Statin Use and Prognosis in Patients With Diffuse Large B-Cell Lymphoma and Follicular Lymphoma in the Rituximab Era

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A B S T R A C T

Purpose

Statins have antilymphoma properties but have also been shown to inhibit the binding of rituximab to the CD20 antigen, resulting in reduced antitumor activity of rituximab in vitro. The clinical impact of statin use on the outcome of lymphoma patients treated with a rituximab-containing regimen is unknown.

Patients and Methods

Consecutive patients with newly diagnosed, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) were enrolled onto a registry and observed prospectively. The impact of statin use on patients' outcomes was analyzed.

Results

Two hundred twenty-eight patients with DLBCL and 293 patients with FL were enrolled from September 2002 through June 2007; 21% of patients with DLBCL and 19% of patients with FL were on statins at diagnosis, and 20% and 17% remained on statins during lymphoma treatment, respectively. All patients with DLBCL and 39% of patients with FL received initial therapy containing rituximab. The median follow-up time was 47 months (range, 13 to 80 months). Statin use had no impact on the overall response rate ($P = .67$), overall survival ($P = .76$), or event-free survival (EFS) in patients with DLBCL (hazard ratio [HR] = 0.85; 95% CI, 0.43 to 1.68). Statin use at diagnosis was associated with improved EFS in patients with FL (HR = 0.45; 95% CI, 0.26 to 0.77), including subgroups treated with rituximab or a rituximab-containing regimen (HR = 0.38; 95% CI, 0.14 to 1.07) and patients who were observed only (HR = 0.38; 95% CI, 0.17 to 0.84).

Conclusion

The concurrent use of statins during the treatment of patients with DLBCL and FL in the rituximab era did not adversely affect outcome. The apparent benefit of statin therapy on FL outcome requires further studies.

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INTRODUCTION

Rituximab has changed the natural history of non-Hodgkin's lymphoma. The time to treatment failure and overall survival are improved with immunochemotherapy in diffuse large B-cell lymphoma (DLBCL).¹⁻⁵ Rituximab has also significantly improved the outcome for patients with follicular lymphoma (FL).⁶⁻¹⁰ Statins are one of the most frequently prescribed classes of drugs in Western countries, primarily indicated in the treatment of hyperlipidemia. An estimated one in 10 adults and one in four individuals ≥ 60 years old are on statin therapy.¹¹ Consequently, many

individuals diagnosed and treated for lymphoma are already receiving statin therapy.

Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which is the rate-limiting enzyme of the mevalonate pathway required for the synthesis of isoprenoids such as cholesterol.¹² The impact of statins on cholesterol and isoprenoid synthesis may have anticancer effects through at least two primary mechanisms, which include impairment of protein prenylation¹³ and interference with the formation of cholesterol-rich lipid microdomains called "lipid rafts" within the cell membrane.¹⁴ Both of these processes are critical for the signaling and activity of numerous proteins important

for lymphomagenesis and tumor survival, including Ras.¹⁵ The impact of statins on cell signaling and in vivo activity against tumor cells generated an interest in studying statins as a potential lymphoma therapeutic intervention.^{16,17}

Recent laboratory data, however, suggest that statin use may directly inhibit rituximab binding to CD20 and, therefore, rituximab efficacy.¹⁸ The inhibition of rituximab binding seems to be related to conformational changes of the CD20 receptor. Decreased rituximab binding resulted in decreased rituximab-induced complement and antibody-dependent cell cytotoxicity. Normal B cells isolated from patients on statin therapy showed decreased rituximab binding.¹⁸

These laboratory findings raised significant concerns about statin use during rituximab treatment. Although some oncologists advocate stopping statin at the initiation of lymphoma therapy containing rituximab, others feel there is no evidence that the statin effect is clinically relevant.^{19,20} Thus far, to our knowledge, no study has evaluated the clinical significance of statin use during lymphoma therapy with rituximab or a rituximab-containing regimen, and there are no evidence-based guidelines for clinicians in this regard. Here we report on the impact of statin use on the outcome of a cohort of prospectively observed patients with newly diagnosed DLBCL and FL treated in the rituximab era.

Table 1. Demographics and Clinical Characteristics of Patients With DLBCL and FL: Overall and by Statin Use at the Time of Initiation of Therapy

Demographic or Clinical Characteristic	DLBCL						FL					
	All		No Statin Use at Initiation of Therapy		Statins Use at Initiation of Therapy		All		No Statin Use at Initiation of Therapy		Statins Use at Initiation of Therapy	
	(n = 228)		(n = 189)		(n = 39)		(n = 289)		(n = 230)		(n = 59)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Treatment												
R-CHOP/R-CHOP-like*	228	100	189	100	39	100	57	20	48	21	9	15
Observation							116	40	89	39	27	46
Rituximab only							24	8	19	8	5	8
CVP							16	6	14	6	2	3
R-CVP							39	13	34	15	5	8
RT only							21	7	13	6	8	14
Other chemotherapy							15	5	12	5	3	5
Surgery							1	< 1	1	< 1	0	0
Male	127	56	103	55	24	62	158	55	115	50	43	73†
Age > 60 years	149	65	114	60	35	90†	155	54	107	47	48	81†
Performance status > 2	17	8	15	8	2	5	7	2	6	3	1	2
LDH > ULN	94	47	75	46	19	54	32	13	26	13	6	12
> 1 extranodal site	52	23	43	23	9	24	29	11	23	11	6	11
Stage III or IV	125	55	110	59	15	38†	201	70	167	74	34	58†
B symptoms (any)	50	22	45	24	5	13	19	7	18	8	1	2
Grade III follicular	NA		NA		NA		38	13	30	13	8	14
> 4 nodal groups	NA		NA		NA		96	34	78	35	18	31
Hemoglobin > 12 g/dL	NA		NA		NA		27	10	21	10	6	11
IPI												
0-1	91	42	76	40	15	38	158	55	130	57	28	47
2	65	29	52	28	13	33	102	35	80	35	22	37
3	49	21	45	24	4	10	23	8	15	7	8	14
4-5	23	10	16	8	7	18	6	2	5	2	1	2
FLIPI												
0-1	NA		NA		NA		124	43	97	42	27	46
2	NA		NA		NA		98	34	85	37	12	20
3-5	NA		NA		NA		68	23	48	21	20	34
Statin use at diagnosis	44	19	9	5	35	90	62	21	4	2	58	98
Statin type at treatment												
Atorvastatin	21	48	NA		21	60	28	45	NA		28	48
Simvastatin	15	34	NA		15	43	22	35	NA		22	38
Rosuvastatin	1	2	NA		1	3	1	2	NA		1	2
Pravastatin	2	5	NA		2	6	6	10	NA		6	10
Fluvastatin	0	0	NA		0	0	1	2	NA		1	2
Lovastatin	0	0	NA		0	0	1	2	NA		1	2

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone; RT, radiotherapy; LDH, lactate dehydrogenase; NA, not applicable; ULN, upper limit of normal; IPI, International Prognostic Index; FLIPI, Follicular Lymphoma International Prognostic Index.

*R-CHOP-like therapies included R-CHOP (DLBCL, n = 199; FL, n = 51), epratuzumab + R-CHOP (DLBCL, n = 4), and R-CHOP plus another agent (eg, intrathecal methotrexate; DLBCL, n = 25; FL, n = 6).

†Denotes significant difference at $P = .05$.

PATIENTS AND METHODS

Study Population

This study was reviewed and approved by the Human Subjects Institutional Review Board at the Mayo Clinic (Rochester, MN), and informed consent was obtained in accordance with the Declaration of Helsinki from all participants. All patients in this analysis were selected from the Molecular Epidemiology Resource of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE). Briefly, since late 2002, all consecutive patients with non-Hodgkin's lymphoma who were evaluated at Mayo Clinic Rochester and the University of Iowa within 9 months of their initial diagnosis at presentation, were US residents, and were age 18 years or older were offered enrollment onto a prospective cohort study of non-Hodgkin's lymphoma outcomes (Molecular Epidemiology Resource). Exclusion criteria included HIV infection, non-English speaking, or unable to provide written informed consent.

All pathology was reviewed by a lymphoma hematopathologist for each patient to verify the diagnosis and to classify each patient into the WHO classification of neoplastic diseases of the hematopoietic and lymphoid tissues.²¹ Baseline clinical, laboratory, and treatment data were abstracted using a standard protocol. Treatment response data were abstracted from medical records; response was based on treating physician documentation only. All patients were systematically contacted every 6 months ($\pm$ 4 weeks) for the first 3 years after diagnosis and then contacted annually thereafter. At each follow-up time point, patients were either met in the clinic or contacted by phone to determine vital and disease status, new treatments, second cancers, and onset of new comorbidities. When a participant reported disease recurrence, progression, or a new cancer, medical records were requested, abstracted, and entered into the SPORE database as a follow-up report. We verified patients' reports of no disease progression on an annual basis against their physician's report. For decedents, we obtained a copy of the death certificate as well as medical records associated with death; a study physician assigned a cause of death using definitions developed for the Eastern Cooperative Oncology Group Intergroup Trial 4494.³

This analysis included patients enrolled onto the Mayo component of Molecular Epidemiology Resource from September 1, 2002 through June 30, 2007 with a diagnosis of DLBCL ($n = 238$) or FL ($n = 292$). For DLBCL, 10 patients were excluded either because they were not treated with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapy or because their treatment information was not available, leaving 228 patients available for analysis. For FL, three patients were excluded because treatment information was not available, leaving 289 patients available for analysis. Three patients (two patients with DLBCL and one with FL) were missing follow-up information and were censored at time 0 for the event-free survival (EFS) and overall survival (OS) analysis.

Statin Use

Statin use at the time of initial diagnosis and at the time of initiation of therapy was abstracted from medical records. All statins and statin-based combinations approved in the United States by the US Food and Drug Administration were considered.²²

Statistical Analysis

The primary analysis was to assess the association of statin use at the time of treatment with treatment response, EFS, and OS. Response was categorized as complete response, unconfirmed complete response, partial response, or no response.²³ EFS was defined as the time from diagnosis to disease progression, re-treatment, or death as a result of disease. OS was defined as the time from diagnosis to death from any cause. Patients without an event or death were censored at the time of last known follow-up. Patients with non-lymphoma-related deaths were censored at the time of death for EFS. Cox proportional hazards regression models²⁴ and Kaplan-Meier²⁵ curves were used to assess the association of statin use with EFS and OS. Cox modeling for EFS and OS was performed both univariately as well as adjusted for treatment (rituximab plus CHOP [R-CHOP] ν cyclophosphamide, vincristine, and prednisone [CVP] plus rituximab ν CVP ν observation ν rituximab only ν

other), grade (FL III ν FL I or II), and International Prognostic Index (IPI)/Follicular Lymphoma International Prognostic Index (FLIPI) as appropriate (Table A1, online only). Likelihood ratio tests were used to assess significance of statin association in EFS and OS models.²⁶ Logistic regression models were used to assess the association of statin use with clinical characteristics and response. All analyses were performed using SAS v9.1.3 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Two hundred twenty-eight newly diagnosed patients with DLBCL and 289 newly diagnosed patients with FL were included in this analysis. Patient characteristics are listed in Table 1. All patients with DLBCL received R-CHOP or R-CHOP-like chemotherapy. For FL, 39% of patients received rituximab or rituximab in combination with chemotherapy, 40% were observed, and 21% received other therapies. At a median follow-up time of 47 months (range, 13 to 80 months), 63 patients (28%) with DLBCL and 125 patients (43%) with FL had an event, and 52 patients (23%) with DLBCL and 21 patients (7%) with FL had died. Of the deaths, for DLBCL and FL, 83% and 62% were attributable to lymphoma, respectively.

Statin Use

At diagnosis, 44 patients (19%) with DLBCL and 62 patients (21%) with FL were on a statin therapeutic intervention. At initiation of therapy, 39 patients (19%) with DLBCL and 59 patients (21%) with FL were on a statin (Table 1). Thirteen patients discontinued statins from the time of diagnosis to initiation of therapy, and five patients initiated statin use. Clinical characteristics of patients with DLBCL who were on statin therapy during lymphoma treatment were similar to those of patients who were not on statin therapy (Table 1). For patients with DLBCL, those on statin therapy at the initiation of therapy, compared with those not on statin therapy, were more likely to be older than age 60 years (90% ν 60%, respectively; $P < .05$) and were less likely to have stage III or IV disease (38% ν 59%, respectively; $P < .05$). The IPI²⁷ was not statistically significantly different for statin users compared with nonusers (trend $P = .43$). For FL patients, those on a statin at the initiation of therapy, compared with those not on

Table 2. Statin Use and Response to Treatment With Rituximab-Containing Therapies

Response	Statin Use at Initiation of Therapy				OR	95% CI	<i>P</i>
	No		Yes				
	No. of Patients	%	No. of Patients	%			
DLBCL							
No response	24	13	6	15	1.00	Reference	
CR/CRu/PR	164	87	33	85	0.81	0.21 to 2.12	.67
FL*							
No response	13	13	3	15	1.00	Reference	
CR/CRu/PR	91	88	17	85	0.81	0.21 to 3.15	.76

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; OR, odds ratio; CR, complete response; CRu, unconfirmed complete response; PR, partial response.

*Treated with rituximab or rituximab and chemotherapy.

statin therapy, were more likely to be male (73% v 50%, respectively) and older than age 60 years (81% v 47%, respectively) and less likely to have stage III or IV disease (58% v 74%, respectively; all $P < .05$). There was no statistically significant difference in the FLIPI²⁸ for statin users compared with nonusers (trend $P = .30$).

Fig 1. Kaplan-Meier plots for event-free survival (EFS) and overall survival (OS) in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) based on statin use. Statin use during rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like therapy did not affect (A) EFS and (B) OS in patients with DLBCL. (C) Statin use was associated with prolonged EFS in patients with FL.

Impact of Statin Use on Response to Treatment

Response rates of patients with DLBCL and FL are listed in Table 2. There were no statistically significant differences in response rates on the basis of statin use among patients with DLBCL treated with R-CHOP or R-CHOP-like chemotherapy. Similarly, there were no differences in response rates by statin use among patients with FL treated with rituximab or rituximab plus chemotherapy (immunochemotherapy).

Statin Use and EFS and OS

The impact of statins on EFS in DLBCL and FL are shown in Figure 1 and Table 3. There was no association in EFS based on statin use during lymphoma therapy in patients with DLBCL (unadjusted $P = .76$; IPI adjusted $P = .63$; Fig 1A). Results were similar for OS (IPI adjusted hazard ratio [HR] = 0.89; 95% CI, 0.42 to 1.90; $P = .76$; Fig 1B). However, statin use was associated with improved EFS in patients with FL (Fig 1C). After adjusting for FLIPI and first course of therapy, statin use at initiation of therapy was associated with better EFS in all patients with FL (HR = 0.45; 95% CI, 0.27 to 0.77; $P = .001$). This observed association was consistent for patients treated with rituximab or rituximab plus chemotherapy (HR = 0.38; 95% CI, 0.14 to 1.07; $P = .04$) and patients whose initial therapy was observation only (HR = 0.38; 95% CI 0.14, 1.07; $P = .008$) as reported in Table A2 and Figure A1 (online only). There were too few deaths to evaluate OS in FL. In a sensitivity analysis, all results were similar when statin use was evaluated at the time of diagnosis. Finally, there was no significant difference in EFS by type of statin used (atorvastatin v simvastatin v other) at either diagnosis or initiation of therapy, although there was low power to evaluate associations by specific type of statin (data not shown).

DISCUSSION

This study provides important clinical observations regarding statin use in patients with DLBCL or FL and the subsequent impact on outcomes of statin use in patients with newly diagnosed DLBCL or FL treated in the rituximab era. These results challenge the clinical significance of in vitro studies.¹⁸ In this population of patients with newly diagnosed DLBCL and FL, statin use was relatively common (20%) and closely corresponded to statin use rates in the general adult US

Table 3. Statin Use and Prognosis

Prognosis	HR	95% CI	Likelihood Ratio P
DLBCL (EFS)			
Unadjusted	0.90	0.46 to 1.77	.76
Adjusted for IPI	0.85	0.43 to 1.68	.63
DLBCL (OS)			
Unadjusted	0.94	0.44 to 1.99	.86
Adjusted for IPI	0.89	0.42 to 1.90	.76
FL (EFS)			
Unadjusted	0.51	0.30 to 0.86	.006
Adjusted for FLIPI, grade III, and treatment	0.45	0.26 to 0.77	.001

Abbreviations: HR, hazard ratio; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; IPI, International Prognostic Index; OS, overall survival; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index.

population.¹¹ We found no evidence that statin use at the time of diagnosis or at the initiation of therapy was associated with inferior EFS or OS for patients with DLBCL treated with R-CHOP or R-CHOP-like therapy, broadly regarded as the current standard of care.²⁹ Furthermore, among patients with FL, statin use was associated with a statistically significant prolongation of EFS. This association strengthened after adjusting for clinical and treatment variables and was consistent across subgroups including patients treated with rituximab-containing regimens and patients who were initially managed with observation only.

Strengths of this study include prospective enrollment of newly diagnosed patients, baseline clinical predictors and treatment data, and nearly complete follow-up of the patient cohort for EFS and OS. There are also limitations. An observational study design was used, and unmeasured confounding could impact the results. However, we were able to adjust for established clinical predictors of outcome, which reinforced our results after accounting for these factors. Treatment, evaluation of response, and follow-up were based on routine clinical practice as opposed to standardized evaluation, as would be conducted in a controlled clinical trial. Although statin use was abstracted from medical records at the time of diagnosis and the initiation of therapy, these records would be expected to have reasonable validity. We do not know, however, whether patients actually took these medications regularly. Although the full medical record was used to abstract the medication record, not all statin use may have been captured. This study was not population based, although the distribution of clinical variables, treatments, and outcomes is similar to population-based studies,^{4,30} so these results are likely to have a broader generalization.

The issue of statin use during rituximab therapy recently came to the center of attention as a result of laboratory data suggesting that statins may negatively affect rituximab efficacy by interfering with binding to CD20 antigen.^{18–20} There are at least two plausible explanations behind this apparent discordance between the in vitro results and our clinical results. First, the degree of inhibition of rituximab binding to CD20 antigen by statins observed may not be clinically significant, being either incomplete or transient and reversible enough to allow for sufficient clinical activity of the antibody. Second, the negative effect of statins on rituximab binding is counteracted by the potential antilymphoma effect of statins through the inhibition of protein prenylation, lipids raft formation, or both. Although the analysis of clinical data cannot be easily used to distinguish between these two potential mechanisms, the lack of impact of statin use on overall and complete response rates after treatment supports the first hypothesis—that observed in vitro interference with rituximab binding to the CD20 antigen is not clinically significant—because the addition of rituximab to chemotherapy is associated with significantly improved response rates in DLBCL and FL.^{1,3,6}

Contrary to the lack of impact on EFS in patients with DLBCL and despite no effect on response rates, statin use was associated with an improvement in EFS in all patients with FL. The apparent statin benefit in this group was seen across the subgroups defined by grade

and initial therapy, including the protective effect in the observation group, representing 40% of patients with FL in this study. Patients on statins had similar clinical characteristics, including FLIPI, to those not on statins. The observed improvement in lymphoma-specific EFS suggests that statins may indeed have activity against lymphoma. A number of laboratory studies indicated that statins have direct cytotoxic effects on lymphoma cell lines.^{15,31,32} Statins might also have an impact on microenvironment and immune cells.^{15,33,34} Microenvironment plays an important role in FL,^{35,36} and effects of statins on the microenvironment and immune system could underlie the apparent beneficial statin effect in this disease. Further independent clinical studies are required to confirm potential benefit of statins in patients with FL and other indolent lymphomas.

In summary, concurrent use of statins during the treatment of patients with DLBCL and FL in the rituximab era did not adversely affect outcome. The unexpected better outcome of patients with FL on statins warrants further follow-up.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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