the following reasons: first, a potential confounder is HIV RNA levels. However, 56% of the participants did not have an HIV RNA measurement at baseline, prohibiting us from adjusting or imputing for this variable in the analysis. In addition, undercoding of certain risk factors

Table 2. Characteristics of statin and nonstatin lipid-lowering therapy users.

	History of statin use			History of nonstatin LLT use		
	Never use ($N=1356$)	Ever use ($N=198$)		Never use ($N=1445$)	Ever use ($N=109$)	
	Number (%) or mean (SD)		*P* value	Number (%) or mean (SD)		*P* value
Age mean (SD, years)	42.5 (8.8)	47.7 (8.5)	<0.0001	43.0 (8.9)	45.7 (8.2)	<0.01
Male sex	1297 (95.7%)	191 (96.5%)	0.60	1381 (95.6%)	107 (98.2%)	0.20
Race						
White	809 (59.7%)	121 (61.1%)	0.70	867 (60.0%)	63 (57.8%)	0.65
Nonwhite	547 (40.3%)	77 (38.9%)		578 (40.0%)	46 (42.2%)	
Nonstatin LLT use	50 (3.7%)	59 (29.8%)	<0.0001	–	–	
Statin use	–	–	–	139 (9.6%)	59 (54.1%)	<0.0001
Baseline CD4 cell count, mean (SD, per μl)	348.3 (280.4)	390.4 (321.9)	0.08	353.3 (283.7)	368.8 (323.3)	0.61
Baseline HIV RNA level						
Median (interquartile range, per ml)	6844 (97–47 761)	3551 (50–29 878)	0.02	6090 (75–44 499)	5553 (75–28 838)	0.07
Duration of ART use (years)	1.4 (2.1)	3.3 (2.6)	<0.0001	1.5 (2.1)	3.7 (2.7)	<0.0001
Clinical AIDS diagnosis prior to index	131 (9.7%)	25 (12.6%)	0.19	142 (9.8%)	14 (12.8%)	0.31
History of co-morbidity						
Hepatitis B	20 (1.5%)	2 (1.0%)	0.61	22 (1.5%)	0 (0%)	0.19
Hepatitis C	37 (2.7%)	3 (1.5%)	0.31	36 (2.5%)	4 (3.7%)	0.45
Diabetes	31 (2.3%)	18 (9.1%)	<0.0001	41 (2.8%)	8 (7.3%)	0.01
Obesity	41 (3.0%)	7 (3.5%)	0.70	45 (3.1%)	3 (2.8%)	0.83

ART, antiretroviral therapy; LLT, lipid-lowering therapy.

such as obesity in electronic medical records can be expected and could contribute to the potential residual confounding. Similarly, the considerable number of missing CD4 cell count measurement at study baseline may also result in residual confounding, despite the use of multiple imputation. Another limitation that should be considered when interpreting the results of this study is the limited study power for several categories of statin use as well as nonstatin LLT use. The limited number of users in these subgroups likely contributed to the wide confidence interval of the estimates.

Despite these limitations, our study was based on a well defined HIV-positive cohort, complete incident NHL ascertainment, and selection of closely matched controls. The use of Kaiser Permanente's electronic medical records also eliminated recall bias on statin use and minimized selection bias from differential study participation. In addition, our study is among the few studies to our knowledge that have examined preventive factors for the development of NHL in HIV-positive patients beyond use of ART and maintenance of immune function. In conclusion, our data indicate

Table 3. Hazard ratio estimates for history of statin use and nonstatin lipid-lowering therapy use on risk of non-Hodgkin's lymphoma in HIV-positive individuals from multivariable conditional logistic regression[a].

	Statins		Nonstatin LLT	
	Hazard ratio; (95% confidence interval)	*P* value	Hazard ratio; (95% confidence interval)	*P* value
Ever use	0.55 (0.31–0.95)	0.03	0.89 (0.46–1.71)	0.72
Nonregular use (use <12 months continuous use)	0.54 (0.30–0.97)	0.04	0.82 (0.41–1.66)	0.58
Regular use (≥12 months continuous use)	0.61 (0.16–2.31)	0.46	1.58 (0.31–8.11)	0.58
Short-term use (<12 months cumulative use)	0.64 (0.31–1.28)	0.21	0.88 (0.41–1.88)	0.73
Long-term use (≥12 months cumulative use)	0.50 (0.23–1.10)	0.09	0.91 (0.28–2.93)	0.87
Duration of use (per month)	0.98 (0.96–1.00)	0.08	0.99 (0.96–1.02)	0.41
By statin lipophilic/hydrophilic property				
Lipophilic statins				
Duration of use (per month)	0.99 (0.97–1.01)	0.16	0.99 (0.96–1.02)	0.41
Hydrophilic statins				
Duration of use (per month)	0.97 (0.93–1.02)	0.26		

LLT, lipid-lowering therapy.
[a]Model adjusted for matching factors, Kaiser Permanente region (Northern or Southern California), clinical AIDS diagnosis prior to index date (yes/no), duration of antiretroviral therapy (ART) use (years), baseline CD4 cell count level (<200, 201–500, and >500/μl), and history of selected co-morbidity (yes/no), that is, history of hepatitis B and C, diabetes, and obesity.

a potentially protective effect of statin medication and risk of NHL among HIV-positive patients, although the likelihood of confounding by indication cannot be excluded at this point. As lymphoma continues to be a significant source of morbidity for HIV-positive individuals, further risk reduction measures are needed. Thus, large prospective studies are warranted to further clarify the association between statin use and risk of HIV-related NHL.

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Conflicts of interest

There are no conflicts of interest.

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