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LETTERS

Statins in lymphangioleiomyomatosis: a word of caution

To the Editors:

Lymphangioleiomyomatosis (LAM) is a rare progressive cystic lung disease affecting primarily females, characterised by the proliferation of neoplastic LAM cells with mutations in the *tuberous sclerosis complex* (*TSC*)1 or *TSC*2 genes. There is no proven therapy for LAM, but results of studies with sirolimus, an inhibitor of the mammalian target of rapamycin (mTOR), have been promising [1]. Motivated by the finding [2] that *in vitro*, statins, which inhibit 3-hydroxy-3-methyl-glutary-coenzyme-A (HMG-CoA) reductase, inhibited the growth of *TSC*2$^{-/-}$ cells, we evaluated the effects of statins on the decline of lung function in 335 patients with LAM.

METHODS

We conducted a retrospective chart review on 504 patients with LAM referred to the National Institutes of Health since 1996, and enrolled in the National Heart, Lung, and Blood Institute (NHLBI) protocol 95-H-0186, approved by the NHLBI Institutional Review Board. All patients gave informed consent before enrollment. Patients were excluded if they were: 1) recipients of lung or kidney transplant; 2) receiving off-label sirolimus, or enrolled in the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus trial, or taking another mTOR inhibitor; 3) taking doxycycline [3]; 4) not followed long enough to calculate rates of decline in lung function; or 5) taking statins for an unknown length of time. Complete data for analysis were available for 335 patients. Univariate and multivariate analysis were conducted, comparing LAM patients receiving statins with the general LAM patient population.

In addition, we matched LAM patients receiving statins to LAM patient controls for variables known to affect decline of pulmonary function in LAM; *i.e.* age, number of years of follow-up, initial % predicted diffusion capacity of the lung for carbon monoxide ($D_{L,CO}$) and forced expiatory volume in 1 s (FEV_1) [4]. Analyses were performed using SAS v9.0 (SAS Institute Inc., Cary, NC, USA).

FINDINGS

Univariate analysis comparing 42 LAM patients taking statins with 293 LAM patients not on statins showed that LAM patients on statins were significantly older, had shorter follow-up time, lower initial $D_{L,CO}$ %, and a lower yearly rate of decline in FEV_1 % pred (table 1). The multivariate analysis, adjusting for age, showed that yearly rates of decline in FEV_1 % pred were not significantly different in the two groups (p=0.718).

Of the 42 patients who were taking statins, we were able to match 37 patients to LAM patient controls. LAM patients receiving statins had lower minimum low density lipoprotein cholesterol levels than their matched controls, consistent with the statin inhibition of HMG-CoA reductase. Patients on statins had a statistically significant greater yearly decline in $D_{L,CO}$ % pred with a mean difference of -3.7% (95% confidence interval -6.6– -0.7; p=0.016; table 2).

TABLE 1 Baseline characteristics and lung function decline of lymphangioleiomyomatosis patients treated or not with statins

	Statin[#]	No statin[¶]	p-value[+]
Age yrs	53.1±1.09	41.2±0.54	<0.001
Follow-up yrs	2.5±0.29	4.3±0.17	<0.001
Initial FEV_1 % pred	72.3±3.84	79.1±1.48	0.086
Initial $D_{L,CO}$ % pred	65.7±3.40	77.4±1.51	0.003
Yearly change in FEV_1 % pred	-0.4±1.06	-2.4±0.33	0.039[§]
Yearly change in $D_{L,CO}$ % pred	-3.8±0.97	-3.2±0.34	0.549

Data are presented as mean± SE, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; % pred: % predicted; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide. [#]: n=42; [¶]: n=293; [+]: unadjusted; [§]: statin was not a significant predictor of FEV_1 % rate after adjusting for age (p=0.718).

DISCUSSION

In addition to the beneficial effects of statins on lowering cholesterol levels and in the prevention of cardiovascular diseases, statin therapy has been advocated or is currently in clinical trials for a variety of lung diseases (*e.g.* pulmonary hypertension, sarcoidosis). However, a recent report details cases of statin-induced interstitial lung diseases [5]. Moreover, to date, no therapeutic success has been observed with statins in *in vivo* studies of TSC disease. Furthermore, statin treatment did not decrease cystadenomas size in *TSC*$^{+/-}$ mice [6]. There was no correlation between statin use and angiomyolipoma response to sirolimus in patients with TSC or sporadic LAM [1].

In the current retrospective study, we found that LAM patients on statins had a significantly greater yearly rate of decline of $D_{L,CO}$ % pred than their matched controls. LAM patient controls had a relatively stable $D_{L,CO}$ over the follow-up period, which confirms earlier findings that rates of decline in lung function are lower in older post-menopausal females than in younger patients [4]. Two major limitations of the present study are; first, the small sample size, and secondly, as is inherent to all retrospective studies, the difficulty in establishing causality.

TABLE 2 Differences of mean of baseline characteristics, yearly decline in lung function and cholesterol levels in 37 lymphangioleiomyomatosis (LAM) patients receiving statins and 37 matched[#] LAM patient controls not receiving statins

	Statin	No statin	Mean difference	95% CI	p-value[¶]
Age yrs	52.2±1.1	51.6±1.2	0.5	-1.1–2.1	0.498
Follow-up yrs	2.5±0.3	3.0±0.3	0.2	-0.4–0.8	0.523
Initial FEV_1 % pred	72.6±4.7	75.0±4.5	-2.4	-14.4–9.6	0.687
Initial $D_{L,CO}$ % pred	68.1±4.0	72.7±3.5	-4.6	-15.4–6.2	0.392
Yearly change in FEV_1 % pred	-1.2±0.8	0.7±1.0	-1.9	-4.4–0.6	0.128
Yearly change in $D_{L,CO}$ % pred	-3.6±1.0	0.13±1.1	-3.7	-6.6– -0.7	0.016
Minimum cholesterol levels[+] mg·dL^{-1}					
Cholesterol	163.9±5.5	182±6.3	-17.5	-36.9–1.8	0.074
HDL	54.5±2.5	55.1±2.2	0.4	-7.5–8.2	0.928
LDL	96.1±4.4	113.3±5.3	-17.1	-33.2– -1.0	0.038
Triglycerides	97.8±8.3	90.1±8.0	4.6	-20.6–29.7	0.713

Data are presented as mean±SE, unless otherwise stated. CI: confidence interval; FEV1: forced expiratory volume in 1 s; % pred: % predicted; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; HDL: high-density lipoprotein; LDL: low-density lipoprotein. [#]: matched for age, years of follow-up, initial $D_{L,CO}$ % and FEV_1; [¶]: based on the paired t-test, some comparisons of lipids are based on fewer pairs (n=32 or 33) due to missing values; [+]: lowest measured cholesterol over the follow-up period.

The mechanism through which statins might increase the decline of lung function in LAM is unknown. However, elevated vascular endothelial growth factor (VEGF)-D levels were found in serum from LAM patients, and statins were reported to upregulate VEGF-D under normoxic conditions [7]. Higher levels of VEGF-D could enhance lymphangiogenesis in LAM nodules that contain lymphatic structures, and line lung cysts, thereby affecting $D_{L,CO}$ and not FEV_1.

The decision to start patients with LAM on statins should be carefully weighed against the possibility of decline in lung function, and should probably not be done except as medically indicated or as part of a placebo-controlled trial.

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