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ABSTRACT

An adverse prognostic impact of statin use in lymphoma was first suspected from *in vitro* data showing an impairment of anti-CD20 antibody binding. However, further clinical studies suggested an improved outcome associated with their use in hematological malignancies. In particular, a survival benefit was reported for patients with follicular lymphoma on statins. Our objective was to assess the outcome of follicular lymphoma patients treated in the PRIMA study with immunochemotherapy according to the use of statins. Among the 1217 patients enrolled in the PRIMA study, 1135 were included in the present study. Concomitant treatments at registration were available for all patients. Among those 1135 patients, 119 were on statins (10.4%) at diagnosis. Adverse events frequencies, event-free survival (EFS), time to next lymphoma treatment (TTNLT), time to next chemotherapy (TTNCT) and overall survival (OS) were evaluated according to the use of statins. The rates of overall and specific cardiovascular adverse events between the 2 groups of patients were comparable both during induction and maintenance. Outcome in terms of response rates or EFS, TTNLT, TTNCT and OS were similar regardless of the use of statins (P=.57, P=.85, P=.30 and P=.43 respectively) in univariate analysis and after further adjustments for potential confounding factors in multivariate analysis. In conclusion, statin use does not impact the prognosis of patients with follicular lymphoma treated with immunochemotherapy.

INTRODUCTION

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin lymphoma (NHL). Most patients have disseminated disease at presentation, but immediate treatment with immunotherapy or immunochemotherapy is not always required since the disease usually follows an indolent course.[1] When treatment is initiated, FL is characterized by a high initial response rate but in most patients the disease will ultimately relapse, although recent data suggest that prolonged PFS can be achieved with first line treatment.[2,3] However, subsequent remissions are usually of sequentially shorter durations.[4] After decades of disappointing results, overall survival has recently improved since the addition of rituximab to the therapeutic armamentarium in FL.[5-11] However, no cure of the disease is suggested in recent trials or long-term follow-up studies of conventional chemotherapy despite the broad use of anti-CD20 containing regimen.[12,13] New treatment strategies are therefore needed to improve the prognosis of patients with FL, especially those exhibiting adverse prognostic characteristics at diagnosis. To this end, new monoclonal antibodies and/or combined targeted therapies are currently in development or evaluated within clinical trials with promising results.[14,15]

Little is known about the possible beneficial effect of concomitant non-antineoplastic medication when immunochemotherapy is utilized. In this regard, conflicting results have been published to date concerning the impact of statin use on the prognosis of patients with NHL treated with a rituximab-containing first-line regimen. Accumulating evidence suggests that statin use has a potential antitumor effect[16] in addition to their known ability to improve dyslipidemia and reduce cardiovascular morbidity and mortality.[17] Recent studies suggest reduced cancer-specific mortality after prostate cancer diagnosis among statin users.[16,18] Paradoxically, an adverse prognostic impact of statin use in lymphoma was suspected from *in vitro* data showing an impairment of anti-CD20 antibody binding due to changes in

conformational epitopes of the molecule by an outer plasma membrane cholesterol-dependent mechanism. As a result, statins were found to decrease anti-CD20 induced complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity.[19,20]

Several groups worldwide attempted to assess the outcome of patients concomitantly receiving statins and rituximab for NHL. No detrimental effect was observed across studies for patients with diffuse large B-cell lymphoma treated upfront with R-CHOP or R-CHOP-like regimens[21,22] or for patients with chronic lymphoid leukemia (CLL) either during "watchful waiting" or treatment with a rituximab-containing therapy.[23] However, an unexpected prolongation of event-free survival (EFS) was observed for patients with FL receiving statins in a study from Nowakowski et al.[21] Several caveats of the study precluded definitive conclusions to be drawn; including treatment heterogeneity, the enrollment of patients who did not receive rituximab, the retrospective assessment of statin use through medical charts and the consideration of EFS as the primary endpoint without specific evaluation of overall survival (OS).[21] Notably, another recent study demonstrated a favorable outcome for patients with relapsed/refractory CLL both on statins and aspirin and treated by a rituximab-fludarabine-cyclophosphamide (FCR) regimen.[23] The impact of statin use on the prognosis of patients with FL therefore requires further investigation.

The PRIMA study is an international open-label phase III trial in which 1217 patients with de novo FL were enrolled. The trial demonstrated a favorable outcome in terms of EFS for patients receiving a 2-year maintenance treatment with rituximab on a bi-monthly basis following an induction immunochemotherapy regimen.[24] Since all concomitant medications were registered at enrollment, the study provided the opportunity to specifically analyze the effect of statin use during initial treatment on outcome.

Our objective is to determine whether the outcome of follicular lymphoma patients treated in the PRIMA study with immunochemotherapy was favorably effected by the antineoplastic

action of statins or detrimentally effected by the potential adverse action of statins on anti CD20 binding.

PATIENTS AND METHODS

Study Population

The randomized, open-label PRIMA study enrolled 1217 patients with *de novo* FL from 223 centers in 25 countries. Patients achieving at least a partial response following frontline therapy with physician-selected R-CHOP, R-CVP or R-FCM were randomized between 2-years rituximab maintenance (every 8 weeks) or observation.[24]

Patients with grade 1, 2, or 3a FL were eligible for induction if they were older than 18 years and presented with at least one high burden criterion among the following: any nodal or extranodal tumor mass with a diameter greater than 7 cm, involvement of three nodal sites with a diameter greater than 3 cm, systemic symptoms, substantial splenic enlargement, any compression syndrome (ureteral, orbital, gastrointestinal), or serous effusion (irrespective of cell content), elevated serum levels of lactic dehydrogenase (LDH) or $ß_2$-microglobulin (above upper normal limit).

Patients with responding disease (either complete or partial) were randomly assigned in a 1:1 ratio to receive 2 years of rituximab maintenance therapy (375mg/m^2 IV every 8 weeks) or observation (see flowchart in supplementary figure 1) but all enrolled patients before the induction phase were considered in the present study.

The PRIMA study was registered on the National Institute of Health website, number NCT00140582.

The protocol was approved by local or national ethics committees according to the laws of each country and the study was in accordance with the declaration of Helsinki. All patients gave written informed consent before registration.

The trial demonstrated a significant improvement of the primary endpoint (i.e. progression-free survival (PFS) from randomization) in the rituximab maintenance arm.[24] 3-year PFS was

74.9% (95% CI 70.9-78.9) in the rituximab maintenance group and 57.6% (95% CI 53.2-62.0) in the observation group (stratified log rank, *P*<.0001).

Statin Exposure

All concomitant treatments at study enrollment, including the use of statins, were prospectively collected. Concomitant treatments at therapy initiation were registered only if continuing at least up to 4 weeks during the trial.

Statistical analysis

Statistical analyses were performed using SAS version 9.2 for PC (SAS Institute, Cary, NC). A *P* value <.05 was considered as statistically significant. All statistical tests were 2-sided.

Baseline demographic characteristics between patients on statins and those not on statins were compared with the use of a Chi-square test. In the original PRIMA study publication,[24] all time-to-event evaluations were calculated from the date of randomization to the date of the event considered. Since effect of statins use during induction therapy was of interest in the present study, all time-to-event endpoints presented here were calculated from the date of the first induction course with R-CHOP, R-CVP or R-FCM. EFS, time-to-next lymphoma treatment (TTNLT) and time-to-next chemotherapy (TTNCT) were defined according to IWG 1999.[25] Specifically, EFS was defined as the interval between the date of induction to the date of first documented disease progression, relapse, initiation of a new anti-lymphoma treatment or death from any cause. EFS was used as an endpoint instead of PFS so that results could be compared to previously published data concerning the prognostic impact of statins in patients with FL.[21] Patients with ongoing responding disease and patients who were lost to follow-up were censored at their last tumor assessment date.

All endpoints were examined in univariate and multivariate analyses. Three different multivariate hazard ratio Cox regression models were used to assess the prognostic value of statin use after adjustment for potentially confounding factors.

A first model included imbalanced prognostic variables between statin patients and non-statin patients with a level of significance set up at 0.1 (as listed in Table 1) except FLIPI score. A second model was built considering the actual FLIPI score instead of its individual components included in the first multivariate model (i.e. age, stage and LDH). Finally, a third model using stepwise regression comprising alternating forward and backward elimination steps was used to find the most parsimonious set of covariates with independent statistical significance among the following: statin use, age, sex, stage, performance status, B symptoms, $ß_2$-microglobulin level, LDH, hemoglobin, bone marrow involvement, induction treatment (continuous variables incorporated into the model were dichotomized as presented in Table 1). Given a proportion of patients did not achieve at least PR to induction and therefore were not randomized to the maintenance/observation phase, maintenance as such could not be included as a variable in the models. Level for entry into the model was set at 0.2 with a stay level of 0.05. Importantly, statin use was forced into the model since it was the variable of interest in the study.

RESULTS

Patient Characteristics at Baseline

Among the 1217 patients enrolled in the PRIMA study, 1135 were included in the present study. Fifteen were excluded because of premature sites closure, 58 because of other lymphoma subtype diagnosis at central histological review and 9 because of consent withdrawal before any treatment (Supplementary Figure S1). Concomitant treatments at registration were available for all patients. Among those 1135 patients, 119 were on statins (10.5%) at diagnosis. Patient characteristics according to statin use are presented in Table 1. Details on statin subtypes for the study population are provided in Supplementary Table S1 and a flowchart according to statin use is presented in Supplementary Figure S1.

The use of any statin was associated with an older age at registration and, partly as a consequence, to a higher FLIPI risk score. Median age for the cohort was 57 years (range, 22-87). Overall 50 of 733 (6.8%) of those age ≤60 used statins, whereas 69 of 402 (17.2%) of those age >60 (P<.001). In the high FLIPI risk category, 14% of patients were on statins compared to 5% in the low risk category (P<.001). Male sex and disseminated disease was also overrepresented among statin users, although not significantly (P=.076 and P=.074 respectively). LDH was more frequently above the upper normal limit (P=.03). No other differences were observed with regards to demographic data, induction treatment or maintenance allocation according to statin use (Table 1 and Supplementary Table S2).

Treatment Toxicities According to Statin Use

The rate of adverse events (AE) between the 2 groups of patients was comparable, in terms of both the incidence of AE of any grade or of grade 3/4. This was observed when analyzing the entire treatment schedule (induction and maintenance) or just the induction phase using R-CHOP or R-CVP regimens (Supplementary Table S3). No difference in terms of specific

cardiovascular AE were observed (Supplementary Table S4). Three deaths potentially due to cardiovascular events were observed for patients without statin (reported in flow chart as cardiorespiratory arrest for one patient and sudden death for two patients) versus none for patients prescribed statins. No difference in premature withdrawal during induction or maintenance was associated with statin use (data not shown). No difference was observed between second cancer incidences between the 2 groups of patients as well (Supplementary Table S5).

Disease Response Rate According to Statin Use

No differences in overall response rate to induction regimen, nor in the quality of the response (CR/CRu *versus* PR *versus* others) was noted (*P*=.52) (Table 2). No further differences were found at the end of the maintenance period (*P*=.67). Subgroup analyses by maintenance arm displayed similar response rates either for patients in the observation arm compared to the rituximab treatment arm (data not shown).

Survival According to Statin Use

Outcome in terms of EFS, TTNLT, TTNCT and OS were similar regardless of the use of statins (*P*=.57, *P*=.85, *P*=.30 and *P*=.43 respectively) in univariate analysis (Fig 1A-D). Importantly, further adjustments for potential confounding factors such as age, sex, stage or LDH in the first multivariate model, sex and FLIPI in the second model or with the use of a forward/backward selection process in the third model did not reveal any potential effect of statin use on EFS or OS (Table 3). No significant effect of statins after further adjustment on maintenance arm was found (data not shown).

DISCUSSION

Biologically, statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase and impair cholesterol synthesis through inhibiting the mevalonate pathway. Such inhibition is thought to have antitumor effect by interfering with lipid cell-membrane formation and protein prenylation. Several oncoproteins such as Ras undergo prenylation, thus farnesyl transferase inhibitors such as statins might impair tumor growth.[26] Accumulating evidence suggests that statins have a potential antitumor effect[16] in addition to their known ability to improve dyslipidemia and reduce cardiovascular morbidity and mortality.[17] Notably, recent studies suggest a reduced cancer-specific mortality after prostate cancer diagnosis among statin users.[16,18] In lymphoma, statins were recently shown to induce apoptosis by promoting ROS generation and Akt, Erk and p38 signalling pathway regulation.[27] Malenda et al also demonstrated that HMG-CoA reductase inhibitors impair glucose uptake in tumor cells possibly by inhibiting a putative cholesterol-binding motif in the juxtamembrane fragment of glucose transporter 1 (GLUT-1).[28]

In patients treated on the PRIMA study there was no significant effect of statins on response rate or survival, even after adjustment for potential confounding factors (especially age and gender), was observed. 10.5% of patients were on statins at enrollment consistent with the estimated one in ten adults in the general population among US adults.[29] Importantly, all patients on this prospective randomized trial presented with stage II, III or IV disease with at least one high tumor burden criterion and required immediate treatment for FL. They were homogeneously treated with a rituximab-containing immuno-chemotherapy regimen at induction (mainly R-CHOP or R-CVP therapy) and, in case of response, were further randomized between observation and rituximab maintenance for 2 years. Those results are in accordance with findings by Ennishi et al. in diffuse large B-cell lymphoma where no

detrimental effect was observed among patients on statins.[30] They also confirm that no treatment interruption is required for statins at lymphoma diagnosis in FL subtype.

In 2009, a report from the Mayo Clinic, Rochester, described a benefit of statin therapy on FL outcome, as assessed by EFS based on a registry data and prospective observation (N=289).[21] Notably, 35% of patients in the present cohort were older than 60 years compared to 54% in the FL subpopulation of the aforementioned study. As a result, at least in part, 21% of patients were on statins compared to 10% in our study. Furthermore, patients had undergone heterogeneous treatments; 40% of patients with FL were in a "watch and wait" approach, and only 41% received a rituximab-containing therapy. Although all patients in this study seem to benefit from statin use, a more significant impact was observed among patients on observation. Hence, the prolonged EFS observed with statin use was consistent across patients treated with rituximab-based regimen or whose initial therapy was observation only but within a thinner range of confidence interval for the later (95% CI 0.14-1.07 versus 0.17-0.84). This therefore raises the question as to whether the known treatment advantage of immunochemotherapy in all patients in the PRIMA study negated any potential advantageous effect of statin use.

As with other subtypes of NHL, the use of statins in patients with FL in the rituximab era appeared safe and was not associated with an inferior outcome as initially suggested by *in vitro* experiments.

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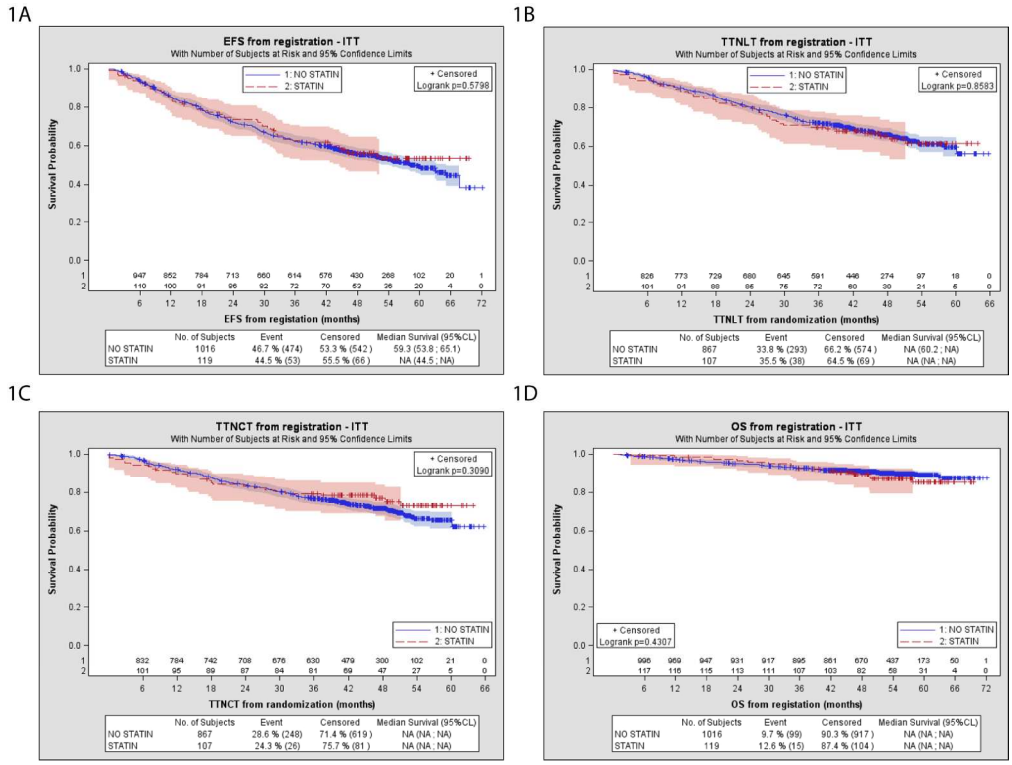

Figure 1. Outcome according to statin use. A. Event-free survival; B. Time to next lymphoma treatment; C. Time to next chemotherapy; D. Overall survival.
193x146mm (300 x 300 DPI)

Table 1. Patient characteristics according to statin use

		N (%)		
	Missing Data (N)	No Statin use (N=1016)	Statin use (N=119)	*P*
Age, yrs	0			**<.001**
≤60		683 (93)	50 (7)	
>60		333 (83)	69 (17)	
Sex	0			.076
Female		497 (91)	48 (9)	
Male		519 (88)	71 (12)	
ECOG	0			.73
0		648 (90)	74 (10)	
1-2		368 (89)	45 (11)	
B symptoms	0			.20
no		685 (89)	87 (11)	
yes		331 (91)	32 (9)	
Stage	0			.074
I-II		103 (94)	6 (6)	
III-IV		913 (89)	113 (11)	
Nodal sites involvement, N	0			.43
≤4		448 (90)	48 (10)	
>4		568 (89)	71 (11)	
Bone marrow involvement	34			.35
no		422 (91)	44 (9)	
yes		564 (89)	71 (11)	
Extranodal sites involvement, N	0			.14
≤2		914 (89)	112 (11)	
>2		102 (94)	7 (6)	
LDH	5			**.030**
≤UNL		684 (91)	68 (9)	
>UNL		328 (87)	50 (13)	
Hemoglobin, g/dL	0			.35
≥12		809 (89)	99 (11)	
<12		207 (91)	20 (9)	
ß2-microglobulin, mg/L	85			.47
≤3		640 (90)	69 (10)	
>3		303 (89)	38 (11)	
FLIPI	2			**.001**
Low (0-1 factor)		227 (95)	12 (5)	
Intermediate (2 factors)		366 (90)	39 (10)	
High (≥3 factors)		422 (86)	67 (14)	
Induction therapy	0			
R-CHOP		756 (90)	84 (10)	.064
R-CVP		219 (87)	34 (13)	
R-FCM		41 (98)	1 (2)	

Abbreviations: yrs, years; ECOG, eastern cooperative oncology group; LDH, lactate dehydrogenase; UNL, upper normal limit; FLIPI, follicular lymphoma prognostic index); R-CHOP, rituximab cyclophosphamide doxorubicin vincristine prednisone; R-CVP, rituximab cyclophosphamide vincristine prednisone; R-FCM, rituximab fludarabine cyclophosphamide and mitoxantrone.

Table 2. Adverse events during treatment (induction and maintenance) or induction only according to statin use

	N (%)		
	No Statin use (N=1016)	Statin use (N=119)	*P*
At least one AE during treatment			
No	10 (1.0)	1 (1.9)	.87
Yes	1006 (99.0)	118 (99.2)	
Intensity during treatment[1]			
Grade 1, 2	190 (18.7)	27 (22.7)	.18
Grade 3, 4	796 (78.3)	89 (74.8)	
At least one AE during induction			
No	10 (1.0)	2 (1.7)	.48
Yes	1006 (99.0)	117 (98.3)	
Intensity during induction[1]			
Grade 1, 2	222 (21.9)	31 (26.1)	.24
Grade 3, 4	772 (76.0)	85 (71.4)	

Abbreviations: AE, adverse event.

[1]*Sum of percents might not equal 100 since unknown grade and grade 5 AE are not taken into account.*

Table 3. Multivariate Cox analysis models

	EFS			OS		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Model 1[1]						
Age, yrs						
>60 (*v* ≤60)	0.99	0.82-1.18	.91	1.91	1.31-2.78	<.001
Sex						
Male (*v* female)	1.29	1.08-1.54	.003	1.51	1.03-2.21	.032
Stage						
III-IV (*v* I-II)	1.64	1.16-2.32	.004	2.10	0.85-5.15	.10
LDH						
>UNL (*v* ≤UNL)	1.37	1.15-1.63	<.001	2.24	1.54-3.25	<.001
Statin use						
Yes (*v* no)	**0.85**	**0.63-1.14**	**.29**	**0.93**	**0.53-1.62**	**.81**
Model 2[2]						
Sex						
Male (*v* female)	1.35	1.13-1.61	<.001	1.47	1.01-2.17	.044
FLIPI						
(high *v* low)	1.97	1.54-2.52	<.001	4.78	2.30-9.94	<.001
(Intermediate *v* low)	1.32	1.02-1.72	.034	2.48	1.14-5.39	.020
Statin use						
Yes (*v* no)	**0.81**	**0.61-1.08**	**0.16**	**1.04**	**0.60-1.80**	**0.87**
Model 3[3]						
Age[4]						
>60 (*v* ≤60)	-	-	-	1.93	1.28-2.90	.001
Sex						
Male (*v* female)	1.39	1.15-1.67	<.001	1.82	1.20-2.78	.005
Bone marrow involvement[5]						
Yes (*v* no)	1.43	1.17-1.75	<.001	-	-	-
LDH						
>UNL (*v* ≤UNL)	1.23	1.02-1.50	.027	1.95	1.30-2.92	.001
Hemoglobin, g/dL						
<12 (*v* ≥12)	1.62	1.29-2.03	<.001	2.46	1.57-3.84	<.001
ß2-microglobulin, mg/L						
≥3 (v <3)	1.55	1.27-1.89	<.001	1.66	1.08-2.54	.020
Induction arm						
R-CVP (*v* R-CHOP)	1.40	1.13-1.72	.001	1.57	1.00-2.45	.045
R-FCM (v R-CHOP)	1.00	0.61-1.64	.97	4.70	2.44-9.03	<.001
Statin use						
Yes (*v* no)	**0.98**	**0.72-1.32**	**.91**	**1.17**	**0.65-2.09**	**.58**

Abbreviations: yrs, years; LDH, lactate dehydrogenase; UNL, upper normal limit; FLIPI, follicular lymphoma prognostic index); EFS, event-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

[1]imbalanced parameters between patients on or off statin use (with a level set up at P<.1) were incorporated into the model. The model is based on n=1130 patients for both EFS (523 events and 607 censored data) and OS (113 events and 1017 censored data).

[2]FLIPI individual parameters were replaced by the FLIPI composite score. The model is based on n=1133 patients for both EFS (526 events and 607 censored data) and OS (114 events and 1019 censored data).

[3]a stepwise regression model based on baseline population characteristic and treatment induction was performed with statin use forced into the model. The model is based on n=1018 patients for both EFS (472 events and 546 censored data) and OS (101 events and 917 censored data).

[4]Age was retained in the final stepwise regression model for OS but not EFS.

[5]Bone marrow involvement was retained in the final stepwise regression model for EFS but not OS.