Statin Use Is Associated With Protection Against Acute Cholangitis in Patients With Primary Sclerosing Cholangitis: A Multicenter Retrospective Cohort Study

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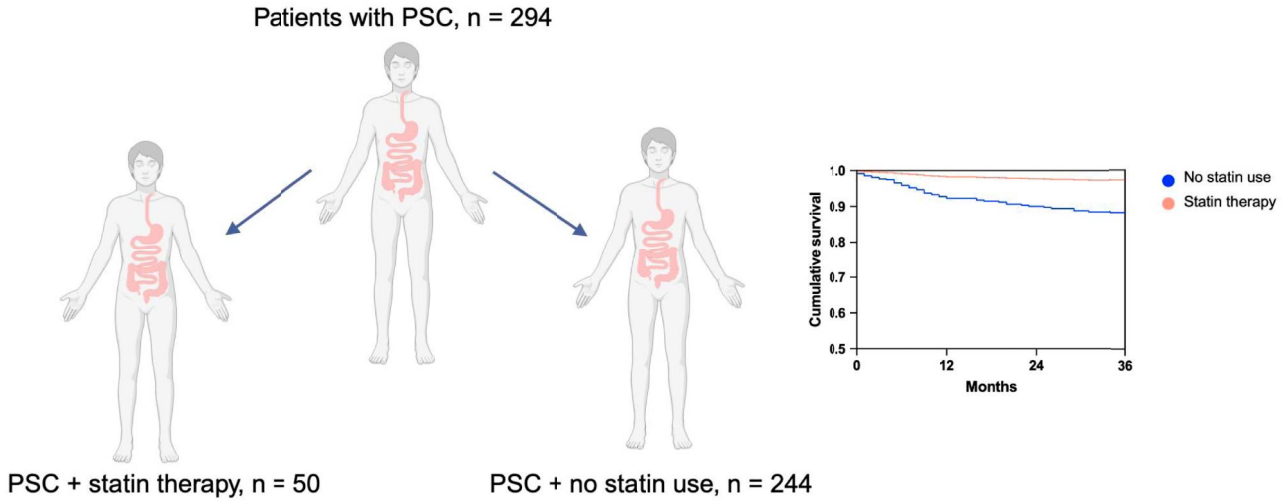
INTRODUCTION: **Patients with primary sclerosing cholangitis (PSC) are at increased risk of acute cholangitis. The epidemiological risks of cholangitis are poorly studied despite the high morbidity associated with this infection. The aim of this study was to understand the impact of statins on acute cholangitis in PSC.**

METHODS: **This multicenter, retrospective cohort study assessed data from 294 patients with PSC at Stanford Medical Center, Baylor Medical Center, and Valley Medical Center. Clinical factors associated with the development of cholangitis were identified using multivariable Cox regression.**

Statin therapy is associated with reduced risk of cholangitis in PSC



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RESULTS: **The patients were predominantly male (68.7%) with a median age at enrollment of 48 years (interquartile range [IQR]: 31.0–60.8). Fifty patients (17.0%) were prescribed statins. The median follow-up time was 6 years (IQR: 2.0–12.0), in which 29.6% (n = 87) developed cholangitis. In multivariable analysis, statins were associated with an 81% reduction in cholangitis (HR 0.19, 95% confidence interval 0.03–0.64). Statins were associated with a lower adjusted incidence of cholangitis at 36 months compared with patients not on statin therapy (incidence of 2.8% vs 12.2%, $P < 0.001$). Statins were also associated with increased time-to-stricture ($P = 0.004$), an outcome known to be associated with PSC complications.**

DISCUSSION: **Statin therapy is associated with reduced risk of cholangitis in PSC, possibly by delaying the time to develop dominant or high-grade strictures. In patients with PSC, use of statin therapy may be a beneficial modality to prevent the development of cholangitis and warrants further investigation.**

KEYWORDS: primary sclerosing cholangitis; acute cholangitis; statins; dominant stricture

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/B271

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BILIARY

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a progressive, cholestatic liver disease that is characterized by injury to cholangiocytes, resulting in biliary inflammation and fibrosis. The median age for diagnosis of PSC is approximately 42 years (1–3). Sixty to 80% of patients with PSC have concomitant inflammatory bowel disease (IBD) (4).

PSC is characterized by beading and stricture formation in the bile ducts, and up to 20% of patients have a dominant stricture at the time of diagnosis (5). Dominant strictures can predispose patients to episodes of bacterial cholangitis (5,6). Among patients undergoing scheduled dilation of dominant strictures vs on-demand endoscopic retrograde cholangiopancreatography (ERCP), the patients undergoing scheduled dilation had increased transplant-free survival (7).

Acute bacterial cholangitis is one of the key adverse sequelae of PSC, affecting approximately 30%–40% of patients (8). The,ortality rate related to an episode of bacterial cholangitis is approximately 5% (9). Furthermore, a subgroup of patients with PSC develops recurrent acute bacterial cholangitis, which is considered an indication for liver transplantation (10).

Despite the clinical burden of cholangitis in PSC, to date, minimal investigation has been conducted in this area (6). Besides liver transplantation, there are no approved disease-modifying treatments available for PSC. Statin therapy has been associated with lower all-cause mortality and lower risk of liver transplantation in patients with PSC (11). A Mendelian randomization study showed a causal relationship between 3-hydroxymethylglutaryl-coenzyme A reductase and PSC risk, suggesting statins would be of therapeutic benefit in PSC (12). In preclinical models of chronic liver disease, statin therapy has been shown to reduce paracrine activation of hepatic stellate cell and attenuate oxidative stress, thereby reducing hepatic fibrosis (13). In preclinical infection models, statin therapy has been shown to attenuate infection through modulation of cytokines, T-cell signaling, and endothelial nitric oxide production (14,15). In clinical studies, patients with chronic liver disease without cirrhosis who were prescribed statins had decreased progression to cirrhosis. In compensated cirrhosis, use of statins has been associated with decreased progression to decompensated cirrhosis and death (16,17). Furthermore, in clinical studies, statin use has been shown to attenuate the risk of infection in patients with cirrhosis (18,19). Based on this body of literature, a randomized clinical trial of simvastatin in PSC was announced, although the results are not anticipated until 2028 (20). However, to date, the impact of statin therapy on cholangitis in PSC is entirely unknown. We hypothesized that statins reduced cholangitis by lowering the risk of stricture formation through modulation of inflammatory and fibrotic pathways.

METHODS

Patient population

The study was a multicenter, retrospective cohort study in which we examined risk factors for the development of acute cholangitis in patients with PSC. Considering the diagnostic complexities associated with acute cholangitis in patients with PSC, we defined an episode of cholangitis as any documentation in the electronic medical record of hospitalization for IV antibiotics, along with physician documentation (during the hospitalization), stating that a patient had an episode of bacterial cholangitis, consistent with previous studies defining cholangitis in patients with PSC (8,21).

We included any patient aged older than 18 years with an established diagnosis of PSC, defined by American College of Gastroenterology guidelines (22). We excluded any patient with secondary sclerosing cholangitis or patients who developed PSC only after liver transplantation. We did not include episodes of cholangitis from patients who developed cholangitis within 2 weeks after ERCP. If a patient had multiple episodes, data were analyzed from the index episode.

Data collection

We retrospectively collected data from patients diagnosed with PSC at Stanford Medical Center, Baylor Medical Center, and Valley Medical Center, a county healthcare system. Patients were screened for a diagnosis of PSC by *the International Classification of Diseases, Tenth Revision, Clinical Modification* code (K83.01) and were enrolled if they met American College of Gastroenterology diagnostic criteria (22). All cases were manually reviewed by the investigators to confirm the diagnosis, and patients were followed from the date of PSC diagnosis until study completion.

Demographic data, including patient age, sex, and race/ethnicity, were collected. To calculate Mayo PSC risk score and Model for End Stage Liver Disease sodium (for patients with

cirrhosis), laboratory data were collected at the time of PSC diagnosis. Clinical data including presence and type of hepatic decompensation, presence of dominant stricture, IBD phenotype, medications relevant to PSC (statins, bile acid sequestrant [BAS], ursodiol, and oral vancomycin), and comorbid medical conditions were collected. All patients included underwent magnetic resonance cholangiopancreatography on an annual basis. The presence of high-grade stricture by magnetic resonance cholangiopancreatography or dominant stricture by ERCP was determined. For ERCP, a dominant stricture was defined per previous definitions (23).

Medications and all other covariates were considered a risk factor of acute cholangitis if they were present before the index episode of acute cholangitis. Dates of therapy initiation and cessation, if applicable, were recorded. Patients with acute cholangitis were followed from the date of PSC diagnosis through their first episode of cholangitis; all other patients were followed from the date of PSC diagnosis through death or study completion.

Statistical methods

Descriptive statistics were applied to the demographic and clinical characteristics of patients with and without statin use. The primary outcome was the development of acute cholangitis, and no minimum time of exposure was required for statin therapy. Given the uncertainty regarding the optimal latency time window, we performed secondary analysis with exposure lag of 1 year. We also performed secondary analysis to assess the impact of duration of statin use on the development of acute cholangitis. We also assessed the impact of statin therapy in patients aged younger than 50 years. We performed sensitivity analyses to understand the impact of cirrhosis and hepatic decompensation on the risk of acute cholangitis.

Using a forward, stepwise variable-selection process based on Akaike Information Criterion, risk factors for cholangitis were included in the multivariable Cox regression model. In addition, we also included clinical factors previously shown to be associated with PSC severity, including patient age, Mayo PSC risk score, and Charlson Comorbidity Index (24–26). T_0 was defined as the date of diagnosis of PSC. For patients prescribed statins, time from T_0 until prescription for statin was classified as untreated and was classified as treated after prescription to avoid misclassification or exclusion of immortal time. In the Cox regression model, dominant or high-grade stricture and statin use were time-dependent covariates, and all other variables were fixed. Time to the development of cholangitis and strictures was evaluated.

Data analysis was performed in R (Version 4.0; R Foundation for Statistical Computing, Vienna, Austria), and data visualization was performed in GraphPad Prism (Version 8; GraphPad Software, San Diego, California).

RESULTS

Baseline clinical characteristics

The study population consisted of 294 patients with PSC enrolled across 3 sites. At least one episode of cholangitis occurred in 29.6% (n = 87) of patients. The baseline clinical characteristics of patients included in the cohort are presented in Table 1. The median age for this cohort was 48.0 years (IQR, 31.0–60.8 years), and there was expected male predominance (68.7%). The cohort was 57.8% White, 8.5% Black, 7.8% Asian, 6.8% Hispanic, and 18.4% other. The median duration of PSC was 6 years (IQR, 2.0–10.0 years). Sixty 5 percent of the cohort had comorbid IBD. Approximately 20% of the cohort had hepatic decompensation, and the median MELD at the start of follow-up was approximately 10.

Table 1. Demographic and clinical characteristics, median (IQR), or N (%)

Characteristic	All patients (n = 294)
Median age (IQR)	48.0 (31.0–60.8)
Male (%)	202 (68.7%)
Race and ethnicity (%)	
White	170 (57.8%)
Black	25 (8.5%)
Asian	23 (7.8%)
Hispanic	20 (6.8%)
Other	54 (18.4%)
Median duration of PSC (IQR)	6.0 (2.0–10.0)
Cirrhosis (%)	131 (44.6%)
MELD-Na	9.6 (7.3–14.9)
Compensated cirrhosis	59 (20.1%)
Decompensated cirrhosis	72 (24.5%)
Variceal bleeding	28 (9.5%)
Ascites	58 (19.7%)
Hepatic encephalopathy	28 (9.5%)
Spontaneous bacterial peritonitis	9 (3.1%)
Hepatorenal syndrome	2 (0.7%)
IBD (%)	191 (65.0%)
Ulcerative colitis	156 (53.1%)
Crohn's disease	35 (11.9%)
Statin therapy	50 (17.0%)
Lipophilic statin	35 (11.9%)
Hydrophilic statin	15 (5.1%)
Bile acid sequestrants	35 (11.9%)
Ursodiol	167 (56.8%)
Oral vancomycin	44 (15.0%)
Mayo PSC risk score	0.5 (–0.5 to 1.6)
Charlson Comorbidity Index	1.2 (0.4–2.2)
Platelets (U/L)	240 (117–330)
Total bilirubin (mg/dL)	0.8 (0.5–1.8)
Gamma glutamyl transferase (U/L)	269 (102–476)
Total cholesterol (mg/dL)	181.0 (151.0–216.0)
High-density lipoprotein (mg/dL)	51.0 (41.0–73.0)
Low-density lipoprotein (mg/dL)	105.0 (82.0–132.0)
Triglycerides (mg/dL)	94.5 (68.0–140.0)

Table 1 shows the baseline demographic and clinical characteristics of all patients in the cohort. MELD-Na was calculated only for patients with cirrhosis. IBD, inflammatory bowel disease; MELD-Na, Model for End-Stage Liver Disease sodium; PSC, primary sclerosing cholangitis.

Effect of statin therapy on cholangitis

Characteristics at start of therapy were compared between patients prescribed statin therapy and those who were not (Table 2). The median age for patients prescribed statins was more than those who were not (59.5 vs 42.0, $P < 0.001$). They were less likely to be prescribed per os vancomycin. Patients prescribed statins were more likely to have a Mayo PSC score of one or 2 vs a score of zero (76.0% vs 59.4%, $P = 0.001$). Patients on statin therapy had an increased Charlson Comorbidity Index compared with patients who were not prescribed statins (3.0 vs 1.0, $P < 0.001$). Patients prescribed statins were less likely to have comorbid IBD, but incorporation of IBD and biologic therapy as risk factors in the multivariable regression did not alter the protective association of statin therapy. Patients prescribed statins were equally likely to have dominant or high-grade strictures at baseline but were less likely to develop new strictures after being prescribed statin therapy ($P = 0.009$). Among the subgroup of patients with a stricture, use of statin therapy was still associated with decreased risk of cholangitis ($P = 0.039$). The indications for statin therapy are detailed in Supplementary Digital Content (see Supplementary Table 1, http://links.lww.com/CTG/B271).

Univariate and multivariable Cox regression models assessing clinical risk factors for developing acute cholangitis in patients with PSC are presented in Table 3. Statin therapy was associated with an 81% reduction (hazard ratio [HR] 0.19; 95% confidence interval [CI] 0.03–0.64) in the risk of developing cholangitis. Using a lag time of 1 year, statins were associated with a similar 78% reduction (HR 0.22; 95% CI 0.10–0.46) in the risk of developing cholangitis. BAS were associated with a 198% increase in risk (HR 2.98; 95% CI 1.77–4.87). Only 6 of 50 patients (12.0%) on statin therapy developed cholangitis, compared with 81 of 244 patients (33.2%) not on statin therapy ($P < 0.001$). Total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides before and during treatment were not associated with increased or decreased risk of cholangitis. We evaluated for interaction between low-density lipoprotein, high-density lipoprotein, triglycerides, and statin use (given hyperlipidemia was the most common indication for statin therapy) on the risk of cholangitis and observed no significant effect.

Statin therapy was associated with benefit in patients with and without cirrhosis and was equally likely to be prescribed to both groups of patients (odds ratio 0.86, 95% CI 0.45–1.63). Liver-related clinical factors associated with increased risk of developing cholangitis included hepatic decompensation (HR 2.13; 95% CI 1.28–3.56) and presence of stricture (HR 2.95; 95% CI 1.84–4.81). We examined the effect of age on response to statin therapy. Statins were similarly effective in patients less than or equal to the age of 50 years (HR 0.07, 95% CI 0.02–0.72). In addition, the effect of duration of therapy was analyzed by comparing predefined categories of statin use (1–3 years, and ≥3 years). Patients with 1–3 years of statin therapy had decreased risk of cholangitis (HR 0.13, 95% CI 0.02–0.78). Patients with more than or equal to 3 years of statin therapy had decreased risk of cholangitis as well (HR 0.09, 95% CI 0.01–0.66).

Table 2. Demographic and clinical characteristics of patients on and off statin therapy, median (IQR), or N (%)

Characteristic	Statin therapy (n = 50)	No statin therapy (n = 244)	*P* value
Median age (IQR)	59.5 (46.8–70.5)	42.0 (28.5–58.0)	<0.001
Male (%)	34 (68.0%)	75 (61.5%)	0.554
Race and ethnicity			
White	27 (54.0%)	146 (59.8%)	0.837
Black	7 (14.0%)	18 (7.4%)	0.077
Asian	5 (10.0%)	17 (7.0%)	0.348
Hispanic	3 (6.0%)	17 (7.0%)	0.929
Other	8 (16.0%)	46 (18.9%)	0.844
Median duration of PSC (IQR)	5.0 (3.0–11.0)	7.0 (2.0–12.0)	0.970
Cirrhosis (%)	19 (38.0%)	111 (44.8%)	0.651
MELD-Na	12.3 (8.6–12.9)	11.3 (8.8–18.2)	0.159
Compensated cirrhosis	14 (28.0%)	49 (20.1%)	0.438
Decompensated cirrhosis	5 (10.0%)	62 (25.4%)	0.023
Dominant or high-grade stricture			
Before statin therapy	17 (34.0%)	92 (37.1%)	0.852
New after statin therapy	6 (12.0%)		
Ursodiol	28 (56.0%)	140 (56.5%)	0.984
Oral vancomycin	2 (4.3%)	41 (16.5%)	0.001
Mayo PSC score (1/2 vs 0)	38 (76.0%)	145 (59.4%)	0.001
Charlson Comorbidity Index	3.0 (1.0–4.0)	1.0 (0.0–2.0)	<0.001

Table 2 compares the demographic and clinical characteristics of patients who are prescribed statin therapy to those who were not. Continuous variables were compared by the Wilcoxon rank-sum test, and categorical variables were compared by the χ^2 or Fisher exact test as appropriate.
IBD, inflammatory bowel disease; MELD-Na, Model for End-Stage Liver Disease sodium; PSC, primary sclerosing cholangitis.

Table 3. Univariate and multivariable cox regression analysis of risk factors for acute cholangitis in patients with PSC

	Univariate HR (95% CI)	*P* value	Multivariable HR (95% CI)	*P* value
Age	1.22 (0.98–1.29)	0.075	1.06 (0.89–1.27)	0.502
Male	0.78 (0.45–1.36)	0.395		
White	Reference	n/a		
Black	1.81 (0.77–4.26)	0.172		
Asian	0.49 (0.16–1.49)	0.209		
Hispanic	0.99 (0.36–2.71)	0.983		
Other	0.81 (0.41–1.61)	0.544		
IBD	1.26 (0.73–2.17)	0.419		
Crohn's disease	1.49 (0.71–3.10)	0.300		
Ulcerative colitis	1.22 (0.74–2.01)	0.453		
Cirrhosis	2.78 (1.66–4.67)	<0.001		
Compensated cirrhosis	0.76 (0.39–1.47)	0.321		
Decompensated cirrhosis	4.21 (2.41–7.34)	<0.001	2.13 (1.28–3.56)	0.003
MELD-Na	2.28 (0.93–5.74)	0.074		
Dominant or high-grade stricture	5.56 (3.23–9.55)	<0.001	2.95 (1.84–4.81)	<0.001
Ursodiol	0.87 (0.71–1.12)	0.367		
Statin therapy	0.27 (0.11–0.67)	0.005	0.19 (0.03–0.64)	0.009
Bile acid sequestrants	4.32 (1.97–9.45)	<0.001	2.98 (1.77–4.87)	<0.001
PO vancomycin	0.51 (0.23–1.13)	0.090		
Mayo PSC risk score	2.81 (2.07–7.42)	<0.001	1.42 (0.75–2.79)	0.286
Charlson Comorbidity Index	2.35 (1.22–4.62)	0.010	0.88 (0.46–1.28)	0.231
Total cholesterol (mg/dL)	1.00 (0.99–1.01)	0.960		
Low-density lipoprotein (mg/dL)	1.00 (0.98–1.01)	0.360		
High-density lipoprotein (mg/dL)	0.98 (0.97–1.00)	0.170		
Triglycerides (mg/dL)	1.02 (0.99–1.00)	0.340		

Eight risk factors of cholangitis in the univariate analysis were incorporated into a multivariable Cox regression model that was controlled for age, severity of PSC, and comorbidities. Each hazard ratio is presented with its 95% CI. For age, hazard ratios are calculated on a per 10-year basis.
CI, confidence interval; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; PO, per os; MELD-Na, Model for End Stage Liver Disease sodium.

Effect of demographics and comorbid illness on cholangitis

Age, race, ethnicity, and comorbid IBD were not associated with of increased hazard of cholangitis. Univariate analysis showed that increased severity of PSC as measured by Mayo PSC risk score was associated with increased risk of cholangitis, but this was not shown in multivariable analysis. Neither ursodiol nor oral vancomycin increased or decreased the chance of cholangitis.

We performed sensitivity analysis to understand the impact of the clinical risk factors in the subgroup of patients with cirrhosis, both with and without hepatic decompensation; we also performed sensitivity analysis for patients with cirrhosis, but no evidence of hepatic decompensation. In both analyses, there were no significant differences in the risk factors of acute cholangitis compared with the primary analysis (see Supplementary Tables 2 and 3, http://links.lww.com/CTG/B271).

Risk of cholangitis over time

Statin therapy increased time to cholangitis (Figure 1, $P = 0.002$). Among those on statin therapy (n = 50), adjusted incidence of cholangitis was 2.8% by 3 years, and in contrast, for patients not on statin therapy, the adjusted incidence was 12.2% by 3 years.

Given the data showing increased risk of cholangitis among patients with dominant strictures along with increase transplant-free survival among patients who went scheduled dilation (instead of on-demand dilation), we evaluated the impact of statins on the development of strictures (6,7). Time to stricture was longer in patients prescribed statin therapy ($P = 0.004$). Incidence of dominant or high-grade stricture in patients prescribed statin therapy was 5.1% by 3 years. By contrast, the incidence was 15.8% by 3 years in patients without statin therapy, which tracks well with the proportion of patients not receiving statins who developed cholangitis.

DISCUSSION

Acute cholangitis is a significant complication of PSC that is associated with high morbidity but remains understudied. This is the first study showing that statin therapy is associated with decreased likelihood of developing cholangitis in PSC. We also show that statin therapy is associated with a longer time to develop strictures, suggesting a novel plausible mechanism by which statin therapy may provide protection against cholangitis. Our cohort is racially and ethnically diverse, in contrast to many other

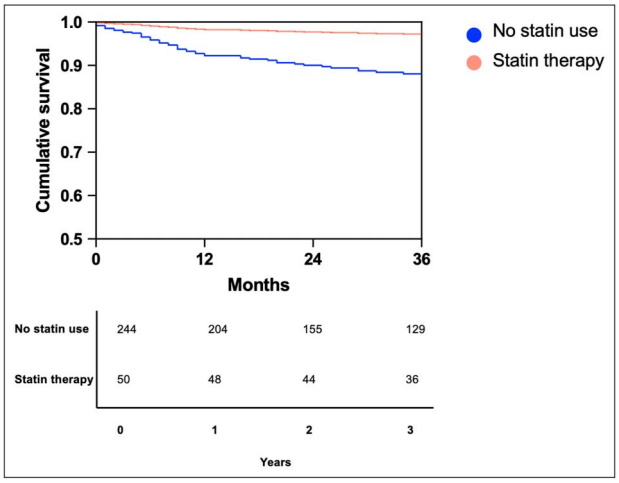

Figure 1. Cumulative adjusted survival curve for patients on and off statin therapy.

studies of PSC. It is notable that this association is present even though patients prescribed statins were on average older, had increased severity of PSC as measured by Mayo PSC score, and had increased medical comorbidities.

To date, there is no proven disease modifying medical therapy for PSC. Statins are a safe, widely prescribed class of medications. In this study, we show the potential for statins to be used as a disease-modifying drug though this finding will require validation in randomized, controlled clinical studies. Existing preclinical data suggest that statins have a beneficial effect in murine models of infection through modulation of the immune response, including reductions in mevalonate and farnesyl pyrophosphate, which play crucial roles in intracellular signaling; these findings have been corroborated in clinical studies (13,14,18,19). These studies provide a plausible biologic basis for the protective effect of statins in cholangitis. In addition, our work adds to the literature on statins in PSC, building on a prior study, which showed that statin therapy was associated with increased transplant-free survival (11). In a prospective German cohort of patients with PSC, patients who underwent scheduled dilation of dominant strictures had increased transplant-free survival (7). Taken together with our analysis for dominant and high-grade strictures, this suggests a mechanism by which statin therapy may provide overall benefit in PSC, potentially for protection against cholangitis and liver transplant-free survival.

Short-term (1–3 years) and long-term (≥3 years) statin therapy reduced the likelihood of cholangitis. Statin therapy was associated with benefit across age groups. We performed secondary analysis to understand the impact of age, as most patients with PSC are diagnosed in their 40s (3,27). Even when restricted to patients aged younger than 50 years, statin therapy still had a strong protective effect. Given that hyperlipidemia/primary prevention was the most common indication for patients prescribed statin therapy in this study, we evaluated for interaction between lipid levels and cholangitis and found no association. Statins were associated with reduced risk of cholangitis in patients with and without cirrhosis and notably were prescribed equally to both groups of patients. Patients with hepatic decompensation of any type were more likely to have an episode of cholangitis. This likely reflects the predisposition toward infections because of a relatively immunosuppressed state, in addition to the possibility of cholangitis, resulting in hepatic decompensation. However, patients with hepatic decompensation were less likely to be prescribed statin therapy than those without (odds ratio 0.13, 95% CI 0.06–0.29), likely reflecting the concerns about the safety of statins in this group. Only 5 patients with decompensated cirrhosis were prescribed statins, and all of these patients had a MELD less than 15.

Patients prescribed statin therapy were less likely to have comorbid IBD but had higher PSC disease severity. Notably, incorporation of IBD status was not associated with cholangitis. These findings are consistent with prior literature, which showed that PSC-IBD and isolated PSC had similar risk of cholangitis and other liver-related outcomes (28,29).

BASs are widely prescribed medications for the management of cholestatic pruritus in PSC, and their use was strongly associated with cholangitis, even when excluding patients who had strictures. However, patients prescribed of BAS may have fundamental differences compared with patients without cholestatic itching, so this should be interpreted cautiously.

Our study has some limitations. First, some patients started statin therapy months to years after their diagnosis of PSC, so in these patients, it is possible that the burden of stricturing disease would be advanced compared with baseline burden at the time of diagnosis, leading to selection of sicker patients in the statin arm. However, it is notable that we still show an association with protection, as this would bias toward underestimation of the effect of statin therapy. Furthermore, in the time-to-event analysis for statin therapy, we were mindful of this and took care to avoid misclassification or exclusion of immortal time for patients prescribed statins. Second, hepatic decompensation was associated with increased risk of cholangitis and may have resulted in overestimated effect size for statin therapy as less patients with hepatic decompensation were prescribed statin therapy. However, to address this limitation and the potential for selection bias, we performed subgroup analysis, analyzing patients with and without hepatic decompensation separately, and the association was present in both groups supporting the robustness of our results. We further attempted to control for severity of illness through incorporation of the Charlson Comorbidity Index and PSC risk score in our model. Furthermore, it is possible that patients who survive to an age in which statin therapy is typically prescribed might have biological difference from other patients; however, to address this limitation, we performed analysis evaluating the effect of statin therapy on patients aged younger than 50 years and the protective effect of statins remains. In addition, the retrospective nature of the study makes it impossible to assess compliance with the medications. Finally, there is a risk of misclassification of patients who may have been prescribed a statin from another health system as nonstatin users. However, given the association with protection seen with statin therapy, this would in fact bias against detection of a difference between the 2 groups.

The strengths of the study include the identification of a plausible mechanism for protective effect of statins through time-to-event analyses; this finding will require prospective validation. In addition, our cohort was racially and ethnically diverse population from the United States, in contrast to most studies of PSC, which have a predominantly White population. Furthermore, the study population was derived from multiple centers, increasing the generalizability of the study.

Our study provides a comprehensive overview of the risk factors for the development of cholangitis in patients with PSC. To date, there is no evidence that any medical therapy modifies outcomes in patients with PSC, including episodes of cholangitis,

although over the last decade there is growing evidence that statins are associated with improved outcomes in chronic liver disease by slowing progression of fibrosis through decreased activation of stellate cells (16,17,30,31). Reduced activation of these pathways may explain reduction in the formation of fibrotic biliary strictures with statins. Our study adds to the growing body of literature that shows the protective effect of statin therapy in PSC (11,12).

We have identified, for the first time, a medication that is associated with reduction in acute cholangitis in PSC. We show that treatment with statins delays both time to cholangitis and time to stricture. Identification of a plausible biologic mechanism for the protective effect of statin therapy adds to the strength of our findings. Statin therapy seems to be a notable protective factor in PSC, warranting further study.

Study Highlights

WHAT IS KNOWN

✓ There is growing evidence that statin therapy is associated with improved outcomes in chronic liver disease, including PSC.

WHAT IS NEW HERE

✓ We identified, for the first time, that statin use is associated with 81% reduction in the risk of cholangitis in patients with PSC.

CONFLICTS OF INTEREST

Guarantor of the article: Sidhartha R. Sinha, MD.

Specific author contributions: C.K., G.C., and S.S. designed the study. Data collection was conducted by C.K., T.F., J.R., S.K., S.M., R.L., and A.K. Data analysis and interpretation was performed by C.K., G.C., A.M., P.J., A.A., J.V., A.G., and S.S. C.K., T.F., J.R. and S.M. drafted the article. G.C., R.L., P.J., A.M., A.A., J.V., A.G., and S.S. perform critical revision of the article. All author approved the final version to be published.

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