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ORIGINAL ARTICLE

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Ida Henriksson[a], Ruzan Udumyan[b], Emma Nilsson[c], Kristina Önnerhag[d], Fredrik Rorsman[e], Mårten Werner[f], Hanns-Ulrich Marschall[g], Staffan Wahlin[h], Nils Nyhlin[a] and SweHep

[a]Department of Internal Medicine, Division of Gastroenterology, Örebro University Hospital, Örebro, Sweden; [b]Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Örebro, Sweden; [c]Department of Clinical Sciences, Gastroenterology Division, Skåne University Hospital, Lund, Sweden; [d]Department of Gastroenterology and Hepatology, Skåne University Hospital, Malmö, Sweden; [e]Department of Gastroenterology and Hepatology, Uppsala University Hospital, Uppsala, Sweden; [f]Department of Public Health and Clinical Medicine, Umeå University Hospital, Umeå, Sweden; [g]Sahlgrenska Academy, Institute of Medicine, Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden; [h]Department of Upper GI Diseases, Karolinska University Hospital, Stockholm, Sweden

ABSTRACT

Objectives: Primary biliary cholangitis (PBC) is an autoimmune liver disease that may progress into liver cirrhosis. Ursodeoxycholic acid (UDCA) is known to prevent or delay the disease progression, but little is known about work incapacity in PBC patients. We aimed to compare clinical outcomes (transplantation-free survival; cirrhosis development) and sick leave in patients with PBC with and without UDCA therapy.

Methods: The medical records of 526 patients with PBC diagnosed from 2004 to 2016 were reviewed retrospectively. Sick leave data retrieved from the Swedish Social Insurance Agency were analysed for a sub-cohort of patients and matched controls. Cox regression was used for analysis of clinical outcomes. Logistic and conditional logistic regressions were used for sick leave analysis.

Results: A total of 10.6% of patients died and 3.4% received liver transplantation over a median follow-up time of 5.7 years. UDCA-untreated patients (HR 3.62 (95%CI 2.02–6.49)) and UDCA non-responders (HR 3.78 (95% CI 1.87–7.66)) had higher mortality or transplantation rates than UDCA responders. Patients with PBC had higher odds of sick leave (OR 2.50; 95% CI 1.69–3.70) than matched controls. Untreated patients were more likely to be on sick leave (OR 3.22; 95% CI 1.12–9.25) two years after diagnosis than UDCA responders.

Conclusion: Both untreated patients and UDCA non-responders had lower liver transplantation-free survival rates than UDCA responders. Patients with PBC were more likely to be on sick leave compared to matched controls from the general population.

Introduction

Primary biliary cholangitis (PBC) is a chronic immune-mediated cholestatic liver disease characterized by the destruction and loss of intrahepatic bile ducts. The disease can progress into end-stage liver disease [1]. PBC is the most common autoimmune liver disease and is found worldwide [2]. Incidence and prevalence seem to be rising and are highest in studies from northern Europe and North America [1]. In a recent Swedish nation-wide population-based report the incidence rate in Sweden was 2.6 per 100 000 person-years and the prevalence 34.6 per 100 000 inhabitants [3]. PBC is a predominantly female disease with a female to male ratio ranging from 4:1 to 9:1 [3–5]. The disease is often diagnosed around 60 years of age [1].

Many patients are asymptomatic at diagnosis and a raised serum alkaline phosphatase (ALP) raises the suspicion of PBC.

In symptomatic patients, the most predominant complaints are pruritus and fatigue. Pruritus is reported in 20–70% of patients and tends to fluctuate during the disease course. Fatigue is reported in up to 80% of PBC patients and is associated with depression, inability to work and increased mortality [1]. Fatigue has been shown to lower the quality of life in PBC patients but not to affect employment status [6]. A Finnish study on the ability to work after liver transplantation showed that patients with PBC, compared to patients with other liver diseases, had a lower probability of returning to employment after liver transplantation [7]. Whether or not patients with PBC are more or less on sick leave than the general population is not known.

For almost 30 years, ursodeoxycholic acid (UDCA), at a recommended dose of 13–15 mg/kg/day, has been the standard treatment for PBC. UDCA has been shown to prevent progression toward severe liver disease in most patients, but

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20–40% are non-responders and have a worse prognosis [4,8]. Several dichotomous scores, based on clinical laboratory data, have been developed to identify UDCA non-responders, who may be considered for second-line treatment [9–13]. Other scores assess the risk of death and the need for liver transplantation [8,14]. In the nation-wide Swedish PBC cohort [3], UDCA was prescribed for only 79.9% of PBC patients with response rates of 59–73%, depending on which dichotomous score was used [3]. Patients with PBC had an increased risk of death compared to the general population. It is unclear whether this was related to response to UDCA treatment or not. Several studies have compared UDCA responders to non-responders [15,16], but less is known about UDCA-untreated PBC patients. In a report from Iceland, UDCA-untreated were older and had lower ALP compared to treated [17], while in a British study, UDCA-untreated were the same age at diagnosis but had higher ALP than UDCA non-responders two years after diagnosis [18].

The primary aim of this study was to investigate the association between UDCA treatment and clinical outcomes (liver transplantation-free survival, cirrhosis) in a Swedish cohort of patients with PBC. Secondary aims were to investigate associations between disease-related factors and long-term sickness absence among patients with PBC and to compare sick leave rates between patients with PBC and matched controls from the general population.

Materials and methods

Patients diagnosed with PBC (ICD-10 code K74.3) between January 2004 and December 2016 were identified from all seven university hospitals in Sweden. Only patients fulfilling established diagnostic criteria were included in the study, i.e., alkaline phosphatase (ALP) >1.5 times the upper limit of normal, positive anti-mitochondrial antibodies and/or a liver biopsy consistent with PBC [4,19]. The patients' medical records were reviewed manually. We collected data on year of diagnosis, age at diagnosis, sex, height, weight, autoantibody serology, liver histology and existing symptoms at diagnosis and during follow-up, concurrent autoimmune disease, UDCA treatment and treatment doses. Complications to liver disease were also noted: year of liver transplantation, cirrhosis (diagnosed by liver histology, elastography, radiological exam or physician's clinical judgement) and cirrhosis complications (varices, ascites, encephalopathy or hepatobiliary cancer). Laboratory values were collected at the time of diagnosis, after one year of treatment and at the last follow up.

Response to UDCA treatment was calculated with the dichotomous scores: Paris-1 [9] (main analysis) and Toronto score [13] (sensitivity analysis). Patients were classified as non-responder, responder and response unknown after one year of UDCA treatment. UDCA untreated patients and patients who were treated for less than a year were regarded as untreated.

For transplantation-free survival analysis, patients were followed from the date of PBC diagnosis until the date of death or liver transplant, date of emigration or date of medical records review, whichever occurred first. For cirrhosis, patients were followed from date of PBC diagnosis until date of cirrhosis, date of emigration, death or liver transplantation or date of medical records review, whichever occurred first.

Data on sick leave and disability pension were provided by the Swedish Social Insurance Agency. Their registration of ICD-10 diagnoses only includes main categories on a two-digit level. Subcategories such as K74.3 (PBC) cannot be distinguished from other liver diseases within the K74 group. We, therefore, chose to analyse sick leave due to all causes. The Swedish Social Insurance Agency pays sickness benefits from day 14. Register data were therefore not available for sick leave periods shorter than 14 days. If a sick leave period was ongoing at the time of PBC diagnosis, the number of sick leave days preceding the date of diagnosis was registered and included as well. Dates and specifications of full-time or part-time sick leave were noted. Sick leave days within one year before PBC diagnosis were categorized as 0, 1–30 and >30 register net days. One net day is one full-time calendar day with sick leave, e.g., two calendar days on 50% part-time sick leave are counted as one net day. Disability pension was categorized as present (>0 days) or absent. The retirement age in Sweden has traditionally been age 65, and after that sick leave is not paid. Patients older than 65 years will not be included in the analysis.

To compare sick leave between patients with PBC and the general population, a reference group of up to ten individuals for each patient was randomly selected from the Swedish Population Register and matched on sex, birth year and county of residence. For the matched controls, sick leave days were counted from the date on which the matched patient was given a PBC diagnosis. If a sick leave period was ongoing, the days preceding the date of diagnosis were registered as detailed above. Long-term sick leave was defined as sick leave >30 net days/year, including disability pension. The regional ethics review board in Uppsala approved the study (Dnr:2016-262).

Statistical analysis

Patient characteristics at diagnosis were tabulated by treatment categories and compared using the Fisher's exact or Kruskal-Wallis test as appropriate. Time-dependent Cox regression models with time since diagnosis in years as the underlying time scale were fitted to estimate hazard ratios (HR) and 95% confidence intervals (CI) for associations between treatment and clinical outcomes (transplantation-free survival and cirrhosis). Multivariable Cox regression models included age at diagnosis, sex and cirrhosis at diagnosis. The multivariable fractional polynomials method [20] was used to assess the functional form of age at diagnosis in the log-hazard function. A test of Schoenfeld residuals was used to evaluate the proportional hazards assumption, which was satisfied for all variables.

Sick leave analysis was limited to patients with PBC aged 20–65 at diagnosis who were not on a disability pension during the year preceding diagnosis. Logistic regression analysis was used to estimate odds ratios (ORs) with 95% CI for the

association between the PBC-related factors and sick leave (>30 net days) during the first and second years after diagnosis among patients with PBC.

Conditional logistic regression analysis was used to compare the odds of sick leave (>30 days) between patients with PBC and the matched reference group. In a sensitivity analysis, conditional logistic regression analysis was run also after excluding patients with fatigue, pruritus, cirrhosis or concurrent autoimmune disease to see if potential differences in sick leave between patients with PBC and the general population were influenced by these clinical factors. Statistical analyses were performed using STATA, version 14/SE for Windows (StataCorp). Tests were two-sided, and statistical significance was defined as $p < .05$.

Results

In total, 526 patients diagnosed with PBC between January 2004 and December 2016 were included in the study. Most were female (86.7%) and the median age at diagnosis was 60 years (IQR 51–69). Concurrent autoimmune diseases were present in 173 (33%) of the patients, with a broad range of diseases mostly found in rheumatology and endocrinology. Several patients had more than one concurrent autoimmune disease. Most common were thyroid diseases (53 cases) followed by the sicca-complex including Sjögren's syndrome (34 cases) and psoriasis (15 cases). Fifty-nine (11%) had cirrhosis at diagnosis. The median time of follow-up was 5.7 years (range 1 day-13.9 years). Over a total observation period of about 3,200 person-years, 74 (14%) patients either died ($n = 56$) or underwent liver transplantation ($n = 18$).

Of the 430 (82%) patients treated with UDCA at a median dose of 13.7 mg/kg (IQR 11.9–15.0), 350 (81.4%) were classified as treatment responders according to the Paris-1 score, and 317 (73.7%) according to the Toronto score. Twenty-two patients began UDCA treatment but had a follow-up of less than one year and were regarded as untreated in the analysis.

Table 1 shows patients' characteristics at PBC diagnosis categorized by treatment, as untreated, non-responder, responder and response unknown. The response was evaluated according to Paris-1. Untreated and non-responders

were more likely to have cirrhosis at the time of diagnosis, and untreated were in general older than those with treatment. Non-responders had higher bilirubin and ALP at diagnosis than responders and those without treatment. These findings were not significantly different when the Toronto score was used for evaluating treatment response (Supplemental Table 1).

Transplantation-free survival in relation to treatment

When adjusting for age, sex and cirrhosis at the time of diagnosis, untreated patients (HR 3.62 (95%CI 2.02–6.49)) and non-responders (HR 3.78 (95% CI 1.87–7.66)) had statistically significantly higher rates of death or transplantation compared to responders according to Paris-1 score (Table 2). Lower-magnitude and statistically non-significant associations were suggested for non-responders when treatment response was assessed according to the Toronto score (Table 2).

Cirrhosis in relation to the treatment

In total, 117 (22%) patients had liver cirrhosis, 59 at the time of diagnosis and an additional 32 during follow-up. Information on the date of cirrhosis diagnosis was not available for 26 patients. In the Cox regression analysis among patients free of cirrhosis at PBC diagnosis ($n = 438$), adjusted for age and sex, the risk of developing cirrhosis was significantly higher for non-responders compared to responders according to Paris-1 (HR 4.25 (95% CI 1.63–11.04)) and Toronto (HR 2.74 (95% CI 1.13–6.66)). Statistically non-significant associations were found for untreated compared to UDCA responders according to Paris-1 (HR 1.93 (95% CI 0.74–5.05)) or Toronto (HR 2.09 (95% CI 0.77–5.65)) for developing cirrhosis.

PBC-related factors and long-term sick leave (≥30 net days)

The sick leave analyses included 277 (53%) patients with PBC, aged 20–65 (median 53 years) who were not on a disability pension ($n = 50$), during one year preceding PBC

Table 1. Baseline characteristics for patients with PBC by treatment categories according to Paris-1 ($n = 526$).

	Untreated ($n = 96$)	Non-Responder ($n = 56$)	Responder ($n = 350$)	Response unknown* ($n = 24$)	p-value**
Age at diagnosis, years, median (IQR)	63.0 (53.5–74.5)	54.0 (43.5–66.5)	60.0 (51.0–68.0)	60.5 (49.0–68.0)	.003
Female, n (%)	83 (86.5%)	47 (83.9%)	304 (86.9%)	22 (91.7%)	.838
Cirrhosis at diagnosis, n (%)	18 (18.8%)	9 (16.1%)	30 (8.6%)	2 (8.3%)	<.001
Variables not included in Cox regression					
ALP IU/L, median (IQR)***	192 (126–330)	582 (300–828)	228 (150–360)	282 (210–336)	<.001
Bilirubin μmol/L; median (IQR)	9.1 (6.2–15.0)	20.0 (10.0–28.0)	9.0 (7.0–13.0)	8.6 (6.0–17.0)	<.001
Globe score, high risk n (%)****	–	26 (53.1%)	17 (4.9%)	–	–
Positive AMA, n (%)*****	80 (83.3%)	52 (92.9%)	323 (92.3%)	23 (95.8%)	.779
Concurrent autoimmune disease, n (%)	40 (41.7%)	11 (19.6%)	114 (32.6%)	8 (33.3%)	.029
Fatigue, n (%)	17 (17.7%)	9 (16.1%)	70 (20.0%)	4 (16.7%)	.992
Pruritus, n (%)	14 (14.6%)	27 (48.2%)	68 (19.4%)	3 (12.5%)	<.001

*Responder status could not be evaluated due to missing laboratory data after one year on UDCA. **Kruskal-Wallis is used for continuous variables, Fisher's exact test is used for categorical variables. ***ALP: ALP, alkaline phosphatase (IU/L), ****Globe score, large number of missing cases in untreated and response unknown *****AMA: antimitochondrial antibody.

Table 2. Cox regression for transplantation-free survival (n = 526).

	Unadjusted HR 95% CI	p	Adjusted HR 95%CI	P
Response according to Paris-1				
Responder (n = 350) (ref)	1.00	–	1.00	–
Untreated (n = 96)	4.28 (2.43–7.55)	<.001	3.62 (2.02–6.49)	<.001
Non-responder (n = 56)	4.06 (2.03–8.10)	<.001	3.78 (1.87–7.66)	<.001
Response unknown* (n = 24)	3.64 (1.39–9.51)	.008	4.89 (1.85–12.94)	.001
Response according to Toronto				
Responder (n = 317) (ref)	1.00	–	1.00	–
Untreated (n = 93)	3.75 (2.13–6.60)	<.001	3.08 (1.72–5.50)	<.001
Non-responder (n = 95)	1.68 (0.84–3.35)	.140	1.57 (0.78–3.18)	.210
Response unknown* (n = 20)	4.42 (1.69–11.56)	.002	5.43 (2.06–14.33)	.001

Cox regression for transplantation-free survival, adjusted for age at diagnosis, sex and cirrhosis at diagnosis. *Response unknown = Response to treatment according to Paris-1 or Toronto score could not be calculated due to missing laboratory data after one year of treatment with UDCA.

Table 3. Logistic regression for the association with sick leave ≥30 registered net days per year in patients with PBC.

	Sick leave during first year (n = 277) OR 95% CI	p	Sick leave during second year (n = 277) OR 95% CI	p
No UDCA treatment	2.28 (0.93–5.62)	.073	3.22 (1.12–9.25)	.030
Treatment (ref)	1.00	–	1.00	–
Age at diagnosis	1.00 (0.96–1.03)	.922	1.03 (0.98–1.07)	.227
Sex (male)	0.55 (0.19–1.57)	.264	0.12 (0.02–0.97)	.046
Sick leave before diagnosis				
0 net days* (ref)	1.00	–	1.00	–
1–30 net days	2.44 (0.95–6.29)	.064	2.03 (0.68–6.08)	.206
>30 net days	11.92 (5.60–25.35)	<.001	8.31 (3.39–20.40)	<.001

The logistic regression model was adjusted for age at diagnosis, sex, UDCA treatment and sick leave one year before diagnosis. Only adjusted numbers shown. *One net day is one full-time calendar day with sick leave, e.g., two days with 50% part-time sick leave constitute one net day.

diagnosis. Among the included patients, 241 (87%) were women and 246 (89%) were on UDCA, 64 (23%) had pruritus, 57 (21%) had fatigue, 82 (30%) had other concurrent autoimmune diseases, and 21 (8%) had cirrhosis at the time of PBC diagnosis. Within one year before diagnosis, 70 (25%) had registered for sick leave.

During the first year after diagnosis, 64 (23%) patients had registered sick leave >30 net days (10 with disability pension, 51 with sick leave, 3 with both). During the second year after diagnosis, 51 (22%) patients had registered sick leave >30 net days (15 with disability pension, 34 with sick leave, 2 with both).

Pruritus, fatigue, other autoimmune diseases and cirrhosis at the time of diagnosis were not associated with long-term sick leave in crude analyses and were not included in the adjusted model. In the multivariable logistic regression analysis including age, sex, treatment and pre-diagnostic sick leave, the untreated patients had higher odds of long-term sick leave compared with the treated patients, and a dose-response association was observed for pre-diagnostic sick leave (Table 3). Age at PBC diagnosis was not associated with long-term sick leave during the first or second years after diagnosis. Men were less likely than women to be on long-term sick leave during the first and second years after diagnosis, but this association was statistically significant only in the second year (Table 3).

No statistically significant difference was observed regarding long-term sick leave between non-responders and responders to both Paris-1 (OR 0.54 (95% CI 0.15–1.89)) and Toronto (OR 0.65 (95% CI 0.25–1.69)) response criteria. UDCA untreated were more likely to be on long-term sick leave

during the second year after diagnosis than responders according to the Paris-1 (OR 3.13 (95% CI 1.07–9.15)) or the Toronto (OR 3.10 (95% CI 1.05–9.14)) score.

Long-term sick leave (≥30 net days/year) compared to matched controls

This analysis included 165 (31%) patients with PBC and 1,642 matched controls aged 20–65 and not on a disability pension for one year before PBC diagnosis. One year before PBC diagnosis, 55 (33%) patients and 223 (14%) controls had registered for sick leave. During the first year after PBC diagnosis, 64 (39%) patients and 245 (15%) controls had registered for long-term sick leave. In comparison with the matched controls, patients with PBC were more likely to be on long-term sick leave for any cause one year after diagnosis (OR 2.50 (95% CI 1.69–3.70)) (Table 4). Patients with PBC were more likely to be on long-term sick leave than matched controls also in a sensitivity analysis including patients without a) treatment b) responder to treatment c) non-responders to treatment d) cirrhosis; e) concurrent autoimmune diseases; f) pruritus or g) fatigue at diagnosis (Table 4).

Discussion

This retrospective study on patients with PBC in seven Swedish university hospitals analysed disease outcomes and sick leave in relation to UDCA therapy. Sick leave rates were further compared with those of matched controls from the general population.

Table 4. Conditional logistic regression analysis on sick leave one year after diagnosis in patients with PBC compared to matched controls.

	PBC*/matched controls (n)	OR (95% CI)
All	165/1,642	2.50 (1.69–3.70)
Excluding untreated	145/1,438	2.28 (1.50–3.46
Excluding all but responder Paris-1**	116/1,153	2.18 (1.36–3.47)
Excluding all but non-responder P1***	20/191	2.19 (0.62–7.76)
Excluding cirrhosis	143/1,423	2.34 (1.54–3.55)
Excluding other AID****	111/1,078	2.16 (1.32–3.51)
Excluding pruritus	119/1,190	2.54 (1.59–4.06)
Excluding fatigue	90/895	3.30 (2.01–5.43)

*Patients with missing data on each comorbidity were excluded from respective analysis. **Responder-status one year after diagnosis, ***P1 short for Paris 1. ****AID, concurrent autoimmune diseases.

All-cause mortality during a median 5.7 year follow-up occurred in 10.6% of patients with PBC, which is in line with findings in our earlier study on the nation-wide Swedish PBC cohort [3], although our current data set did not allow for analysis of specific death causes. When the Paris-1 criteria [9] assessed UDCA response, the risk of death or liver transplantation was increased in both untreated (HR 3.62) and UDCA non-responders (HR 3.78) when compared to UDCA responders. When instead of using the Toronto criteria [13], the risk was higher only for untreated patients with PBC, a more expected finding according to the literature [1]. That transplantation-free survival is better among responders [16,18] is well known, but our finding that non-responders and untreated are at similar risk is new. A study from the UK found that the elderly PBC patients without UDCA treatment had about the same mortality rate as the background population [21]. Our untreated group was older, more often had cirrhosis at diagnosis, but had bilirubin and ALP levels like those of the UDCA responders. UDCA non-responders had similar ages but higher bilirubin and ALP levels than UDCA responders. One might speculate that older patients die of other causes than liver diseases and that non-responders die from liver-related causes.

Sick leave in patients with PBC has earlier only been studied after liver transplantation [7]. The present study is to our knowledge the first to report on rates of sick leave in PBC. Patients with PBC had a more than two times higher risk of being on long-term sick leave one year after PBC diagnosis than matched controls from the general population. UDCA-untreated patients had a three times higher risk of being on sick leave two years after PBC diagnosis than those with UDCA treatment (HR 3.22 (95% CI 1.12–9.25)). Those on longer sick leave before PBC diagnosis were also more likely to be on sick leave after PBC diagnosis. Sick leave for more than 30 net days during the year before diagnosis was more frequent among PBC patients than among matched controls.

We chose to compare sick leave in PBC with sick leave in matched controls from the general population, as this has not been done before. PBC has previously been demonstrated to be associated with more physical impairment than e.g., autoimmune hepatitis [22]. Future studies may benefit from including other chronic liver diseases as comparators.

Sick leave rates are relatively high from an international perspective [23,24]. Two factors may contribute: Sweden has the highest employment rate among women in the European Union: 80% in 2018 compared to e.g., 75% in Denmark or 68% in France [23]. Swedish women have more sick leave than Swedish men [24]. However, in our PBC cohort, we found no association between sick leave and age or sex.

In our cohort the rates of fatigue (21%) and pruritus (23%) at the time of PBC diagnosis that are lower than reported elsewhere (fatigue up to 80% and pruritus 20–70%) [1]. This may explain the absence of statistically significant associations between sick leave and these symptoms. In a sensitivity analysis, we excluded patients with clinical factors (cirrhosis, fatigue, pruritus, concurrent autoimmune diseases, see Table 4) that may potentially influence sick leave rates, but the higher rates of sick leave among patients with PBC remained. Patients with PBC are reported to have high rates of depression, anxiety and autonomic symptoms, especially in younger patients [18], which may affect the ability to work. Our data set included no information on these symptoms.

We defined UDCA response according to the Paris-1 score [9] in our main analyses since our cohort had a median age of 60 years and a high proportion with advanced liver disease at diagnosis. We used the Toronto score [13] for confirmation of the results. Since both scores were originally designed to evaluate response after one year, we used that time as a cut-off, even if signs of response may be seen earlier in clinical practice. Patients who are not on UDCA therapy are often excluded from studies [17,18]. A recent study on patients with PBC and compensated cirrhosis reported that UDCA responders had a better clinical outcome than partial responders, but untreated patients were not included [15,16]. In our cohort, UDCA-untreated patients were older, more often had cirrhosis at the time of diagnosis and had higher rates of other autoimmune diseases. The reasons for not prescribing UDCA are unclear, however; the medical charts seldom state a clear rationale for not giving UDCA. The median UDCA dose is slightly below the recommended. Similar "real-life" median doses have been described earlier in large cohort studies [8,25]. Obeticolic acid is seldom if ever, prescribed in Sweden since it is not included in the prescribed drug discount and patients need to pay the whole cost themselves.

This is a retrospective study, and results should therefore be interpreted with caution. The study period was chosen to match the start of electronic medical records. Clinical data were not complete, especially regarding PBC-related symptoms. Pruritus and fatigue were not evaluated in a structured way, and this may impact the reported rate of symptoms. The follow-up time is short for PBC. The data set on sick

leave was, however, virtually complete except for some missing data on sick leave among controls during the year before the corresponding PBC patients were diagnosed.

Clinical data were retrieved from university hospitals, and this may introduce referral bias towards sicker patients. Our recent nation-wide registry study on PBC in Sweden, however, found similar age at diagnosis and rates of treatment and death. In that, study the female to male ratio was 4:1, and 80% were prescribed UDCA. Second-line treatment with fibrates was only prescribed to 0.5% [3]. In the present cohort, the UDCA treatment rate is somewhat higher (82%), but very few received second-line treatment. Whether and how the inclusion of data from primary care or regional hospitals would influence study results is unknown.

Our main and novel finding in this paper is that patients with PBC that did not receive UDCA treatment were much more likely to be on sick leave than UDCA-treated patients, whether responders or not. Patients with PBC were more often on sick leave than matched controls from the general population. Our study confirms that PBC has a negative impact on health and the daily life of those affected by the disease.

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Disclosure statement

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