Primary sclerosing cholangitis associated with inflammatory bowel disease: an observational study in a Southern Europe population focusing on new therapeutic options

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Background Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease with a strong association with inflammatory bowel disease (IBD). Medical treatment for PSC is still disappointing, whereas immunomodulators and biologics have been proven to be effective in IBD.

Aims This study aimed to analyze (i) the natural history of patients with PSC with or without IBD and (ii) the long-term efficacy of biologics in patients with PSC and concomitant IBD or rheumatological disorders.

Patients and methods This study included 92 consecutive PSC patients, 50 (54.3%) men and 42 (45.7%) women, with a mean age of 32.0 ± 14.3 years at diagnosis and a mean follow-up duration of 103.8 ± 86 months. Forty-nine (53.3%) patients had associated IBD (38 ulcerative colitis, 10 Crohn's disease, one indeterminate colitis).

Results No significant differences were found between PSC patients with and without associated IBD in terms of liver transplantation, cancer, and death rates. Cholangiocarcinoma was only identified among patients with PSC alone, whereas other cancers (hepatocellular carcinoma, colorectal, and gallbladder cancer) were found only in the group with associated IBD. Five PSC patients were treated with biologic agents: three with adalimumab and one with infliximab for IBD or for rheumatoid arthritis, and one patient with rituximab for rheumatoid arthritis. Adalimumab decreased alkaline phosphatase in two of three patients after 6 and 12 months, infliximab reduced γ-glutamyltransferase after 6 and 12 months, but liver function tests tended to deteriorate thereafter. Cholangiography changes remained stable in all patients.

Conclusion Biologic agents may improve liver function tests in PSC patients, but may be associated with adverse events including deterioration of liver function. Eur J Gastroenterol Hepatol 28:508–513
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Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by an inflammatory and fibrotic process affecting the intrahepatic and extrahepatic biliary tree, and leading to irregular bile duct obliteration and the formation of multifocal bile duct strictures [1]. The estimated incidence of PSC ranges between 0.9 and 1.3 cases per 100 000 population a year [2] and the male-to-female ratio is 2 : 1 [3].

PSC is considered an autoimmune disease and is often associated with extrahepatic conditions, mainly inflammatory bowel disease (IBD) in particular. The prevalence of IBD in PSC patients is in the range of 60–80%. The type of IBD most commonly associated with PSC is ulcerative colitis (UC), which can be diagnosed in up to 80% of cases, whereas Crohn's disease (CD), usually localized in the colon, occurs in about 13% of PSC patients [2–4].

PSC has a slowly progressive course that can lead to liver cirrhosis and liver failure. The median overall or transplant-free survival is ~ 8–14 years [5]. PSC is the main risk factor for cholangiocarcinoma (CCA): PSC patients have a 10–15% lifetime risk of developing CCA and about one in three CCAs are found in the first year after PSC has been diagnosed; the remainder are identified with a frequency of about 1.5% a year [6]. Colorectal cancer (CRC) is a possible complication of IBD, particularly in UC patients, and a meta-analysis of 11 studies established that patients with concomitant UC and PSC are at a higher risk of CRC; in particular, patients with UC–PSC are more likely to develop colorectal dysplasia and carcinoma than those with UC alone [7]. Having both PSC and IBD also carries an up to 4-fold higher CRC risk than in patients with IBD alone and an up to 10-fold higher risk than in the general population [6].

The poor prognosis in PSC is at least partly because of the lack of an effective medical therapy. Data on the efficacy of ursodeoxycholic acid (UDCA), an effective treatment for primary biliary cirrhosis, are controversial. Although some studies reported biochemical or histological improvements in patients on UDCA therapy (at the standard dose of 10–15 mg/kg/day) [8–10] and worsening liver function tests after UDCA withdrawal [11], the role

European Journal of Gastroenterology & Hepatology 2016, 28:508–513

Keywords: biologic agents, inflammatory bowel disease, primary sclerosing cholangitis

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Received 31 October 2015 **Accepted** 11 January 2016

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of UDCA in reducing symptoms and, more importantly, in preventing the disease's progression and prolonging survival is still uncertain [12]. It has also been shown that administration of higher doses of UDCA fails to improve its efficacy, but results in a higher risk of adverse events [13].

The guidelines for PSC of the American Association for the Study of Liver Disease (AASLD) recommend against the use of high-dose UDCA, and although they will be changed soon, other drugs as medical therapy have not been recommended so far. Instead, they recommend corticosteroids and other immunosuppressants in PSC patients with overlapping autoimmune hepatitis (AIH) [4]. Moreover, EASL guidelines state that the available database shows that UDCA (15–20 mg/day) improves serum liver tests and surrogate markers of prognosis, but does not show a proven benefit on survival [3].

Immunosuppressants are used widely to treat steroid-dependent and steroid-resistant IBD. One of the most important inflammatory mediators involved in the pathogenesis of IBD is tumor necrosis factor α (TNFα). In recent years, numerous studies, including randomized clinical trials and meta-analyses, have reported the efficacy of monoclonal antibodies against TNFα in inducing and maintaining remission, mucosal healing, improving quality of life, and reducing the need for hospitalization and surgery in both CD and UC. The anti-TNFα drugs most commonly used to manage IBD are infliximab (IFX) and adalimumab (ADA) [14–18].

Biological agents, especially in the form of TNFα inhibitors, are also a well-established treatment option for patients with immunoinflammatory rheumatic diseases, including rheumatoid arthritis (RA), which may be associated with other autoimmune diseases such as IBD [19, 20]. Among other biologics, one of the most indicated for rheumatological disorders is rituximab (RTX), a monoclonal chimeric anti-CD20 antibody [21,22].

Few studies have reported on the use of biological agents in PSC. A double-blind, placebo-controlled randomized study including 10 PSC with UC patients failed to show any efficacy of IFX in PSC in terms of a histological improvement or reduction in serum alkaline phosphatase levels [23]. Two case reports described an improvement in liver function tests in PSC patients treated with biological agents for other autoimmune diseases [24,25].

The aim of this study was to analyze the natural history of PSC patients with and without associated IBD and to assess the efficacy of biological agents in improving liver function in patients with PSC and IBD or rheumatological disorders.

Patients and methods

This study included 92 consecutive PSC patients seen at our outpatients clinic (Department of Surgical and Gastroenterological Sciences, Gastroenterology Section, University of Padova) between 1984 and 2014 with at least 1 year of follow-up. From 1984 onwards, PSC patients were prospectively registered and routinely followed up with a clinical examination and biochemical tests every 4–6 months. The biochemical parameters measured were aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase (γGT), immunoglobulins, bilirubin, red and white cell counts, prothrombin time, carcino-embryonic antigen, and α-fetoprotein. Liver ultrasound was performed every 6 months. Endoscopic retrograde cholangiopancreatography was performed if liver function tests deteriorated. Magnetic resonance cholangiography from 1998 onwards was also performed every 18 months. Patients with a diagnosis of IBD underwent colonoscopy with multiple biopsies every 2 years.

PSC was diagnosed in the presence of elevated serum markers of cholestasis (AP and γGT) and characteristic bile duct changes, with multifocal strictures and segmental dilations on magnetic resonance cholangiography or endoscopic retrograde cholangiopancreatography once secondary causes of sclerosing cholangitis had been excluded. A small duct PSC was diagnosed in patients with clinical, biochemical, and histological features compatible with PSC, but normal cholangiograms. A diagnosis of AIH/PSC overlap syndrome was established when the following criteria were fulfilled: (i) a total aggregate score for AIH more than 15 (histologically 'definite' disease); (ii) antinuclear antibodies or anti-smooth-muscle antibodies in a titer of at least 1 : 40; and (iii) liver histology compatible with piecemeal necrosis, lymphocyte rosetting, moderate or severe periportal, or periseptal lobular inflammation.

Any association with IBD was tested in each case by colonoscopy with multiple biopsies and/or barium enema (in the case of clinical symptoms of malabsorption). The diagnosis of UC was confirmed by conventional endoscopic, histological, and clinical criteria according to the Truelove–Witts classification [26]. Crohn's colitis was diagnosed if chronic inflammatory colonic disease was associated with extensive small bowel involvement and the typical histological and endoscopic signs of CD, or with segmental inflammation and a histologically normal rectum. In conjunction with clinical evidence of granulomas, focal inflammation, fissures, preserved epithelium, mucin production, or lymphoid aggregates were considered the most discriminating features of CD. In terms of its ileal localization, the diagnosis of CD was confirmed on the grounds of radiological criteria (small bowel barium enema) and endoscopic/histological criteria [27]. IBD clinical activity was scored according to the Harvey–Bradshaw Severity Index for CD [28] and the Modified Truelove–Witts Severity Index for UC [26]. Endoscopic IBD activity was scored according to the Simple Endoscopic Score for CD [29] and the endoscopic Mayo score for UC [30].

CRC was diagnosed with colonoscopy and confirmed histologically with multiple biopsy performed during endoscopy and then with histological analysis after surgical intervention. CCA, hepatocellular carcinoma (HCC), and gallbladder cancer were diagnosed with imaging analysis (abdominal computed tomography scan/abdominal MR) and then confirmed histologically after surgery.

The 92 PSC patients included 50 men and 42 women; their mean age at diagnosis was 32.0 ± 14.3 years and they had a mean 103.8 ± 86.0 months of follow-up. Forty-nine (53.3%) patients had associated IBD: 38 had UC, 10 had CD, and one had indeterminate colitis.

All patients were treated with UDCA (15–20 mg/kg/day) and had a physical and biochemical follow-up every 6 months after their initial diagnosis.

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Table 1. Clinical features of primary sclerosing cholangitis patients with and without associated inflammatory bowel disease

Events	PSC with IBD ($n=49$)	PSC without IBD ($n=43$)	P
Males [n (%)]	29 (59.2)	22 (51.2)	0.44
Mean follow-up (mean ± SD) (months)	113.8 ± 90.3	92.4 ± 80.4	0.24
Mean age at diagnosis (mean ± SD) (years)	29.2 ± 14.8	35.2 ± 13.0	0.04
Overlap PSC with AIH [n (%)]	3 (6.1)	5 (11.6)	0.35
Small duct PSC [n (%)]	1 (2.0)	1 (2.3)	0.93

AIH, autoimmune hepatitis; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.

The clinical and biochemical data of patients treated in an open-label study with biological agents were assessed before starting the treatment and at each scheduled interval of infusion. Informed consent was obtained from all individual participants included in the study after an explanation of the nature of the procedures involved was provided. The study protocol was reviewed and approved by the local ethical committee. The investigation was carried out in accordance with the principles of Good Clinical Practice, and the ethical standards established in the 1964 Helsinki Declaration and its subsequent amendments.

ADA induction involved the administration of 160 mg of ADA, subcutaneous, at week 0 and 80 mg, subcutaneous, at week 2; then, ADA maintenance treatment was 40 mg, subcutaneous, every 2 weeks.

IFX induction was 5 mg/kg, intravenous, at week 0, week 2, and week 6; then, IFX maintenance treatment was 5 mg/kg, intravenous, every 8 weeks.

Before RTX infusion, patients received 100 mg of methylprednisolone intravenously. Safety assessments included a clinical examination and laboratory tests performed on the day of the infusion and 4, 8, 16, 24, 36, and 52 weeks afterwards. Each intravenous infusion consisted of 1000 mg of RTX.

PSC patients with and without associated IBD were compared in terms of the onset of hepatobiliary tumors, liver transplantation, and death using Fisher's test.

Patients treated with biological agents for associated IBD or rheumatic disease were analyzed in detail, recording data on the type of drug and its administration schedule, liver function test findings, and Mayo PSC risk scores [31], during a 12-month follow-up.

Statistical analyses

Quantitative data were expressed as means and SDs. The t-test was used for qualitative data (with Fisher's exact test, where appropriate), the χ^2 for qualitative data, and Wilcoxon's test for matched pairs. The statistical analyses were carried out using SPSS software (SPSS Inc., Chicago, Illinois, USA).

Results

Among the 92 PSC patients, 83 (90.2%) had large bile duct involvement (intrahepatic or extrahepatic bile ducts), one (1.1%) had a small duct PSC, and eight (8.7%) fulfilled the criteria for a PSC–AIH overlap syndrome.

Forty-nine patients had associated IBD and 43 patients had PSC without IBD. The clinical characteristics of these groups are summarized in Table 1. However, no differences were found in the two groups in sex, length of follow-up, and the rate of overlap syndrome with AIH or the small duct variant, whereas patients with IBD had a younger age at diagnosis compared with PSC patients without IBD (29.2 ± 14.8 vs. 35.2 ± 13.0 years, $P=0.04$). During the follow-up, 14 (15.2%) patients underwent liver transplantation, two (2.2%) developed a CCA, two (2.2%) had a HCC, and one (1.1%) had a gallbladder carcinoma. Five (5.4%) other patients developed CRC. The comparison between PSC patients with and without associated IBD in terms of cancer onset (CCA, HCC, gallbladder cancer, CRC), liver transplantation, and death showed no significant differences between the two groups (Table 2). CCA was only detected in patients with PSC alone (4.6%), however, whereas HCC, gallbladder cancer, and CRC only occurred in the PSC with IBD group (4.1, 2.0, and 8.2%, respectively). The group of PSC patients with associated IBD developed significantly more extrabiliary cancers than the group with PSC alone (14.6 vs. 0%, $P<0.05$). There was no difference in the mean age at diagnosis of patients who developed cancer versus those who did not (35.0 ± 7.3 vs. 31.7 ± 14.8 years, $P=$ NS), whereas the follow-up was significantly longer in those who developed cancer (176 ± 85.1 vs. 95.9 ± 82.9 months, respectively, $P=0.007$).

Table 2. Clinical events in primary sclerosing cholangitis patients with and without associated inflammatory bowel disease during the follow-up

Events	n (%) PSC with IBD ($n=49$)	n (%) PSC without IBD ($n=43$)	P
Liver transplantation	7 (14.3)	7 (16.3)	1
CCA	0	2 (4.6)	0.22
HCC	2 (4.1)	0	0.5
Gallbladder cancer	1 (2.0)	0	1
CRC	4 (8.2)	0	0.12
Extrabiliary cancers	7 (14.3)	0	0.013
Death	5 (10.2)	5 (11.6)	0.74

CCA, cholangiocarcinoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.

The majority of patients with PSC with IBD (85.7%) were treated with mesalazine. Immunosuppressant therapy was administered to 20 patients (Table 3): 19 (95%) were administered prednisone [15 in monotherapy, three in combination with azathioprine (AZA), and one in combination with mycophenolate mofetil], and one (2.0%) was administered AZA in monotherapy. Five (10.2%) patients were administered biologics as a second-line treatment, subject to their written consent: two patients with PSC with UC had ADA in monotherapy or ADA + AZA, one patient with CD had IFX in monotherapy, and one other patient with PSC with UC was treated with RTX for associated RA (Table 2). One of the

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Table 3. Treatment in patients with primary sclerosing cholangitis and associated inflammatory bowel disease

Drugs	Patients ($N=49$) [*n* (%)]
Mesalazine	42 (85.7)
AZA	1 (2.0)
Prednisone	15 (30.6)
ADA	1 (2.0)
AZA + prednisone	3 (6.1)
AZA + ADA	1 (2.0)
IFX	1 (2.0)
Mycophenolate mofetil + prednisone	1 (2.0)
RTX (for RA)	1 (2.0)

ADA, adalimumab; AZA, azathioprine; IFX, infliximab; RA, rheumatoid arthritis; RTX, rituximab.

PSC patients without IBD was treated with ADA because of active RA.

After 12 months, a sustained clinical remission of IBD was observed in two patients treated with ADA (their Modified Truelove–Witts Severity Index decreased from 10 to 3 in patient #2, and from 7 to 1 in patient #3); in patient #4, the Harvey–Bradshaw Severity Index decreased from 20 to 7 and the Simple Endoscopic Score for CD decreased from 16 to 12; patients #1 and #5 did not have active IBD.

Table 4 shows the biochemical test findings during the treatment with biologics. ADA decreased AP in two of three patients after 6 and 12 months (patients #1, #2, #3), and then a deterioration in AP was observed thereafter. γGT showed a fluctuation, with a decrease during the first 6 months in the same patients; moreover, serum albumin and bilirubin remained stable throughout the treatment. In patient #4, IFX reduced γGT after 6 and 12 months, but liver function tests tended to deteriorate thereafter. This patient experienced a gradual deterioration in liver function tests and the Mayo score; thus, he was placed on the waiting list for liver transplantation. RTX in patient #5 did not alter liver function tests significantly. Cholangiography changes remained stable in all five patients.

Discussion

The results of our study on a cohort of PSC patients followed up prospectively for up to 30 years at a single center confirm that PSC is a complex disease with a very high risk of neoplastic complications. To our knowledge, this is the observational study with the longest follow-up of Italian PSC patients to date. Considering that PSC is rare in Italy, our findings provide important clinical information on the natural history of this disease. All our patients were recruited consecutively and have always been followed up by the same dedicated staff.

The first aspect of interest emerging from this study is the 53.3% association with IBD in PSC patients. This rate is apparently lower than reported elsewhere, where it has ranged between 60 and 80% [32]. However, data collected by the International PSC Study Group on 6205 patients diagnosed between January 1980 and December 2010 show that this disease varies by geographical location. In particular, its overall association with IBD was 68.7%, but ranged from 45.1% in Southern Europe to 77.7% in Northern Europe [33]. Southern Europe includes Italy, Spain, and Greece; thus, our rate of association is consistent with these figures.

Our most impressive findings are in terms of the natural history of PSC, however, which is characterized by a progressive course that can lead to the decompensated cirrhosis requiring liver transplantation. The life expectancy of PSC patients can also be influenced by the occurrence of both CCA and CRC. It is still unclear whether the risk of cancer in PSC is because of any associated IBD (which is known to be a major risk factor for CRC) [34] or whether PSC carries its own cancer risk [6, 35]. The updated figures from the International PSC Study Group reported a rate of hepatobiliary malignancy (HBM) of 10.9% (749 cases in 6845 patients, with an incidence rate of 11.3 cases per 1000 patient years during the first year) [35]. The following parameters were associated significantly with HBM: male sex, age at diagnosis, large duct PSC, and UC. Our data, although obtained in a small number of cases, confirm the association between HBM and IBD. Large observational studies, however, are warranted to establish the pathogenic role of IBD in PSC.

In our cohort, CCA was diagnosed in 2.2% of patients, with a prevalence lower than that in other studies [36,37], but similar to the figure (2.1%) reported by the International PSC Study Group for Southern Europe [33]. In our sample, CCA was only diagnosed in the group with PSC alone, whereas CRC was only found in the group with PSC with IBD, suggesting that it is the presence of IBD that increased the risk of CRC in these patients. The development of any type of extrabiliary cancer was significantly more frequent when PSC was associated with IBD (14.6 vs. 0%, $P<0.05$), meaning that the presence of IBD adds to the cancer risk.

Few data are available on therapy with biological agents in PSC, whereas anti-TNFα drugs (such as IFX and ADA) are currently used to manage steroid-resistant and steroid-dependent IBD. Some authors have recently reported the efficacy of IFX in the treatment of autoimmune conditions associated with IBD. Silbermintz *et al.* [24] described the case of a 13-year-old female with steroid-dependent CD, PSC, and pancreatitis, who subsequently developed granulomatous lung disease. After investigations that included lung biopsy, IFX therapy was administered: the pulmonary symptoms disappeared, and the gastrointestinal, pancreatic, and hepatobiliary signs and symptoms improved. Duca *et al.* [25] reported on a 68-year-old man with UC, PSC, uveitis, and sacroiliitis who was treated with IFX for steroid-dependent intestinal disease: after 2 years, the patient remained asymptomatic and liver function test findings had improved considerably.

In an abstract of two cases of PSC and associated CD treated with IFX [38], liver function tests improved already after the first infusion. Three further anecdotal cases have been reported in abstract form [39]. All these patients had CD and PSC. However, subsequent IFX infusions (at 2 and 5 weeks) did not improve these patients' liver function tests.

There was an improvement in liver function test findings and the Mayo PSC risk score in three of five patients included in our study who were treated with anti-TNFα; one patient remained substantially stable, whereas one (who already had cirrhosis with portal hypertension before starting IFX) deteriorated during the follow-up. Anti-

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Table 4. Biochemical tests and Mayo score during treatment with biological agents

	At baseline	At 6 months	At 12 months	At 24 months	At 36 months	MRC after biologic agents treatment
Patient #1						
AST (×ULN)	1.11	0.77	0.61	1.34	0.71	Unchanged
ALT (×ULN)	0.80	0.74	0.48	1.49	0.57	
γGT (×ULN)	5.09	1.64	1.38	4.02	1.66	
AP (×ULN)	1.42	0.66	0.77	1.05	0.66	
Bilirubin (g/dl)	0.50	0.60	0.40	0.38	0.53	
Albumin (g/dl)	4.0	4.3	4.3	4.1	4.5	
Mayo PSC score	−0.22	−0.57	−0.95	0.31	−0.001	
Patient #2						
AST (×ULN)	0.32	0.42	0.37	0.42	–	Unchanged
ALT (×ULN)	0.23	0.37	0.26	0.23	–	
γGT (×ULN)	0.27	0.21	0.25	0.21	–	
AP (×ULN)	0.90	1.00	0.80	0.81	–	
Bilirubin (g/dl)	2.10	2.30	1.60	2.9	–	
Albumin (g/dl)	4.6	4.6	4.6	4.6	–	
Mayo PSC score	−0.55	−0.35	−0.50	−0.53	–	
Patient #3						
AST (×ULN)	1.48	1.46	1.53	1.22	–	Unchanged
ALT (×ULN)	3.70	2.13	0.86	1.23	–	
γGT (×ULN)	8.90	7.32	6.65	14.09	–	
AP (×ULN)	1.75	1.83	1.95	2.95	–	
Bilirubin (g/dl)	0.30	0.52	0.43	0.4	–	
Albumin (g/dl)	3.2	3.5	4	4.2	–	
Mayo PSC score	0.21	0.12	−0.24	0.15	–	
Patient #4						
AST (×ULN)	1.07	1.58	2.31	–	–	Unchanged
ALT (×ULN)	1.65	1.29	2.21	–	–	
γGT (×ULN)	6.98	3.14	2.71	–	–	
AP (×ULN)	1.40	2.30	3.10	–	–	
Bilirubin (g/dl)	0.73	1.83	2.28	–	–	
Albumin (g/dl)	4.1	4.0	4.0	–	–	
Mayo PSC score	0.01	0.79	1.15	–	–	
Patient #5						
AST (×ULN)	1.87	1.53	1.37	1.69	–	Unchanged
ALT (×ULN)	1.36	1.15	0.95	1.27	–	
γGT (×ULN)	2.74	2.79	2.25	2.18	–	
AP (×ULN)	3.10	2.52	2.29	2.33	–	
Bilirubin (g/dl)	0.52	0.50	0.48	0.98	–	
Albumin (g/dl)	3.9	3.9	3.9	3.6	–	
Mayo PSC score	0.14	0.01	0.07	0.41	–	

Patients #1–3 were treated with adalimumab, patient #4 with infliximab, and patient #5 with rituximab.
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; γGT, γ-glutamyltransferase; MRC, magnetic resonance cholangiography; PSC, primary sclerosing cholangitis; ULN, upper normal limit.

TNFα and other biologics have a well-demonstrated efficacy in the treatment of various autoimmune conditions, including IBD and rheumatological disorders.

Trials with biological agents for IBD (vedolizumab – a gut-specific a4b7-integrin-neutralizing monoclonal antibody, and CCX282-B – an inhibitor of CCR9) are currently ongoing, and an extension to PSC is appealing because the T-cell effector mechanism plays a pivotal role in its pathogenesis [40].

With the purpose of preventing the progression of liver fibrosis, a phase 2b, dose-ranging, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of simtuzumab (GS-6624), a monoclonal antibody against lysyl oxidase-like 2 (LOXL2), in patients with PSC is ongoing and the estimated completion date is July 2016 (NCT01672853). Moreover, a phase 2 study to determine the safety and efficacy of BTT1023, a monoclonal antibody that targets the vascular adhesion protein (VAP-1) and is used in the treatment of patients with PSC, is still ongoing (NCT0223911).

Our study has several obvious limitations. Among these are the small sample size and the small number of patients taking biologic agents. Indeed, our five cases increase the number of reported cases of PSC patients treated with biologics to 12 [25,38,39].

In conclusion, the association between PSC and IBD seems to increase the risk of cancer, but the risk of CRC may be because of the presence of IBD. Biological agents can improve liver function in PSC patients, but further studies are warranted on larger series of patients to investigate the long-term tolerability and efficacy of biologics and to identify predictors of response to this type of therapy in terms of liver function.

Acknowledgements

This work was partially supported by a University grant (ex 60% fund).

Conflicts of interest

There are no conflicts of interest.

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