Use of hydroxy-methyl-glutaryl coenzyme A reductase inhibitors is associated with risk of lymphoid malignancies

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(Received July 25, 2005/Revised November 4, 2005/Accepted November 5, 2005/Online publication January 23, 2006)

It has been speculated that the use of hydroxy-methyl-glutaryl coenzyme A reductase inhibitors (statins) is associated with the risk of malignant diseases. Considering their immunosuppressive activities, malignant diseases that are associated with an immunosuppressive status seem feasible to examine the association. We therefore examined the association between statin use and development of lymphoid malignancies in a case-control study. Cases were 221 consecutive incident cases with histopathologically proven lymphoid malignancies (lymphoma and myeloma), hospitalized in the Department of Hematology of Toranomon Hospital (Tokyo, Japan) between 1995 and 2001. Two independent control groups, comprising 442 and 437 inpatients without malignancies from the Departments of Orthopedics and Otorhinolaryngology of the same hospital, were selected to test for consistency of association. Controls were matched individually with cases for age, sex and year of admission. Subject information, including statin use, was abstracted from medical records at the time of hospitalization. Strength of association was evaluated as an adjusted odds ratios (aOR) using a conditional logistic regression model. A higher frequency of statin use was found among patients with lymphoid malignancies in comparison with both orthopedic (aOR 2.11, 95% CI 1.20–3.69, $P = 0.009$) and otorhinolaryngology patients (aOR 2.59, 95% CI 1.45–4.65, $P = 0.001$), the significance being maintained when the two control groups were combined (aOR 2.24, 95% CI 1.37–3.66, $P = 0.001$). In conclusion, we observed an elevated risk of lymphoid malignancy with statin use among Japanese patients. Further evaluations in different populations are required to draw conclusions as to the carcinogenicity of lymphoid malignancies with statin use. (*Cancer Sci* 2006; 97: 133–138)

Over the last two decades, statins have become one of the most widely used types of drugs, with a worldwide consumption estimated to be worth approximately US$140 billion. In Japan, statin consumption reached US$1.8 billion in 1999 (pravastatin US$1220 million, simvastatin US$400 million and fluvastatin US$80 million).[1] They are prescribed to lower cholesterol to prevent further cardiovascular or cerebrovascular diseases.

The properties of statins other than their lipid-lowering effects have recently been deduced from several clinical observations. Large randomized control trials have demonstrated that statins decrease the risk of cardiovascular morbidity and mortality in both primary and secondary prevention settings.[2–5] Statin administration after organ transplantation is reported to decrease the incidence of graft rejection and mortality[6] and substantial suppression of chronic graft-versus-host reactions has been noted.[7] The drugs may furthermore reduce the incidence of dementia.[8] The anti-inflammatory and immunosuppressive effects of statins may play essential roles, and *in vitro* studies have started to unravel the molecular mechanisms of their immunomodulating activities.[9–11] Possible tumorigenesis by statins may be explained by such immunosuppressive effects; however, it remains unclear in humans to date.

The incidence of lymphoid malignancies, especially non-Hodgkin's lymphoma, has been rapidly increasing in developed countries over the last few decades, but a limited number of risk factors have so far been identified.[12,13] Among them, immunosuppressed status is one of the strongest risk factors for lymphoproliferative diseases.[14–16] The increased use of statins, which have immunosuppressive properties, in parallel with the increased incidence of lymphoproliferative diseases might indicate statin's contribution, in part, to their genesis. To examine the possible association between statin use and the risk of lymphoproliferative diseases, we conducted the present case-control study.

Patients and Methods

Setting

The present study was conducted at Toranomon Hospital, Tokyo, Japan, a hospital with 1100 beds, including 30, 25 and 45 in the hematology, otorhinolaryngology (ENT) and orthopedic wards, respectively. The study protocol was approved by the institutional review board of the hospital.

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doi: 10.1111/j.1349-7006.2006.00153.x

The primary aim was to determine any association between use of statins and lymphoid malignancies, including acute lymphoblastic leukemia, malignant lymphoma and myeloma. The odds ratios for different histological subtypes of lymphoid malignancies were compared as secondary endpoints.

Subjects

The case group comprised a total of 221 consecutive patients aged at least 40 years who were hospitalized with histopathologically proven lymphoid malignancies in the hematology ward of Toranomon Hospital between April 1995 and March 2001. To confirm or reclassify the pathological diagnoses of malignant lymphomas according to the World Health Organization criteria, two experienced hematopathologists reviewed 126 available samples independently. Approximately 10% of the diagnoses were changed or reclassified, but all of them remained as lymphoid malignancies. Therefore, two to three changes in the diagnosis might have occurred among the 25 remaining subjects diagnosed as having malignant lymphoma whose slides were unavailable for histological review; however, minimal effects were expected, and the 25 subjects were retained for the analysis.

The two hematopathologists replaced the original diagnoses with the equivalent categories in the World Health Organization criteria: B-cell neoplasms, T-cell and natural killer (NK) cell neoplasms, and Hodgkin's lymphoma. Acute leukemia and myelodysplastic syndromes in the remaining 70 patients were categorized by the FAB classification.[17,18] The documented diagnoses were always confirmed by one hematopathologist and two hematologists in our hospital.

In the present study, two independent control groups (orthopedic and ENT inpatients) were selected to examine the consistency of the findings and to avoid potential selection bias. A total of 444 and 437 control subjects were matched individually (2:1) to the case subjects for age, sex and year of admission. We chose these patients as controls under the assumption that their primary diseases were unrelated to hyperlipidemia or malignancies. The reasons for hospitalization were mainly fractures, vertebral canal stenosis, osteoarthritis, otitis media, hearing impairment and sinusitis. Individuals who had a history of any type of malignancy were excluded from both the case and control subjects.

Data collection

A history of the use of statins, as well as the duration, type and dose, were collected from both inpatient and outpatient medical records. Usage was defined as a history of taking prescribed statins of any type and dose, at any time before admission. Age, sex and background medical conditions were also abstracted. In addition, serological status for anti-Hepatitis C Virus (HCV) antibodies and anti-Hepatitis B surface (HBs) antigens was determined. The primary investigators contacted referring doctors, patients and their families by telephone if necessary to obtain missing data.

Statistical analysis

All statistical analyses were carried out using STATA, version 8 software (STATA, College Station, TX, USA). The statistical power was calculated by the 'sampsi' procedure to detect differences between estimated percentages of statin use among patients with and without lymphoid malignancies. The percentage of statin use in the general population was estimated to be 8.7%, based on four million people on prescriptions and a total population of 46 million people aged 45 years and over in Japan. On the assumption that statin use was 10% more frequent (18.7%) among patients with lymphoid malignancies than the general population, the sample size of this study would provide a statistical power of 92.7% and 92.6% for comparisons with the orthopedic and ENT groups, respectively, at an α error of 0.05.

Bivariate analyses were carried out using the χ^2, Fisher's exact or Wilcoxon signed-rank tests when appropriate. We evaluated the strength of associations between the use of statins and lymphoid malignancies in terms of odds ratios (OR) and 95% confidence intervals (CI) using conditional logistic regression analysis. The study group was compared independently with the orthopedic group, the ENT group, and then with the combined control group. For multivariate analysis, serological status of anti-HBs antigen as well as anti-HCV-antibodies were considered as confounders based on our earlier reports[19,20] showing significant risk change by HCV and Hepatitis B Virus (HBV) infection for lymphoid malignancies, in addition to age, sex and year of visit.

Results

Patient characteristics

No significant differences were observed in the age, sex or year of admission between the case and two control groups (Table 1). No patients were positive for anti-Human Immunodeficiency Virus (HIV) antibodies, and three patients who were found to have anti-Human T-cell Leukemia Virus Type-1 (HTLV-I) antibodies in the control groups were excluded from the study.

There were 29 patients with a history of statin use among the total of 221 with lymphoid malignancies (13.3%) (Table 1). Of these 29, 10 had discontinued statin use before admission. Even after contacting referring physicians, patients and their families, the history of statin use remained unclear for three patients in the case group, who were eliminated from the analysis. In contrast, 7.5% and 7.1% of the orthopedic and ENT patients, respectively, were receiving statins at admission. Table 1 also presents the histological subtypes of lymphoid malignancies.

The types, doses and durations of statin use in the three groups are shown in Table 2. Although the number of subjects was limited, controls appeared to take a lower dosage of statin relative to cases, especially for simvastatin ($P = 0.022$ in Fisher's exact test). Regarding the duration of statin use, no obvious differences were observed. The distribution of the types of statins in this study reflected that in the Japanese market during the period of the study.

Association between statins and lymphoid malignancies

As shown in Table 3, the prevalence of statin use in the group with lymphoid malignancies was significantly higher than that in the control groups. All of the OR in the matching factor adjusted model (model 1) showed a statistically significant increased risk. The model adjusted for serological status for anti-HBs antigens and anti-HCV antibodies (model 2) generated OR of 2.11 (95% CI 1.20–3.69, $P = 0.009$) for the orthopedic group, 2.59 (95% CI 1.45–4.65, $P = 0.001$) for

doi: 10.1111/j.1349-7006.2006.00153.x

Table 1. Characteristics of the patients involved in the study

Characteristics	Study group (lymphoid malignancies, *n* = 221)	Control group 1 (orthopedics, *n* = 442)	Control group 2 (ENT, *n* = 437)	Combined control group† (*n* = 879)
Male : female ratio	86:136	172:272	168:272	340:544
Age range, median (years)	46–94, 64	44–95, 63	44–91, 61	44–91, 61
No. patients by age group				
40–49 years	23 (10.4%)	39 (8.8%)	45 (10.4%)	84 (9.6%)
50–59 years	64 (29.0%)	143 (32.4%)	156 (35.7%)	299 (34.0%)
60–69 years	66 (29.9%)	120 (27.2%)	117 (26.8%)	237 (27.0%)
70–95 years	68 (30.8%)	140 (31.7%)	119 (27.2%)	259 (29.5%)
Serum levels of total cholesterol (mg/dL) (mean ± SD)	171.3 ± 43.9	189.0 ± 35.8	189.9 ± 35.1	189.5 ± 35.4
No. patients with hypercholesterolemia‡	21 (9.5%)	78 (17.6%)	84 (19.2%)	162 (18.4%)
History of statin use				
Yes	29 (13.3%)	33 (7.5%)	31 (7.1%)	64 (7.3%)
Pravastatin	25 (86.2%)	24 (72.7%)	17 (54.8%)	41 (64.1%)
Simvastatin	4 (13.8%)	9 (27.3%)	13 (41.9%)	22 (34.4%)
Fluvastatin	0 (0%)	0 (0%)	1 (3.2%)	1 (1.6%)
No	189 (86.7%)	409 (92.5%)	406 (92.9%)	815 (92.7%)
Unknown	3 (1.3%)	0 (0%)	0 (0%)	0 (0%)
No. patients receiving statins/no. patients with hypercholesterolemia‡	3/21 (14.2%)	11/78 (14.1%)	10/84 (11.9%)	21/162 (13.0%)
Anti-HBsAg (positive/negative/unknown)	7/207/7	5/429/8	10/426/6	15/855/14
Anti-HCVAb (positive/negative/unknown)	22/193/6	25/410/7	16/418/8	41/828/15
Histological Subtypes and Phenotypes of Lymphoid Malignancies				
B cell neoplasms	192 (86.9)			
Diffuse large, B	67 (30.3)			
Plasma cell myeloma	59 (26.7)			
Follicular	29 (13.1)			
Mantle cell	8 (4.2)			
Others	37 (19.3)			
T-cell/NK-cell Neoplasms	20 (9.0)			
Peripheral, T	7 (3.2)			
Angioimmunoblastic, T	6 (2.7)			
Others	7 (3.2)			
Hodgkin lymphoma	7 (3.2)			
Classical	6 (2.7)			
Nodular lymphocyte	1 (0.5)			
NHL, unclassifiable	2 (0.9)			

†Two control groups were combined. ‡Patients whose blood cholesterol levels were 200 mg/dL or higher were defined as having hypercholesterolemia. ENT, otorhinolaryngology; HBsAg, Hepatitis B surface antigens; HCVAb, Hepatitis C virus antibodies.

Table 2. Types, doses and duration of statin use for patients involved in the study

Type of statin	Dose (mg/day)	Cases	Control group 1 (orthopedics)	Control group 2 (ENT)
Pravastatin	5	5	4	11
	10	16	17	6
	15	2	0	0
	20	2	3	2
Total		25 (86.2%)	24 (72.7%)	19 (54.8%)
Simvastatin	5	2	9	11
	10	2	0	0
Total		4 (13.8%)	9 (27.3%)	11 (41.9%)
Fluvastatin	20	0 (0%)	0 (0%)	1 (3.2%)
Total		29 (100%)	33 (100%)	31 (99.9%)
Duration of statin use (months) (median, range)		48, 19–96	60, 12–108	48, 3–120

ENT, otorhinolaryngology.

the ENT group, and 2.24 (95% CI 1.37–3.66, $P = 0.001$) for the combined control group. This increased risk with statin use was observed consistently when the analysis was stratified by cholesterol levels at diagnosis. When the subjects were divided into two groups according to median cholesterol levels (185 mg/dL), the OR for below and above median groups were 2.71 (95% CI 1.21–6.0, $P = 0.015$) and 2.78 (95% CI 1.05–7.38, $P = 0.040$), respectively.

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for lymphoid malignancies†

Study group versus	Control group 1 (orthopedics)	Control group 2 (ENT)	Combined control group
OR (model 1)‡	1.86	2.46	2.14
95% CI	1.10–3.15	1.39–4.36	1.33–3.46
P-value	0.021	0.002	0.002
OR (model 2)‡	2.11	2.59	2.24
95% CI	1.20–3.69	1.45–4.65	1.37–3.66
P-value	0.009	0.001	0.001

†Three cases with unknown history of statin use were excluded. ‡Model 1 adjusted for age, sex and year of visit. Model 2 added serological status for anti-Hepatitis B surface antigens (HBsAg) and anti-Hepatitis C virus antibodies (HCVAb) in addition to model 1. ENT, otorhinolaryngology.

Table 4. Age-adjusted odds ratios (OR) according to histological subtype and phenotype

	Study group (lymphoid malignancies, *n* = 221) (statin –/+)	Combined control group (*n* = 879) (statin –/+)	Adjusted OR†	95% CI	*P*-value
Histological subtype					
DLBCL	58/8	248/17	2.1	0.79–5.55	0.136
Plasma cell myeloma	46/13	225/16	3.99	1.75–9.10	0.001
FL	26/2	112/4	1.94	0.35–10.9	0.451
Phenotype					
B-cell neoplasm	161/28	716/51	2.45	1.41–4.28	0.002
T-cell neoplasm	16/1	58/10	0.66	0.06–7.23	0.737

†Adjusted for age, sex, year of visit, and serological status of anti-HBsAg and anti-HCVAb. CI, confidence interval; DLBCL, Diffuse Large B-cell lymphoma; FL, Follicular lymphoma.

Data for different histological subtypes and phenotypes of lymphoid malignancy with reference to the rate of statin use in comparison with the combined control group are summarized in Table 4. Plasma cell myeloma showed the highest rate of statin use compared with the age-matched control group (adjusted OR [aOR] 3.99, $P = 0.001$). The B-cell phenotype was also associated with a significantly higher prevalence of statin use (aOR 2.45, $P = 0.002$). In contrast, no significant relationship was evident for T-cell neoplasms (aOR 0.66, $P = 0.737$).

Discussion

The present study showed a significantly increased risk of lymphoid malignancies with statin use, applying the two independent control groups as well as the combined control group. Recent *in vitro* studies have suggested anti-inflammatory and immunomodulatory properties of statins, including selective blockage of LFA-1-mediated adhesion and costimulation of lymphocytes,[9] downregulation of class II major histocompatibility complexes on antigen-presenting cells[10] and reduction of chemokine synthesis in peripheral blood mononuclear cells.[11] Our findings are thus biologically plausible.

Newman and Hulley reviewed reports on the carcinogenicity of lipid-lowering drugs in rodents, and found that fibrates and statins initiated or promoted the development of cancer.[21] In humans, associations between malignancies and low cholesterol levels, and statin use have been under debate. Some cohort studies[22,23] demonstrated a relationship between low cholesterol levels and increased cancer deaths, but the causality remained questionable as preexisting cancers and other confounding variables might have been involved. Although three recent meta-analyses failed to show an association between statin use and an increased incidence of cancer or all-cause mortality,[24,25,1] the incidence of cancer was not the primary endpoint of the enrolled studies and competing risk by other diseases may have compromised the results. The wide variation in cancer incidence (0.2–6%) among the enrolled studies suggests that the results might have been biased with respect to patient selection.[26] In addition to the meta-analyses,[24,25,1] four case-control studies and one cohort study evaluated statin carcinogenicity for breast cancer,[27] breast and prostate cancers,[28] prostate cancer,[29] colorectal cancer[30] and all sites of cancer,[31] respectively. The results were not consistent enough across the studies to draw a conclusion. Statin's carcinogenicity might be vary according to the pathological subtype.

Among numerous suggested risk factors for lymphoid malignancies,[32–34] immunodeficiency has a strong association, these being the most frequent clonal disorders in patients with rare congenital immunodeficiency disorders.[35] Patients with acquired immunodeficiency, for example, due to immunosuppressive therapy, hematopoietic stem-cell transplantation[36] or HIV infection,[37] have up to 160 times higher incidence of lymphoid malignancies than the general population. We therefore chose lymphoid malignancies for the present study in consideration of the immunosuppressive effects of statins. Our observation that the OR varied among subtypes of lymphoid malignancies (high with myelomas and low with T-cell lymphomas) is very interesting in this context; the underlying mechanisms of statin tumorigenesis now needs to be elucidated.

There were several considerations taken into account in designing this study. To avoid spurious association by chance and to minimize the effects of selection bias of controls in terms of exposure to statin, we obtained two independent control groups in which each case was matched to four individuals for age, sex and year of admission. All three comparisons, with the two independent control groups and with the

doi: 10.1111/j.1349-7006.2006.00153.x

combined control group, showed significantly higher rates of statin use in the case group; therefore, effects of random error and selection bias in this study can be considered minimal. We also selected subjects without malignancies as controls, from ENT and orthopedic inpatients whose reasons for admission were unrelated to statin use. Some orthopedic patients had osteoporosis, for which statins have been speculated to be effective;[38] however, statins are not approved for osteoporosis in Japan. As patients with malignancies tend to have low cholesterol levels and statin treatment is therefore contraindicated, underestimation rather than overestimation of statin tumorigenesis might be expected. Actually, our study showed that 10 out of 29 cases with a history of use had discontinued statin use before admission, as opposed to all 64 controls who had continued the treatment at least up until admission. To evaluate the possible bias that hypercholesterolemia would be more likely to be found and treated by internists than by orthopedic or ENT physicians, the rate of statin treatment in patients with hypercholesterolemia was compared among the three study groups and with those who had myeloid malignancies on the same hematology ward during the same period (data not shown). Hypercholesterolemia was treated similarly in the four groups; interphysician bias in statin treatment was assumed to be acceptably small. Another observation supporting minimal bias is that statin use had usually been initiated by physicians of various specialties or settings, including primary care and community hospitals, prior to referral, regardless of the departments to which the patients were admitted.

One of the weaknesses of this study is that the population was hospital-based rather than population-based. Although a case-control design is a feasible study design to assess the risk of statin use in the rare development of lymphoid malignancies, it does not provide direct evidence of tumorigenesis of statins. Possible confounding factors associated with hypercholesterolemia might have predisposed individuals to lymphoid malignancies. Although the sample size of this study was sufficient to obtain more than 90% power with an estimated two-fold increase in lymphoid malignancies, it may still be small enough to allow generalization of the results. Neither the etiological mechanisms nor the clinicopathological features of statin-associated lymphoid malignancies were clarified in this study. B-cell neoplasms, mostly plasma cell myelomas, had the highest odds ratios and, in contrast, T-cell neoplasms and follicular lymphomas showed no significant association with statin use. However, sample size for the latter was small, and this point needs to be further evaluated. Moreover, lymphoid malignancies associated with immunosuppression have common clinicopathological features, such as Epstein–Barr virus infection,[39] which were not evident in this current study. In depth investigations using pathological and molecular techniques are necessary to clarify the pathogenesis of statin-associated lymphoid malignancies.

The worldwide consumption of statins has been growing rapidly over the past 20 years, and the incidence of lymphoid malignancies has also been increasing rapidly,[12] without clear reasons. As the increase of lymphoid malignancies started before statins came on the market, their influence can only be partial; however, the present study did indicate a significant association. Further investigations with a longer follow-up period are now necessary. In addition, the dose-dependence of statin tumorigenesis could not be investigated in detail in our study although a suggestive difference was observed. *In vitro* studies have provided evidence that statins exert dose-dependent immunosuppressive effects, and that newer-generation drugs are more immunosuppressive.[9] The maximum doses of statins in Japan (pravastatin 20 mg, simvastatin 10 mg, fluvastatin 60 mg and atorvastatin 40 mg) are almost half those used for clinical trials in Europe and the USA,[2,4,5] where newer-generation statins are mostly prescribed in clinical practice. Thus, the risks of developing lymphoid malignancies might be higher than those estimated risks in our study. However, it should be borne in mind that some researchers have reported that statin administration *in vivo* can provide an oncoprotective effect. Bcl-2 expression is downregulated in transformed cells undergoing apoptosis in response to statin exposure, and the apoptotic response is in part due to the depletion of the downstream product geranylgeranyl pyrophosphate.[40] Weis *et al*. reported that statin inhibition has a biphasic dose-dependent effect on angiogenesis. Statins have proangiogenic effects leading to oncogenesis at low therapeutic concentrations, but angiostatic effects leading to oncoprotection at high concentrations.[41]

Although we have presented possible carcinogenic effects for lymphoid malignancies caused by statin use, we have to emphasize the importance of statin use in clinical practice. The effect on mortality, especially for cardiovascular disease as well as stroke, is not negligible, as described in the recent systematic review.[1] Therefore, careful interpretation is required to the apply findings of this study to the clinic.

In conclusion, we here found a significant association between statin use and risk of lymphoid malignancies. Epidemiological evaluation in other populations is required.

Acknowledgments

We are especially grateful to Miss Nakae for collecting clinical information.

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doi: 10.1111/j.1349-7006.2006.00153.x