REVIEW ARTICLE

Concurrent inflammatory bowel disease and primary sclerosing cholangitis: a review of pre- and post-transplant outcomes and treatment options

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ABSTRACT

Primary Sclerosing Cholangitis (PSC) is a chronic cholestatic liver disease which is associated with Inflammatory Bowel Disease (IBD) in 70% of cases. It seems PSC/IBD is a distinct phenotype that is different from PSC, and IBD alone. Hence, we review the epidemiology, pathogenesis, natural course and management of PSC/IBD before and after LT for PSC. Extensive colitis, rectal sparing, backwash ileitis, and mild symptoms are the characteristics of IBD coexisting with PSC. Moreover, PSC patients with concurrent IBD have higher risk of cholangiocarcinoma, and colorectal neoplasia predominantly in right colon and at younger age. Therefore, it is essential to monitor these individuals continuously. It is interesting to note that the course of IBD (ulcerative colitis) after liver transplantation (LT) for PSC varies greatly, and some patients may develop worsening colitis after LT despite immunosuppressive regimens. As well, management of these patients was discussed in this review.

Keywords: Primary sclerosing cholangitis, Inflammatory bowel disease, Liver transplantation, Cholangiocarcinoma, Colorectal neoplasia.

PSC/IBD definition

PSC is a rare chronic progressive cholestatic liver disease with unrecognized cause which is characterized by inflammation, and fibrosis of intra- and extra-hepatic biliary tree which can lead to end stage liver disease and portal hypertension (1, 2).

About 70% of PSC cases are accompanied by IBD which ulcerative colitis (UC) comprises the most common subtype (>75%) (3-5). UC in about 50% to 80% and Crohn disease in 20%, and we can find coexisting PSC in about 2% to 10% of the patients with UC (2, 6-8). It is widely recognized that IBD and PSC are related, and it appears that PSC/IBD is a distinct clinical phenotype with a distinctive clinical presentation from IBD alone (3, 4).

Specific clinical presentations of PSC concurrent with IBD (UC) are elucidated in Table 1 (9, 10).

PSC is the most common disease among a wide range of hepatobiliary disorders which are associated with IBD. IBD-associated hepatobiliary disorders are diseases with various pathogenic mechanisms include an immune-mediated pathogenesis whose courses are independent of the intestinal activity. There is a certain variant of PSC called small-duct PSC where there is a histological evidence of PSC while cholangiogram is normal. In small duct PSC the disease course is more benign as compared to classic PSC and the risk of cholangiocarcinoma (CCA) is not increased (2).

Epidemiology of PSC/IBD

The overall incidence rate of PSC is 0.77 per 100,000 person-years, despite significant variations among studies. According to reports, the incidence of PSC is 1.3, 0.9, and 0.5 per 100,000 person-years in Norway, North America, and the Netherlands, respectively (10). Moreover, a recent systematic review

has reported a prevalence and incidence rate ranging from 0 to 16.2 per 100.000 inhabitants and from 0 to 1.3 per 100.000 inhabitants/year, respectively (11).

Nearly two thirds of PSC patients are men with an average age at diagnosis of 40 years. Women with PSC are usually diagnosed at an older age (10, 11).

Up to 90 percent of PSC patients is reported to have ulcerative colitis based on rectosigmiod biopsis. There is typically no sex preponderance in PSC-UC patients. PSC may accompany crohn's disease (CD). Around 5-10% of PSC patients have concomitant CD. Vice versa, 0.8-5.6 percent of the patients with ulcerative colitis and 0.4-6.4 percent of the patients with CD have concurrent PSC (10, 12-14).

PSC's etiology is uncertain, however several processes have been suggested as potential contributors. The pathogenesis of PSC may be influenced by immunologic, genetic, viral, and ischemic factors. Furthermore, toxic bile acids build-up that are abnormally produced by colonic bacteria may have a part to play in the development of PSC (15).

There are different human leukocyte antigen (HLA) haplotypes which as reported are related to PSC susceptibility. These haplotypes include HLA-B8, HLA-DRB1* 0301 (DR3), HLA-DRB1*0401 (DR4), and HLA-DRB3*0101 (DRw52a) (16). UC-PSC is also recognized as a distinct disease entity, as shown by the occurrence of three UC susceptibility loci that contain the PSC-related genes REL, IL2, and CARD9. While first-degree relatives are exposed to higher risks of PSC as a result of this genetic predisposition, only a minority of PSC cases have genetic factors involved as their main element. It means that the environmental factors play the predominant role in the disease liability (17, 18).

Although clear association between PSC and ulcerative colitis suggests that there is a common pathogenesis, two disorders may occur at different times (13). PSC may occur years after colectomy for ulceractive

colitis and ulceractive colitis may first present following liver transplantation (LT) for PSC (3, 19).

It seems that "leaky gut" and bacterial translocation or absorption of bacterial endotoxins into the portal venous system via a disrupted intestinal epithelial barrier contributes to the pathogenesis of PSC by activating of kupffer cells (3, 20).

As suggested by present evidence, gut microbiome as an independent factor to IBD is relevant to the pathogenesis of PSC. Patients with PSC are typically distinguished from patients with IBD and healthy individuals based on their decreased populations of Bacteroides, Prevotella, and Clostridium cluster II, together with a fecal overrepresentation of Fusobacterium, Ruminococcus, Escherichia, Lactobacillus, and Enterococcus (21-23). One of the signs of gut dysbiosis is the translocation of bacteria into the enterohepatic circulation as well as an increase in gut permeability (24). Another potential liver-gut dialogue in PSC and ulcerative colitis pathogenesis was proposed to be linked to the enterohepatic circulation of lymphocytes. In individuals with ulcerative colitis, intestinally activated T-lymphocytes may contribute to bile duct inflammation. Additionally, the gut microbiota appears to be influenced by genetic and environmental factors (15). FUT2 is one of the genes studied in PSC and IBD that has an effect on intestinal microbiota (25). Likewise, dietary saturated fat via increasing taurocholic acid and changes in the bile acid pool was postulated to alter the microbiota in ulcerative colitis and PSC (26).

Natural course of PSC in PSC/IBD patients without liver transplantation

One of the chronic cholestatic liver diseases is Primary sclerosing cholangitis (PSC), which intra-hepatic and extra-hepatic bile ducts have progressive inflammation and fibrosis. This characterization followed by cholestasis, progressive hepatic fibrosis, and

Table 1. Clinical presentations of PSC/UC

- Extensive colitis/pancolitis
- Rectal sparing
- Backwash ileitis
- Mild intestinal symptoms with a frequently quiescent course, lower rate of the hospitalization, and steroid therapy
- Recurrent pouchitis following total colectomy
- Increased risk for colorectal cancer (76% right-sided distribution, poor prognosis due to a more advanced stage at presentation, and younger age at onset)
- Increased risk for cholangiocarcinoma

finally decompensated cirrhosis in over 10–15 years (27). PSC's natural history is quite unpredictable. 25% of asymptomatic individuals pass away within 7 years, while 50% of symptomatic patients pass away within 8 years. The bleak prognosis has been dramatically improved by LT (28). LT is currently only known option for curative therapy of eligible PSC patients (27). Based on the literature, a median time ranging from 7 to 22 years was reported for diagnosis to death or LT of these patients (29, 30). As evidenced by a study in Sweden on a large group of IBD patients, a lower risk of LT or death was observed when colectomy is performed before PSC diagnosis (24).

Weismüller et al. reported a less progressive clinical course of PSC in patients with CD compared with UC. The absence of IBD was a positive prognostic factor for PSC patients as well (31).

Natural course of PSC in PSC/IBD patients after liver transplantation

The outcome of PSC patients following orthotopic liver transplantation (OLT) is favorable with one- year and 5-year survival of about 95% and 85%, respectively (1, 32).

Recurrence of PSC following LT is not uncommon and affects 15–25% of patients, resulting in a significant number of patients losing their grafts. Following transplantation, recurrence is said to occur on average 4.6 years later (32, 33). Recurrence of PSC after LT was seen in 14.3% of patients which 48.7% of them developed graft failure. Factors associated with rPSC are younger age and presence of UC. Death have 4-fold increasing in rPSC and graft survival rates 1, 5,

and 10-year will decrease to 98%, 84%, and 56% respectively compared to 95%, 88%, and 72% in patients with no rPSC (34).

It seems that PSC recurrence has little effect on patients' survival and the survival of the patients with recurrent PSC is the same as those without an evidence of relapse (35). The fate of PSC patients following OLT can be exacerbated by recurrence of PSC in the allograft as well as deteriorating IBD, according to a research, despite a favorable post-transplant prognosis (1). Recent data showed graft loss in a significant proportion of patients with rPSC after OLT (36), this will affect long-term survival (37).

Known risk factors of PSC recurrence following LT in patients with and without concomitant IBD are shown in Table 2 (33, 35, 38-44).

Natural course of IBD prior to liver transplantation in PSC/IBD patients

Severe progressive PSC requiring OLT is associated with a milder course of UC, decreased incidence of colon dysplasia/cancer and decreased risk of colectomy. Need to OLT, and higher Mayo PSC risk score at diagnosis of PSC independently decreases the need for colectomy while occurrence of dysplasia or cancer increases the chance of colectomy in PSC patients with underlying UC (20).

Colitis in people with PSC and UC manifests earlier in life and has a milder or quiescent course than in those with IBD alone. Most of these patients are asymptomatic, although some have rectal bleeding (45). Frequent pancolitis, infrequent rectal sparing and backwash ileitis (7, 46, 47). Worse prognosis has been

Table 2. Factors associated with PSC recurrence after LT (liver transplant)

		Risk factors of recurrent PSC	Protective factors of recurrent PSC
IBD	At LT	▪ Younger donor age ▪ Active IBD ▪ High INR	▪ Colectomy before or at LT ▪ Good control of intestinal inflammatory activity before and after LT
	Post-LT	▪ Treatment with tacrolimus ▪ CMV infection in the recipient ▪ Presence of at least one episode of acute cellular rejection ▪ De novo IBD ▪ Steroid maintenance therapy	
Non-IBD		▪ Donor-recipient gender mismatch ▪ First-degree relative donor-recipient relationship ▪ HLA-A locus mismatch ▪ Older donor age ▪ Living donors ▪ High MELD score	

seen in patients with large duct disease (48, 49).

Unlike UC, in patients with severe PSC and CD which requiring LT, PSC does not affect clinical consequence of CD (45).

The course of IBD following liver transplantation in PSC/IBD patients

Following LT for PSC, the progression of ulcerative colitis varies greatly (50-52). In a review study, 39–82% of patients exhibited no discernible change, whereas 26-78% of patients reported an improvement in their IBD activity. About 5.9-50% of patients experienced worsening of intestinal inflammatory activity despite the transplant immunosuppressive regime (15, 53-55).

All in all, some risk factors for preexisting IBD deterioration or flares following LT have been suggested in Table 3 (39, 50, 56-61).

A portion of patients, without prior history of IBD, going through LT for PSC, may develop IBD post transplantation despite the transplant immunosuppression which is known as de novo IBD. De novo IBD is reported in 14-30% of PSC patients after LT (25, 39, 41, 62, 63). Post-transplant cytomegalovirus infection is one of the potential risk factors of de novo IBD and may play a pathogenic role (58).

Management of PSC in PSC/IBD patients without liver transplantation

PSC associated with IBD is treated in the same manner as PSC without IBD (5). To date, no specific treatment has been identified that can halt the progression of liver disease in PSC patients. Hence, liver failure and complications of portal hypertension occur in plenty of patients. That time OLT is the only potentially curative option (35, 55).

Treatment of PSC with IBD and without IBD are the same. We have no medical treatments to modify the

course of classic PSC. Several studies showed ursodeoxycholic acid (UDCA) can improve LFT but some of them failed to show benefit from UDCA (64, 65). Despite previous studies, UDCA does not prevent the cancer (CCR or CCA) in PSC (66, 9) so not recommended by PSC guidelines for prevention or treatment of cancer (17, 67), also we do not recommend corticosteroids and immunosuppressant despite the presumed immune-mediated pathogenesis (17). Thus, PSC treatment is control of symptoms and management of complications (cholangitis pruritus, varices, jaundice, liver decompensation and malignancies).

Endoscopic interventions, such as ERCP are a mainstay of PSC management (68), especially in PSC with acute cholangitis for treatment of suspicion of CCA and dominant strictures (6).

Patients with PSC who have advanced liver damage require LT. Recurrent cholangitis, severe pruritus, and a few cases of CCA in the very early stages are further indicators for LT (6). Survival rates after LT for PSC related end-stage liver disease have been reported between 70% to 86% in the patients with 10 years and 5 years after LT respectively (25). 12%-37% of cases may show recurrence of PSC after LT which have impact on long term graft and recipient survival (38).

Management of IBD in PSC/IBD patients prior to liver transplantation

Management of IBD in PSC/IBD patients is not different from that of IBD without PSC (69, 70).

Management of IBD in PSC/IBD patients following OLT

The recommended treatment of IBD after OLT in terms of PSC is the same as overall treatment of IBD (60) (Figure 1). There are little data about optimal therapeutic approach to IBD flares in liver transplanted patients, especially when they are refractory to conventional treatment (57). IBD

Table 3. Risk factors for preexisting IBD deterioration or flares following LT (liver transplant)

- The immunosuppression type after LT can affect ulcerative colitis activity. Tacrolimus-based immunosuppressive regimens are considered a risk factor for IBD flare after LT.
- Short interval of IBD before LT
- Active IBD at the time of LT
- Discontinuation of 5-ASA at the time of LT
- Early steroid withdrawal after LT
- Smoking at the time of LT
- The duration after LT
- CMV mismatch or acute CMV infection after LT

treatment options include immunosuppressive medications used after OLT, such as steroids, azathioprine, and cyclosporine (61). Hence, the course of IBD following OLT is expected to be improved or at least remained mild or asymptomatic just like pre-OLT.

Induction followed by maintenance therapy with oral and topical 5-ASA for mild-to-moderate cases may be appropriate. Some centers initiate 5-ASA empirically shortly after transplantation. Azathioprine, Cyclosporine or combination of them may be an appropriate option for moderate-to-severe cases (52, 57, 60, 71).

There are no significant interactions between 5-ASA compounds, and transplantation-related immunosuppressive agents; although sulfasalazine, mesalamine and balsalazide may have interaction with azathioprine and increase the risk of leukopenia (52).

Induction may be required with oral or intravenous corticosteroids with a prolonged tapering time. In these patients, maintenance therapy with azathioprine (2-2.5 mg/kg body weight per day) may be warranted (50, 52). Therapeutic regimens including tacrolimus seem to be avoided in these patients while azathioprine might be favorite (39, 59).

Anti-TNF α medication may be useful in certain individuals with severe IBD flare-ups who are not responding to intravenous corticosteroids or in IBD patients who are medically resistant. There is minimal knowledge on the effectiveness and long-term safety of these medicines in OLT patients who are also receiving immunosuppression. These agents should be used with caution in terms of potential side effects. Thus, post-transplant anti-TNF therapy can be an effective option for management of refractory moderate-to-severe IBD (43).

It is reported in the literature that so far just 31 cases were treated with anti-TNF α agents including infliximab and adalimumab for IBD recurrence post-OLT. Among these patients, clinical response and mucosal healing were seen in 77.42% and 43% of cases, respectively and in 83.3% of cases steroid withdrawal was possible (72). Active search for opportunistic infections and neoplasm prior to the initiation of anti-TNF agents is mandatory (72).

We know very little about the dangers of severe infections when anti-TNF medication is combined with LT-related immunosuppression for refractory IBD (43, 72–78). According to a research by M.J. Westerouen, immunosuppression brought on by LT has no appreciable impact on the risk of severe infections when combined with anti-TNF medication (73). There are case reports of 11 patients with refractory ulcerative colitis post-OLT that vedolizumab was used for treatment. It was effective at inducing clinical, and endoscopic remission in the majority of patients (12, 43, 79-81). Ustekinumab was reported to be safe and effective in a case of CD unresponsive to anti-TNFα agents, including infliximab, adalimumab, and certolizumab in an OLT patient (82).

On average, 9% of the patients with medically refractory IBD or colorectal carcinoma require proctocolectomy. The experience about the role of colectomy in the course of PSC/UC after LT is limited. Increased short-term risk while no impact on long-term risk of LT or death, decreased risk of colorectal cancer (CRC), and decreased risk of recurrent PSC following
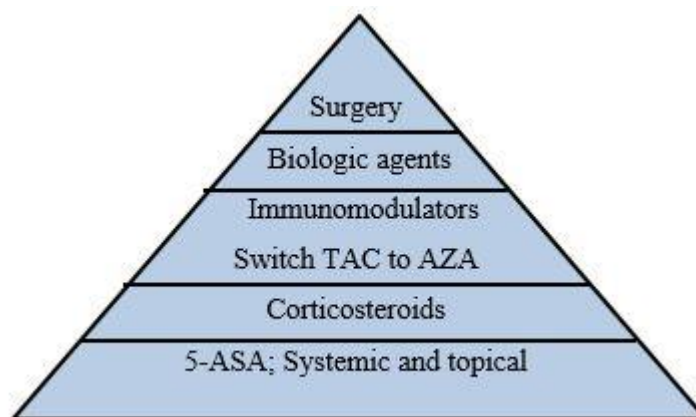

Figure 1. Step-by-step treatment of ulcerative colitis after liver transplantation for PSC

LT are reported as some effects of colectomy on the course of PSC/UC patients (83).

PSC/IBD patients with diarrhea in post-transplant setting

One of the primary signs of IBD is diarrhea. On the other hand, although its real prevalence is unclear, it is frequent in the post-transplant environment (84). The two main contributing factors to its genesis are infections and medicines. Cytomegalovirus and C. difficile are the most common infections should be sought. Other uncommon causes should be considered. It is necessary to evaluate patients for routine enteric pathogens such as campylobacter, salmonella, and shigella. Viral infections such as astrovirus, adenovirus, and rotavirus can cause a severe but self-limited acute diarrhea. Rarely, infections by microsporidia, cryptosporidia, and parasites such as entamoeba histohytica may develop in LT patients (85-87).

Many immunosuppressive medications, such as mycophenolate mofetil, tacrolimus, cyclocporine, and to a lesser degree sirolimus can cause diarrhea as their side effects. It seems that immunosuppressant-related diarrhea is dose dependent and resolves following dose reduction or discontinuation (85, 86, 88).

Besides, considering Roux-en-Y hepaticojejunostomy in PSC patients, small bowel bacterial overgrowth is considered a cause for chronic diarrhea after LT (85).

Patients may develop diarrhea thanks to flare-up of the preexisting IBD or less commonly due to de novo IBD (52, 84).

Other uncommon causes of diarrhea in these patients are graft-versus-host disease (GVHD), post transplantation lymphoproliferative disease (PTLD), and colon cancer (85, 86, 89).

Cholangiocarcinoma in PSC/IBD patients

CCA is a common and lethal malignancy that complicates PSC (90). The incidence of CCA in PSC patients is also 0.5-1% per year, with lifetime prevalence of 5-10%. The first year following a PSC diagnosis is particularly crucial for the development of CCA, however the window between a PSC diagnosis and the onset of CCA is around 6 years. The screening of PSC patients for CCA is interesting because the majority of patients who acquire CCA pass away within a year (31). Patients with concomitant PSC and IBD have an increased risk of CCA. A cumulative risk of 7-14% for CCA was reported in these patients (90).

The risk of CCA in the patients with ulcerative colitis is 1.22 which is significantly higher than PSC patients with CD or without IBD who have a risk of 1.11 and 1.02, respectively (91). A recently performed meta-analysis of observational studies shows that compared to patients with IBD alone, patients with IBD and PSC suffer from 3.41 times higher risk of colorectal cancer. Based on IBD type classification, PSC is recognized as a risk factor for colorectal cancer in people with UC but not CD (92). Additionally, compared to individuals with just UC, people with both PSC and UC had a higher chance of developing CCR quickly after diagnosis (93). Consequently, it is highly recommended to perform cancer surveillance not only in case of PSC-UC patients, but also for patients with ileal pouch-anal anastomosis (IPAA) after colectomy (94). Moreover, the risk of pouchitis in IBD patients with IPAA and PSC is almost two times that of patients without PSC (90).

The following factors may raise the likelihood of CCA in the patients with PSC (10, 31, 90):

- Older age at PSC diagnosis
- Smoking
- Alcohol use
- Elevated bilirubin

Table 4. Summary of studies investigating CRC risk in PSC, UC and PSC/UC patients

	After 5 years	After 10 Years	After 20 years	After 25 years
PSC patients				
Terg et al. (98)	-	11%	18%	-
UC patients				
Fevery et al. (99)	2%	7%	15%	-
Terg et al. (98)	-	2%	7%	-
Broome' et al. (97)	-	2%	5%	10%
PSC/UC				
Claessen et al. (100)	-	14%	31%	-
Broome' et al. (97)	-	9%	31%	50%

- Variceal bleeding
- Polymorphism of the NKG2D gene
- A longer duration of associated IBD
- Presence of colorectal cancer or dysplasia in patients with ulcerative colitis
- History of proctocolectomy

Colorectal cancer in PSC/IBD patients

The annual incidence rate of CRC in PSC patients is less than 0.5%, with a 30-year cumulative risk of 13% (31). IBD patients have a 2% chance of CRC, which is 5 to 15 times greater than the normal population over the course of 30 years. However, those who also have PSC have a higher chance of developing CRC (10, 50). The chance of CRC development can get to 30% at 20 years after diagnosis of concurrent IBD and PSC (90). This association was first proposed by Broome' et al. in 1992 with a cumulative risk of 50% at 25 years for CRC development in PSC/UC patients (14, 96, 97). The risk of CRC development in PSC, UC, and PSC/UC patients is elucidated in Table 4.

Although PSC/UC patients are at greater risk of colorectal cancer, there is a debate that whether LT alters the progression of colorectal neoplasia in these patients or not (101). The risk of CRC in PSC/IBD patients increases after LT (50, 102). CRC occurs within few years after LT in around 7% of IBD patients who transplanted for PSC. Hence, regular annual colonoscopic surveillance with biopsies for CRC appears to be logical (32). Colitis severity, illness duration, early start, familial history of CRC, and the emergence of dysplasia in the affected colon are all well-known risk factors for CRC in people with IBD. PSC in and of itself is thought to be a significant risk factor for CRC in IBD patients. After LT, the risk of CRC might be even more elevated or its occurrence might be speeded up (14, 102). Prophylactic colectomy in selected patients at higher risk for CRC can be an appropriate strategy to prevent CRC, but it is less used in LT centers (50).

Moreover, CRC associated with PSC/UC has distinct characteristics. It usually occurs at a younger age, in more proximal colon (up to 76% of cases have right-sided distribution) and carries a poor prognosis in terms of a more advanced stage at diagnosis (10).

Therefore, overall risk of CRC in PSC/CD is not as strong as PSC/UC and the results are conflicting (14). Lindström et al. found that PSC is a risk factor for development of colonic dysplasia and carcinoma in CD

(OR=6.78) (14, 103). Another study on PSC/IBD patients did not find an elevated risk of CRC or dysplasia in CD (14, 104).

Surveillance

PSC patients with or without accompanying IBD are at specific risk of hepatobiliary and colorectal cancers. As a result, coupled with age-appropriate screening programs, it is essential to be regularly monitored for gallbladder carcinoma, cholangiocarcinoma, colorectal, and hepatocellular carcinoma. This strategy provides the diagnosis of cancer at early and likely treatable stages (10). Recommended surveillance program in PSC/IBD patients is as follows:

- Yearly ultrasound examination for gallbladder cancer (10, 91).
- Imaging assessment of biliary tree via MRI, MRCP, or ultrasound, as well as serum levels of the tumor marker carbohydrate antigen (CA) 19-9 every 6 to 12 months to detect evidence of CCA (10).
- PSC patients without concurrent IBD should undergo surveillance colonoscopy every 3 to 5 years. Surveillance colonoscopy in those with coexistent IBD should be performed every one to two years from the time of diagnosis of PSC (6, 10, 50, 90). Annual colonoscopy in PSC/IBD patients who have had a liver transplant appears more reasonable in terms of more increased risk of colon cancer (10, 50, 90).
- PSC patients with cirrhosis need to be screened for hepatocellular carcinoma (91).

Conflict of interests

There is no conflict of interest for authors of this article.

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