Digestive and Liver Disease 53 (2021) 1020–1027

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Digestive Endoscopy

Use of thiopurines is not a risk factor for post-ERC pancreatitis in patients with primary sclerosing cholangitis

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ARTICLE INFO

Article history:
Received 5 February 2021
Revised 4 May 2021
Accepted 11 May 2021
Available online 8 June 2021

Keywords:
Endoscopic retrograde cholangiography
Post endoscopic retrograde cholangiography pancreatitis
PEP
Primary sclerosing cholangitis
PSC
Thiopurines
Azathioprine
6-mercaptopurine

ABSTRACT

Introduction: Risk of post-ERC pancreatitis (PEP) in patients with primary sclerosing cholangitis (PSC) is 1–7.8%. PSC is often associated with inflammatory bowel disease and autoimmune hepatitis, which are usually treated with thiopurines. The role of thiopurines in PEP risk is still unclear.
Aims and methods: We evaluated the thiopurine use in PEP. The data of 354 PSC patients who underwent 985 ERCs between 2009 and 2018 were collected. 177 patients treated with thiopurines (study group, SG) and 177 controls (CG) were matched with a propensity score (PSM). Odds ratios (ORs) with 95% confidence interval (95% CI) were calculated. Multivariable logistic regression analysis and generalized linear mixed model were performed. The P-value <0.05 was significant.
Results: In matched data, 472 ERCs were performed in SG and 513 in CG. Thiopurines were used in 373/472 (79.0%) ERCs in SG. The PEP rate was 5.3% in SG and 5.7% in CG ($p = 0.889$). Unintentional pancreatic duct cannulation (OR 1.28, 95%CI 1.07–1.51, $p = 0.004$), and periampullary diverticulum (OR 4.87, 95%CI 1.72–11.98, $p = 0.001$) increased the risk of PEP.
Conclusion: Prior or present thiopurine use did not increase the risk of PEP.

1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammation and fibrosis of bile ducts leading to strictures, dilatations and pruning of the entire biliary tree [1] No curative medical treatment is obtainable and the disease may progress to cirrhosis, to end-stage liver disease, death or liver transplantation [1].

Endoscopic retrograde cholangiography (ERC) has been the gold standard for the diagnosis of PSC. However, the less invasive magnetic resonance imaging with magnetic resonance cholangiography (MRI-MRC) has replaced ERC [2], although it seems to play a minor role as a surrogate marker of disease activity and progression in PSC [3]. ERC is indicated in patients with an uncertain diagnosis, a worsening of symptoms or cholestasis and with a progression or an appearance of a new dominant stricture. In addition, ERC allows ductal sampling (brush cytology) and appropriate therapeutic interventions, such as dilatation and stenting [4]. In Helsinki University Hospital (HUS), ERC is performed on all patients with suspected PSC: 1) to confirm the diagnosis and to assess the need of endoscopic treatment, 2) to evaluate the individual risk for stratification of disease progression, 3) to exclude biliary dysplasia [5].

ERC is associated with severe adverse events (AE), such as cholangitis, bleeding, perforation, and post-ERC pancreatitis (PEP) with a frequency of 3.5–9.7% [6]. The risk of PEP in PSC patients 1–7.8% [4,7–11].

Several risk factors for PEP have been identified [6]. PEP prevention with a rectal administration of a non-steroidal anti-inflammatory drug, NSAID, (100 mg diclofenac or indomethacin) is commonly recommended [6], but it does not seem to reduce the risk in PSC patients [12].

PSC is associated with inflammatory bowel disease (IBD) in 70% of the cases and autoimmune hepatitis (AIH), in 7–14% of the cases [1]. Thiopurines [i.e., azathioprine (AZA) and 6-mercaptopurine, (6-MP)] are drugs commonly used to maintain remission [13,14], Thiopurines are associated with an increased risk of pancreatitis [15–18]. In addition, mesalazine and metronidazole are reported to have a definite association with pancreatitis [19]. Whether use of

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https://doi.org/10.1016/j.dld.2021.05.009

these drugs increases the risk of PEP in patients with PSC is still unclear.

2. Aim

Our first aim was to evaluate the effect of present and prior use of thiopurines on the risk of PEP in PSC patients undergoing ERC. Afterwards, we explored the risk of thiopurine use combined with other pancreato-toxic drugs (i.e. mesalazine and metronidazole) commonly used in PSC patients

3. Materials and methods

3.1. Study design

This study is a longitudinal, retrospective, single-center, case-control study.

3.2. Setting, time and population

Patients who underwent ERC between January 2009 and January 2018 for screening or a follow-up of PSC at HUS were identified with international classification of the diseases (ICD) coding and by the indication of the procedure from the hospital's patient records and a HUS PSC registry. The study group (SG) consisted of patients using thiopurines during the ERC procedure ($n = 177$) and a control group (CG) consisted of patients without thiopurines but matched for all baseline characteristics . The treatment indicator was coded, using an as-treated -principle, i.e., thiopurine use was considered as the only true use. The data concerning metronidazole and mesalazine were coded similarly.

3.3. PSC diagnosis

Diagnosis of PSC was based on typical findings on MRC and / or ERC, according to established criteria [20]. Disease severity was assessed by a modified Amsterdam score [5] Advanced PSC was defined when the ERC score was ≥4 or when biliary tract dilatations were needed

3.4. Patient data

Data of patient demographics, comorbidities and regular medication was collected. Indication, prior use of thiopurines and the reason for discontinuation were collected. Thiopurine users were divided to starters (started within three months), chronic users and in discontinuing group. Regular medication was classified as either by an active substance (ursodeoxycholic acid (UDCA), metronidazole, mesalazine, AZA, 6-MP, methotrexate, mycophenolate, cyclosporine, furosemide) or by their pharmacological group (corticosteroids, oral estrogens, angiotensin II receptor blockers / angiotensin converting enzyme (ACE) inhibitors, statins, opioids, biological drugs, i.e., infliximab, adalimumab, and antidepressants). Plasma bilirubin prior to ERC and serum or plasma amylase 4 h after the ERC and, if the patient stayed overnight at the hospital, next morning were assessed.

Data concerning the ERC procedures was collected: ERC indication (confirmation of diagnosis, follow-up for dysplasia, need of endoscopic treatment), cannulation methods and procedures performed (biliary sphincterotomy (BS), transpancreatic biliary sphincterotomy (TPBS), papillectomy, prophylactic pancreatic stenting, dilatations of the biliary duct, biliary stenting), and duration of the procedure. ERC procedures were graded with complexity criteria [21].

3.5. PEP prophylaxis

Since November 2013, all patients without contraindications have received a single-dose of 100 mg diclofenac in HUS as a PEP prophylaxis.

3.6. ERC procedure

The procedures were performed by experienced endoscopists. All patients received a single-dose of intravenous 500 mg levofloxacin prior to ERC. Cannulation was performed by using a sphincterotomy knife (Jagtome RX; Boston Scientific, Miami, Florida, USA) and a 0.035-in, 450 cm guidewire (Jagwire; Boston Scientific, Miami, Florida, USA). After a successful cannulation, BS was performed in all patients without previous BS. After BS, a balloon catheter (Extractor Pro-RX Retrieval Balloon Catheter, Boston Scientific, Marlborough, MA 01752–1234, USA) was inserted into the common hepatic bile duct (HC) and a contrast was injected with balloon occlusive technique to visualize the intrahepatic bile ducts. The balloon was then moved downwards to visualize the extrahepatic bile ducts. All of these images were obtained from at least four different planes in order to visualize the entire biliary tree. The brush cytology was routinely collected from both intra- and extrahepatic bile ducts. The bile sample for bacterial culture and calprotectin measurements was collected routinely. The patients were monitored for, at least, 10 h after the procedure and possible complications were treated appropriately. All ERC images were scored by using the modified PSC score [5].

3.7. Definition of post-ERCP complications and severity

Post-ERC complications (i.e. PEP, cholangitis, perforation, bleeding, other complications) were evaluated. These complications were defined and graded, according to Cotton *et al.* [22]. PEP was defined as a new or worsening abdominal pain with plasma or serum amylase, at least, three times the upper limit of normal (ULN) at 24 h after the procedure and a need for a prolonged hospitalization at least for two days. PEP was classified according to consensus criteria [21].

4. Statistical methods

Continuous variables were expressed as the mean and standard deviation (SD) or as the median and range or interquartile range. Categorical variables were expressed as a number and percentage. Comparison between continuous variables performed with a studentś *t*-test (normally distributed variables) or with a Mann-Whitney U test (non-normally distributed variables) and with crosstabulation. A comparison between categorical variables was performed with crosstabulation and a two-tailed Fisherś exact test.

The covariate balance between the cases and control groups were assessed by using an overall statistical test to decide if the propensity score matching (PSM) was necessary to make groups comparable in regards to the patient's potential use of thiopurines. We found missingness (2.0–2.8%) in three variables (ERC duration, body mass index (BMI) and preoperative bilirubin) and these variables were imputed. Baseline was defined as the first ERC procedure in this data.

An evaluation of the effect of thiopurines performed by using binomial logistic regression and a generalized linear mixed model with a binomial link (GLMM) to take into account the possible correlation of treatment outcome within the same patient. We identified potential explanatory variables associated with PEP, in addition to thiopurines and the number of ERCs per patient. We built three candidate models: a base model a small model and a full

model. The base model includes only our study question variables, thiopurine use and the number of ERCs performed and their interaction. For the full model we used Hochberg method [23] to find statistically significant variables from the candidate variables using P-value < 0.05 as a decision criteria. In addition, we used Harrell's fast backward selection method to see if the all covariates in the full model are needed [24]. This model we call the small model. ll GLMM were ran with and without random slopes. The performance of all candidate models was assessed by using Akaike's (AIC) and Bayesian (BIC) information criterions. If the results conflict we prefer the Bayesian version. The results were presented as an odds ratio (OR) and 95% confidence intervals. A P-value <0.05 was considered to be statistically significant.

The role of other important and commonly used drugs, such as mesalazine and metronidazole, were evaluated as co-factors in a subgroup analysis. We performed a logistic regression analysis with these drugs, thiopurines and prior ERCs.

IBM SPSS Statistics for Macintosh, Version 26.0 and R software version 4.03 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses.

4.1. Ethical aspects

This study was approved by the hospital's study board. All patients in the HUS PSC registry have provided a written patient consent for the data collection and analyses. This study has received approval from HUS Ethics Committee (HUS/1566/2020). The study protocol conformed to the ethical guidelines of the 2018 Declaration of Helsinki.

5. Results

5.1. Baseline characteristics

In the study period, a total of 2112 ERCs were performed for 971 PSC patients. The characteristics of the study population are presented in Tables 1a and 1b, and the whole population in Supplemental Table 1.

5.2. Propensity score matching

According to the omnibus test, the study groups were not comparable (overall statistics $p < 0.0001$), and PSM was needed. The list of the variables included in the PSM is presented in Fig. 1. After matching, a good balance was achieved ($p = 0.957$) with 985 observations from 177 patients per group. The balance before and after matching (part of the variables) is presented in the Supplemental Tables 2a and 2b. In matched data, a total of 472 ERCs in SG and 513 ERCs in CG were performed.

5.3. Thiopurine use and indications

Thiopurines were used in 373/472 (79.0%) ERCsin SG, AZA in 342/373 (91.7%) and 6-MP in 31/373 (8.3%). Indications for thiopurine use were IBD in 386/472 (81.8%), IBD-AIH in 40/472 (8.5%) and AIH in 45/472 (9.5%). In thiopurine group, IBD was diagnosed in 137/177 (77.4%), IBD-AIH in 17/177 (9.6%) and AIH in 22/177 (12.4%) patients. In only case (1/177, 0.6%) the indication was rheumatoid arthritis.

5.4. Thiopurines and adverse events (AEs)

Incidence of PEP was 25/472 (5.3%) in SG vs. 29/513 (5.7%) in CG, $p = 0.889$. In SG, when comparing procedures with vs. without thiopurines, we found PEP in 18/373 (4.8%) vs. 7/99 (7.1%), respectively, pp = 0.447. The number of other AEs was SG vs. CG: cholangitis 6/472 (1.3%) vs. 10/513 (1.9%), $p = 0.457$, bleeding 4/472 (0.8%) vs. 0/513 (0.0%), $p = 0.052$, and perforation 1/472 (0.2%) vs. 2/513 (0.4%), $p = 1.000$. The ERC degree of difficulty was mainly classified as group 1: 330/472 (69.9%) in SG vs. 340/513 (66.3%) in CG, $p = 0.343$.

5.5. Multi-variable analysis

In bivariate screening we found four statistically significant variables: TPBS, BS, unintentional PD cannulation and diverticulum (Supplemental Table 4). For the small model, only unintentional PD cannulation and diverticulum was left as confounding variables (Supplemental Table 3). In the logistic regression the small model with five variables, was the best according to the information criterion. From the GLMM, the small model with common random slope provided the smallest BIC and was chosen. For these models, no outliers or other problems were detected in residual diagnostics, suggesting a reasonable fit for both models (Supplemental Figure 1). The results from these two models are presented in Table 2. Both confounding variables, unintentional PD cannulation and diverticulum, seemed to increase the PEP risk. In the full model, only diverticulum was statistically significant covariate (Supplemental Table 3). Thiopurine use was not a significant factor for PEP.

5.6. Additional models with other drugs

In a logistic regression model combining other drugs as a subgroup analysis, none of these drugs were a risk factor for PEP. This model is presented in Table 3.

In a subgroup analysis, we found PEP in 23/484 (4.8%) ERCs in diclofenac group vs. 31/501 (6.2%), in non-diclofenac group, $p = 0.331$. In diclofenac group, thiopurine use (OR 1.823, 95% CI 0.415–8.002, $p = 0.426$) or thiopurine use combined with prior ERCs (OR 0.731, 95% CI 0.433–1.234, $p = 0.241$) were not significant factors for PEP.

5.7. Biliary dilatations and the PEP risk

We divided the patients into four groups according to the site of stricture and a need for dilatation (i.e. HC, common bile duct (CBD), right and left intrahepatic duct (IHdx and IHsin, respectively). When comparing the dilatation group vs. non-dilatation group, the PEP risk was in HC 9/217 (4.1%) vs 45/768 (5.9%), $p = 0.400$, in CBD 11/200 (5.5%) vs 43/785 (5.5%), $p = 1.000$, in IHdx 6/143 (4.2%) vs 48/842 (5.7%), $p = 0.556$, and in IHsin 5/115 (4.0%) vs 49/860 (5.7%), $p = 0.533$.

5.8. Study group and thiopurine therapy

PEP rate in non-user group was 2/69 (2.9%), in starter group 0/5 (0.0%), in permanent users 18/368 (4.9%) and in prior users 5/30 (16.7%) $p = 0.067$. The reasons for discontinuation of therapy (16 individuals with 30 ERCs) were: no further need in 8/16 (50.0%), ineffective treatment 2/16 (12.5%), acute pancreatitis (AP) in 2/16 (12.5%), elevated liver enzymes in 2/16 (12.5%), cytopenia in 1/16 (6.3%) and unknown in 1/16 (6.3%) patients.

5.9. Control group and previous thiopurine use

We found 36 patients with previous thiopurine use in CG with eighty-seven ERCs performed during the study period. The median time between the thiopurine use and ERC procedure was 63 months (interquartile range 69 months). In a subgroup analysis, PEP risk was similar between the patients with or without prior thiopurine use (3/87 (3.4%) vs. 26/426 (6.1%), $p = 0.448$).

Table 1a
Characteristics at baseline.

	Control group before matching (n = 794)	Study group (n = 177)	Total (n = 971)	p-value
Female sex	359 (45.2)	66 (37.3)	425 (43.8)	0.055
BMI median (range)	25.0 (12.1- 45.0)	24.5 (15.5–41.2)	24.9 (12.1- 45.0)	0.687
Age, years median (range)	41 (16–76)	33 (16–78)	39(16- 78)	<0.001
Naïve Native papilla	458 (57.7)	109 (61.6)	567 (58.4)	0.341
Diverticulum	27 (3.4)	7 (4.0)	34 (3.5)	0.717
Advanced PSC[1]	154 (19.4)	33 (18.6)	187 (19.3)	0.819
ASA class 1	131 (16.5)	30 (16.9)	161 (16.6)	0.911
class 2	477 (60.1)	108 (61.0)	585 (60.2)	
class 3	177 (22.3)	38 (21.5)	215 (22.1)	
class 4	9 (1.1)	1 (0.6)	10 (1.0)	
P-bilirubin µmikromol/l mean (SD)	16.6 (27.1)	15.8 (17.8)	16.4 (25.6)	0.708
AIH	25 (3.1)	34 (19.2)	59 (6.1)	<0.001
IBD	462 (58.2)	148 (83.6)	610 (62.8)	<0.001
UC	365 (46.0)	105 (59.3)	470 (48.4)	
CD	75 (9.4)	40 (22.6)	115 (11.8)	
IBDU	22 (2.8)	3 (1.7)	25 (2.6)	
Rectal diclofenac	260 (32.7)	46 (26.0)	306 (31.5)	0.080
Number of ERCs mean (SD)	2.1 (1.5)	2.7 (2.0)	2.2 (1.6)	<0.001
ERC performance				
BS in this ERC	464 (58.4)	111 (62.7)	575 (59.2)	0.295
TPBS in this ERC	106 (13.4)	10 (5.6)	116 (11.9)	0.004
Guidewire in PD >1	147 (18.5)	25 (14.1)	172 (17.7)	0.167
Dilatations (any)	145 (18.3)	35 (19.8)	180 (18.5)	0.640
Prophylactic PD stent	1 (0.1)	0 (0.0)	1 (0.1)	0.637
ERC duration, minutes median (range)	26 (5–123)	25 (5–63)	25 (5- 123)	0.081
PEP	68 (8.6)	8 (4.5)	76 (7.8)	0.070
PEP grade* 1	40 (5.0)	6 (3.4)	46 (4.7)	0.256
grade 2	21 (2.6)	2 (1.1)	23 (2.4)	
grade 3–4	7 (0.9)	0 (0.0)	7 (0.7)	

Data is presented as number and percentages n (%), as median (range) or as mean (SD).
BMI body mass index (kg/m2).
SD standard deviation.
PSC primary sclerosing cholangitis.
ASA The American Society of Anesthesiologists physical status classification system.
AIH autoimmune hepatitis.
IBD inflammatory bowel disease.
UC ulcerative colitis.
CD Crohn's disease.
IBDU IBD unclassified.
PD pancreatic duct.
BS biliary sphincterotomy.
TPBS transpancreatic biliary sphincterotomy.
PEP post endoscopic retrograde cholangiography pancreatitis.
PEP grade * according to Cotton *et al.* (Cotton, Garrow *et al.* 2009).
[1] Advanced PSC, see Materials and methods – PSC diagnosis.

Table 1b
Drugs used at baseline.

	Control group before matching (n = 794)	Study group (n = 177)	Total (n = 971)	p-value
UDCA	456 (57.4)	115 (65.0)	571 (58.8)	0.065
Mesalazine	272 (34.3)	88 (49.7)	360 (37.1)	<0.001
Salazopyrine	21 (2.6)	4 (2.3)	25 (2.6)	0.770
Metronidazole	63 (7.9)	25 (14.1)	88 (9.1)	0.009
Corticosteroids	77 (9.7)	39 (22.0)	116 (11.9)	<0.001
Oral estrogens	4 (0.5)	1 (0.5)	5 (0.5)	0.918
Furosemide	4 (0.5)	0 (0.0)	4 (0.4)	0.344
Oxychlorine	2 (0.3)	3 (1.7)	5 (0.5)	0.015
AR blockers	16 (2.0)	3 (1.7)	19 (2.0)	0.781
Methotrexate	13 (1.6)	0 (0.0)	13 (1.3)	0.087
Adalimumab	12 (1.5)	3 (1.7)	15 (1.5)	0.858
Cyclophosphamide	1 (0.1)	0 (0.0)	1 (0.1)	0.637
Infliximab	7 (0.9)	4 (2.3)	11 (1.1)	0.117
Cyclosporine	7 (0.9)	4 (2.3)	11 (1.1)	0.541
Metformin	12 (1.5)	1 (0.6)	13 (1.3)	0.322
Thyroxine	33 (4.2)	8 (4.5)	41 (4.2)	0.828
Antidepressants	24 (3.0)	3 (1.7)	27 (2.8)	0.331

Data is presented as number and percentages.
UDCA ursodeoxycholic acid.
AR angiotensin receptor.

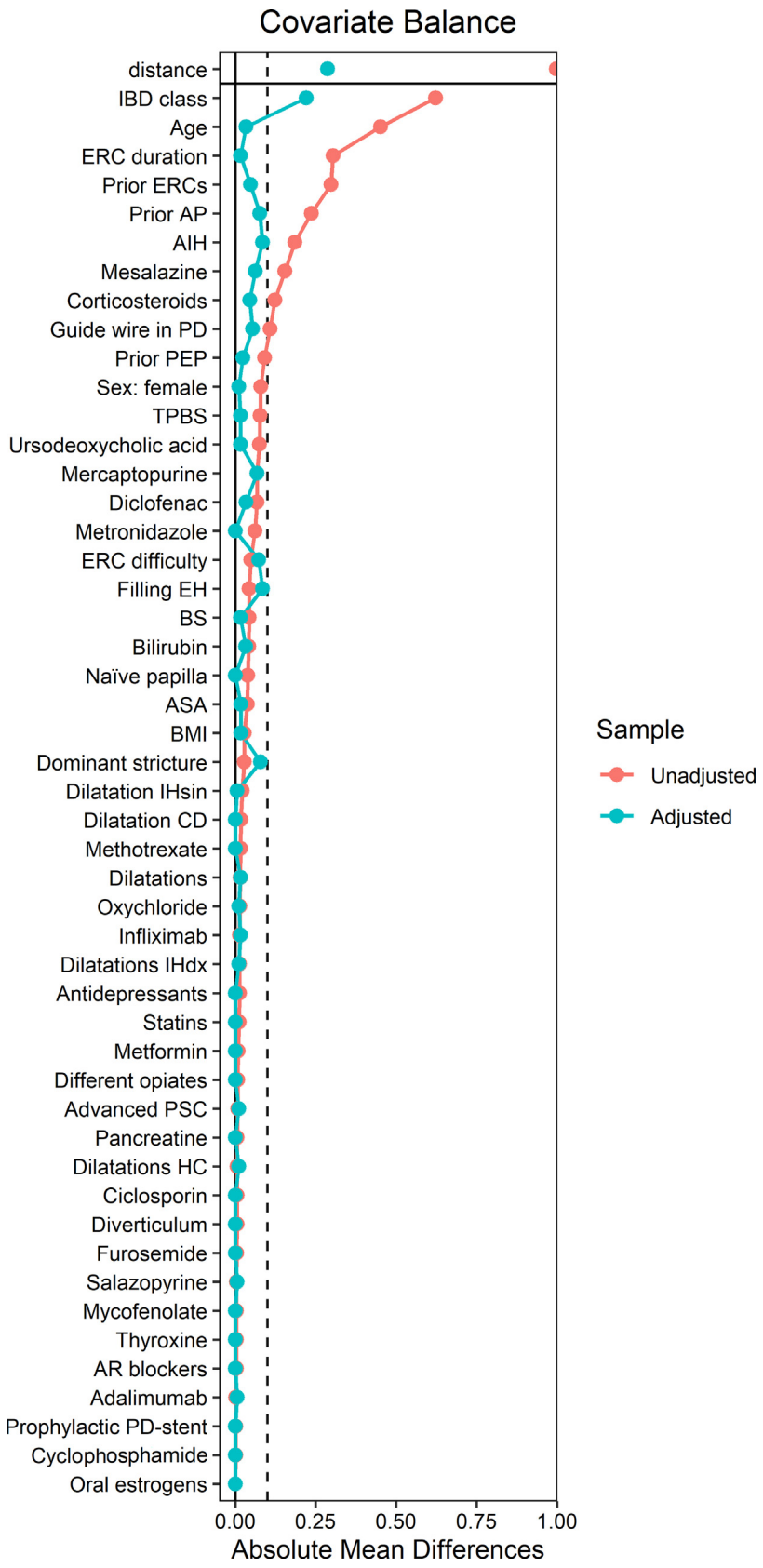

Fig. 1. Covariate balance of the two groups before (unadjusted) and after (adjusted) the propensity score matching.
IBD: inflammatory bowel disease; ERC: endoscopic retrograde cholagiography; AP: acute pancreatitis; AIH: autoimmune hepatitis; PD: pancreatic duct; PEP: post endoscopic retrograde cholangiography pancreatitis; EH: extrahepatic bile ducts; TPBS: transpancreatic biliary sphincterotomy; BMI: body mass index; ASA: The American Society of Anesthesiologists (ASA) physical status classification system; BS: biliary sphincterotomy in this ERC; CBD: common bile duct; IHsin: intrahepatic bile ducts, left side; PSC: primary sclerosing cholangitis; AR: angiotensin receptor; HC: common hepatic duct; IHdx: intrahepatic bile ducts, right side.

Table 2
Final statistical models.

Predictors	PEP GLMM			PEP Logit		
	Odds Ratios	*CI*	*p*	*Odds Ratios*	*CI*	*p*
(Intercept)	0.04	0.02 – 0.09	**<0.001**	0.06	0.03 – 0.10	**<0.001**
Prior ERC	0.94	0.77 – 1.15	0.561	0.95	0.77 – 1.13	0.575
Thiopurine use	0.97	0.32 – 2.87	0.951	0.98	0.35 – 2.73	0.962
Guidewire in PD (n)	1.33	1.09 – 1.62	**0.006**	1.28	1.07 – 1.51	**0.004**
Diverticulum	5.12	1.57 – 16.65	**0.007**	4.87	1.72 – 11.98	**0.001**
Prior ERC and thiopurine use	0.89	0.59 – 1.36	0.593	0.90	0.58 – 1.30	0.606
Random Effects						
σ^2	3.29					
τ_{00}	1.00					
ICC	0.23					
N	354 $_{patientID}$					
Observations	985			985		
AIC/BIC	413.12/440.21			413.46/442.81		

GLMM generalized linear mixed model.
Logit Logistic regression model.
PEP post endoscopic retrograde cholagiography pancreatitis.
ERC endoscopic retrograde cholangiography.
CI confidence interval.
σ^2 variance.
τ_{00} random intercept variance.
ICC intraclass correlation coefficient.
N number of patients.
AIC Akaike's information criterions.
BIC Bayesian information criterions.

Table 3
Logistic regression model with thiopurines, mesalazine, and metronidazole.

Predictors	PEP		
	Odds Ratios	*CI*	*p*
(Intercept)	0.08	0.04 – 0.16	**<0.001**
Thiopurine use	0.73	0.20 – 2.52	0.629
Prior ERC	0.92	0.74 – 1.11	0.434
Mesalazine use	0.91	0.41 – 2.06	0.817
Metronidazole use	0.93	0.30 – 2.58	0.888
Thiopurine use and prior ERC	0.80	0.50 – 1.20	0.318
Thiopurine and mesalazine use	1.94	0.58 – 6.97	0.294
Thiopurine and metronidazole use	1.66	0.42 – 6.16	0.458
Mesalazine and metronidazole use	1.28	0.38 – 4.62	0.693
Observations	985		
R^2 Tjur	0.006		

PEP post endoscopic retrograde cholangiography pancreatitis.
ERC endoscopic retrograde cholangiography.
CI confidence interval.

The reasons for discontinuing the thiopurines were AP in 3/36 (8.3%), elevated liver enzymes in 12/36 (33.3%), cytopenia in 6/36 (16.7%), ineffective treatment in 3/36 (8.3%), no further need in 3/36 (8.3%), and other reasons (pregnancy wish, nausea, headache, abdominal pain) in 9/36 (25.0%.

6. Discussion

6.1. State of principle findings

Pancreatitis is the most frequent complication after ERC, occurring in 1–7.8% of the PSC patients [4,7–11]. Pancreatitis is also a side effect of several drugs [17–19], but data on the impact of these on PEP are scarce. PSC is often associated with IBD and AIH, which are treated with potentially pancreato-toxic drugs. Interestingly, we found no difference in the PEP rate between PSC patients with and without thiopurine use. In addition, no connection between prior or present use of thiopurines and the PEP risk was found.

6.2. Risk of PEP in PSC patients

Patient- and procedure related risk factors for PEP have been identified [6,22]. The PEP rate in PSC patients seems to be slightly higher than in patients without PSC [11]. Ismail *et al.* has reported female sex, accidental PD passages and pre-cut, biliary or pancreatic sphincterotomy as risk factors [9]. However, those are also risk factors for PEP in patients without PSC [6]. We may also speculate that the biliary duct dilatations of the strictures make the ERC procedure more difficult and prolonged, thus increasing the risk of PEP, but data is lacking. Rectally administrated NSAIDs have been shown to reduce the risk of PEP [6], although data is still controversial [25]. We have recently shown that diclofenac does not seem to reduce the PEP risk in PSC patients [12].

After November 2013, rectal diclofenac was adopted as a PEP prophylaxis in our unit. However, the subgroup analysis excluding data prior November 2013 did not change the interpretation of the results in the present study and thiopurine use did not increase the PEP risk.

Patients with PSC are followed-up with MRI-MRC in our center to exclude extra-biliary lesions, cirrhosis, its complications and lymphadenopathy. However, the use of MRI-MRC seems to have a limited role in the follow-up of inflammation and biliary dysplasia in PSC [3].

6.3. Drugs associated with increased risk for pancreatitis

A total of 525 different drugs have been reported to the WHO (the World Health Organization) with suspected drug-induced pancreatitis [17]. However, the lack of randomized clinical trials and systematic reviews hampers drawing a conclusion on the epidemiology, the strength of association, and the pathophysiologic mechanism of drug-induced pancreatitis. The evidence is based on case reports and case-control studies only [19]. The mechanism of toxicity is unclear in the majority of the cases.

To our knowledge, only a few studies have investigated the role of pancreato-toxic drugs in PEP so far [26,27]. No recommendation in the international guidelines is available according to the this is-

sue [4,6,28] and the decision for drug discontinuation is left to the single centers.

Thiopurines are pivotal immunosuppressive drugs used as a therapy of maintenance in autoimmune disorders (e.g., IBD and AIH) and as an immunosuppressives after organ transplantation [29,30]. A population-based study in the UK found that patients using AZA have a 13-fold higher risk of pancreatitis [31]. Similar results were found in a Danish study [16]. However, other studies suggested that IBD, mostly Crohnś disease (CD), might be an independent risk factor for pancreatitis [32,33]. Several other studies have found thiopurines as risk factors for pancreatitis [15,16,32,34]. The pathophysiology of the thiopurine-induced pancreatitis is unknown [17,35] Pancreatitis is usually mild and responds to the drug discontinuation [36]. Re-exposure to thiopurines can be attempted balancing the risk and the benefit, however, the drug should be definitively interrupted in a case of recurrent pancreatitis [19].

Mesalazine was used in 557/985 (56.5%) and metronidazole in 306/985 (31.1%) ERCs in our data. We combined thiopurines, mesalazine and metronidazole in the model where none was found to be significant. A Danish study suggested a higher risk of pancreatitis in patients with IBD treated with mesalazine but the disease itself might play a role [37]. Combining metronidazole with UDCA improves alkaline phosphatase (ALP) levels in PSC patients, without impacting on survival [38]. In addition, metronidazole was found to be a risk factor for drug-induced pancreatitis [39]. However, it was not significant in our data.

6.4. Other factors increasing the risk of PEP

We found unintentional PD cannulation and periampullary diverticulum as risk factors for PEP. The presence of the diverticulum was recorded in the original ERC report. However, retraction of the papilla is also described in PSC patients [4]. Data on intra- and inter-observer agreement for the definition of retracted papilla in PSC patients is not available. Similarly, no data on the best cannulation methods in this setting has been described. The diverticulum was not considered to be a risk factor for PEP in two meta-analyses, including six and twelve studies, respectively [40,41]. The presence of the diverticulum influences the cannulation of the papilla, and may lead to a difficult cannulation situation, thus increasing the risk of AEs.

PD cannulation and PD opacification were considered to be risk factors in the ESGE guidelines with OR 2.1–2.77 and 1.58–2.72, respectively [6]. However, in our study, PD opacification was not a significant factor.Prior PEP has shown to increase the risk of PEP with OR of 3.23–8.7 in the ESGE guidelines [6] and OR of 2.9 (95%CI: 1.87–4.48) in one meta-analysis [40]. In our study, prior PEP did not increase the risk of PEP. We speculated that the site of the stricture and the need of dilation could affect the PEP risk, however, no difference was found.

6.5. Other ERC complications

The rate of cholangitis (1.3% in SG and 1.8% in CG) after cholangiography was relatively low compared to the literature. This might be a consequence to intravenous levofloxacin given PSC patients before the ERC. Moreover, bile sample for bacterial infection is routinely collected and treated when needed. Active dilatation of strictures are performed for collection of cytological samples and to improve the bile flow.

6.6. Statistical consideration

The effect of thiopurines were analyzed using an as-treated principle. A similar propensity score can be interpreted as a similar probability to have the treatment. Thus, ERC procedures in SG without thiopurines were used as controls in analyses. The PSM was built to ensure the similarity of the groups, controlling confounders and interactions. The primary endpoint was to find out if thiopurines increase the risk of PEP. The problem is to demonstrate the association with the especial drug and PEP. Thus, to improve the causality, the PSM performed with 49 different factors balanced and the dividing factor being the thiopurine use.

6.7. Strengths and limitations of the study

To our knowledge, this study is the largest of its kind to evaluate the PEP risk of thiopurines in PSC. This study is based on the hospital‘s real world patient data and HUS PSC registry data.

The variables included in the PSM were considered as clinically interesting factors. However, there might be some factors that were missing or some interactions that can impact on the matching. In logistic regression modeling, we wanted to include risk factors for PEP to the initial model selection step (Supplement 4).

Inclusion criteria was thiopurine use during at least one ERC. However, in the evaluation of historical patient records, we found 36 patients in the CG with previous thiopurine use. This might produce a bias in the patient selection. However, no difference existed in the PEP risk in CG with or without previous thiopurine use.

6.8. Conclusion

Our result suggests that potentially pancreato-toxic drugs used in PSC patients do not increase the risk of post-ERC pancreatitis.

Acknowledgements

Vilja Koskensalo would like to thank the Vatsatautien Tutkimussäätiö/Mary and Georg Ehrnrooth Foundation, Finland and the Helsinki University Hospital Research Funds, Helsinki, Finland for the working grants.

Funding source

Grant from Vatsatautien tutkimussäätiö/Mary and Georg Ehrnrooth Foundation (2020), Finland and support from Helsinki University Hospital Research Funds, Helsinki, Finland.

Conflict of Interest

None.

Financial disclosure

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.05.009.

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