Etiologic and clinical studies in primary sclerosing cholangitis
Ponsioen, C.Y.

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Chapter II

Primary sclerosing cholangitis; a clinical review

Cyriel J. Ponsioen and Guido N.J. Tytgat

Department of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, The Netherlands
SUMMARY

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease characterised by fibro-obliterative inflammation of the entire biliary tree. It is a slowly progressive disease with an undulating course, resulting in terminal biliary cirrhosis after a median period of about 12 years after diagnosis. The etiology of the disease is unknown and there is no effective therapy that can halt disease progression. Around 8% of PSC patients develop cholangiocarcinoma, which, by the time it is diagnosed, cannot be treated curatively.

The purpose of this paper is to review the current knowledge about PSC and to speculate on future strategies to address the issues of etiology and therapy.
INTRODUCTION

Primary sclerosing cholangitis is a chronic progressive cholestatic liver disease characterized by patchy inflammation of the biliary tree leading to obliterative fibrosis. There are several important issues concerning PSC that remain to be resolved. First: the etiology is still unknown. Second: there is at present no therapy that has proven to be efficacious in halting disease progression. Third: there are no reliable markers that can indicate the development of a cholangiocarcinoma in an early - curatively resectable- stage.

The purpose of this review is to outline the current knowledge about PSC and to speculate on future strategies to address the above-mentioned issues.

DIAGNOSIS

The criteria for the diagnosis are listed in table 1 (1).

The diagnosis of PSC is usually made by cholangiography. Hepatic histologic biopsy findings can be non-specific with a considerable degree of sampling variability, because the disease may not be evenly and diffusely spread throughout the liver and the most characteristic lesion, the so called "onion-skinning", can easily be missed (2-4).

We perform liver biopsy pro diagnosi only when endoscopic retrograde cholangiopancreatography (ERCP) fails or leaves considerable doubt. The histologic features of PSC can sometimes be compatible with autoimmune hepatitis (AIH), and together with the frequent finding of antinuclear- and anti-smooth muscle autoantibodies, have given rise to the issue of an overlap syndrome (5, 6). Whether this is a true entity or merely a reflection of the limitations of the scoring system for AIH, as suggested by the careful study of Boberg et al, remains to be resolved (7).

When inflammatory bowel disease (IBD) is present, this can give a clue, given the well-known association of especially ulcerative colitis (UC) and PSC (8-10).

There is a preponderance of HLA DR 52a of up to 55 % in PSC patients, but this has limited predictive value, inasmuch as the prevalence in the general population is around 30 % (11, 12).

There is presently no specific serological marker available for PSC. Antibodies against neutrophils (pANCA) have been found in patients with PSC and UC in 60-86 % and 33-83 % respectively, depending on the method used (13-16). The antigen(s) to which these pANCAs are directed have not been clearly distinguished, but
recently Stoffel et al. reported that in about 40% of sera from IBD and PSC patients, ANCA was directed against bactericidal/permeability-increasing protein (BPI) (17).

Distinguishing between PSC and UC by determination of the ANCA titre and IgG subclass is not regarded to be helpful (16). Therefore, the presence of pANCA can give additional information pointing to PSC only if pre-existing IBD has been ruled out.

So the mainstay of diagnosis is still cholangiography. The classical picture with the beading appearance of the bile ducts together with various strictures of different length and decreased arborization, is easily appreciated as illustrated in Figure 1.

The broad spectrum of abnormalities that can be found is shown by the classification of cholangiographic findings as proposed by Majoie et al. in 1991 and listed in Table 2 (18). In this series of 40 patients from our institution, there were two cases with only intrahepatic involvement. Here the differential diagnosis of primary biliary cirrhosis, systemic mastocytosis, polycystic liver disease, and liver cirrhosis resulting from other causes must be considered (19, 20). Three patients showed only extrahepatic abnormalities. In these cases the possibility of cholangiocarcinoma, ischemic injury, or previous bile duct surgery must be considered.

Magnetic resonance cholangiopancreatography (MRCP) is a new imaging technique that is increasingly being applied in biliary and pancreatic diseases. So far its resolution is too limited to allow accurate diagnosis, especially of the intrahepatic biliary tree.

Table 1. Criteria for Diagnosis of PSC

1. Presence of typical cholangiographic abnormalities of PSC (involving bile ducts segmentally or extensively)
2. Compatible clinical, biochemical, and hepatic histologic findings (recognising that they are frequently non-specific)
3. Exclude the following in most instances:
   - Biliary calculi (unless related to stasis)
   - Biliary tract surgery (other than simple cholecystectomy)
   - Congenital abnormalities of the biliary tract
   - AIDS-associated cholangiopathy
   - Ischemic stricturing
   - Bile duct neoplasms (unless PSC previously established)
   - Exposure to irritant chemicals (such as floxuridine, formalin)
   - Evidence of another type of liver disease, such as primary biliary cirrhosis or chronic active hepatitis

Reproduced with permission from (1).
In general, PSC must be differentiated from other forms of sclerosing cholangitis such as: 1) ascending intestinal bacterial infections as a complication of stone disease or biliodigestive anastomosis; 2) opportunistic infections such as cryptosporidiosis and cytomegalovirus infection in the setting of immunodeficiency (21, 22); 3) vascular injury to the hepatic arterial tree after previous surgery, selective cytotoxic drug infusion, or in the case of paroxysmal nocturnal hemoglobinuria (23-25); 4) congenital abnormalities. The differential diagnosis is reflected in the exclusion criteria of Table 1.

Table 2.

Classification of cholangiographic findings in PSC

<table>
<thead>
<tr>
<th>type of duct involvement/ classification</th>
<th>cholangiographic abnormalities</th>
</tr>
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<tbody>
<tr>
<td>intrahepatic</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Multiple strictures; normal calibre of bile ducts or minimal dilatation</td>
</tr>
<tr>
<td>II</td>
<td>Multiple strictures, saccular dilatations, decreased arborization</td>
</tr>
<tr>
<td>III</td>
<td>Only central branches filled despite adequate filling pressure; severe pruning</td>
</tr>
<tr>
<td>extrahepatic</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>slight irregularities of duct contour; no stricture</td>
</tr>
<tr>
<td>II</td>
<td>segmental stricture</td>
</tr>
<tr>
<td>III</td>
<td>stricture of almost entire length of duct</td>
</tr>
<tr>
<td>IV</td>
<td>extremely irregular margin; diverticulum-like outpouchings</td>
</tr>
</tbody>
</table>

Reproduced with permission from (18).
Histopathology

Depending on the disease stage, the liver histologic picture can vary from some portal infiltration to frank biliary cirrhosis with ductopenia, and extensive periductular fibrosis with obliteration of the ducts, the so-called "onion-skinning", (see Fig. 2).

The portal zones are infiltrated with small and large lymphocytes, some polymorphs,
and occasional macrophages and eosinophils (26). Granulomas are scanty or absent. The ductal epithelium, which is normally cuboidal and regular, becomes atrophic and pleomorphic (4). The duct lumen becomes irregular and eventually the lining epithelium disappears. Together with the epithelial changes, the basement membrane of the duct becomes disrupted and re-duplicated. As the fibrosis increases, the duct converts to a nodular scar, a so-called "tombstone".

Another feature characteristic of PSC is the saccular dilatation of septal bile ducts not invariably associated with stenosis distally (27).

The histologic abnormalities of PSC have been divided into four stages, the so-called Ludwig classification (28). Stage 1 (portal) shows few duct lesions, along with portal inflammation and oedema; stage 2 (periportal) shows widespread duct lesions and portal tract expansion due to piecemeal necrosis and periportal fibrosis; stage 3 (septal) shows bridging fibrosis; and stage 4 shows biliary cirrhosis.

Fig. 2. Portal triad in a liver biopsy specimen of a PSC patient. Concentric periductular fibrosis (PF) and portal lymphocytic infiltration (LI) can be seen. Some of the lymphocytes are in close contact with the ductular epithelium (arrows). A, artery; B, bile duct. (Hematoxylin and eosin X 250).
Epidemiology

There are no direct data available concerning the prevalence of PSC, so it can only be generally inferred from the well-known association of PSC with UC. In an older series from the United Kingdom, the percentage of patients with UC who concomitantly had PSC was 2.4% (29). In a more recent study from Sweden, a point prevalence for UC of 170 per 100,000 inhabitants was found (30). Of these, 3.7% had PSC. This would yield a prevalence of 6.3 per 100,000 inhabitants. In a later retrospective study of 305 Swedish PSC patients, 72% had also UC (8). Adjusting for this proportion would yield a prevalence of 8 per 100,000 inhabitants. About two-thirds of patients are male. The median age at diagnosis is 36-39 years (8, 31).

PSC is strongly correlated with IBD. Ulcerative colitis and Crohn's disease are found in 71-78% and 2-13% of PSC patients, respectively (8, 10, 32, 33). In contrast with these figures are data from Japan, where IBD is only found in 18% of PSC patients (34, 35).

Symptoms

The onset of complaints is usually insidious. Symptoms consist of fatigue, pruritus, intermittent right upper quadrant pain, and/or bouts of cholangitis accompanied by transient jaundice. These attacks can be precipitated by gallstones, which are now regarded to be part of the spectrum of PSC (36, 37). Not infrequently the diagnosis is made upon ERCP for suspected symptomatic gallstone disease. The time lag between the onset of symptoms or liver enzyme disturbances attributable to PSC and the actual diagnosis can be appreciable. In the previously mentioned series of 305 Swedish patients, the median delay was 52 months (range 0-451) (8).

As the disease progresses the symptoms become more chronic and eventually signs of portal hypertension caused by biliary cirrhosis, including ascites and variceal bleeding, may become apparent.

Natural History and Complications

Natural history
The progression of the disease can be highly variable and fluctuating. In our own
series, one patient is known with the disease for more than 21 years now and, without medication, is virtually symptom-free, with no signs of portal hypertension, whereas another patient progressed to intractable decompensated liver cirrhosis within 8 months after the onset of symptoms. This degree of variability is well known in the literature.

There have been three retrospective series reported concerning the natural history of PSC, which contain more than 100 cases. All three series report an estimated median survival until death or liver transplantation of approximately 12 years (8, 32, 38).

Using multivariate regression analysis, independent prognostic variables were looked for. In the Swedish series of 305 patients, age, histological stage, and serum bilirubin were applied as independent variables in a formula, to obtain a prognostic index (8). In a multicenter study comprising 426 patients serum bilirubin, age, histological stage, and splenomegaly were identified as independent variables of a prognostic model (39).

Complications

When a tight stricture occurs in the common bile duct or the main branches to the left and right lobe, it is called a dominant stricture. The exact prevalence of these strictures is not known, but has been estimated to be around 10% in a large group of patients with PSC (40).

Patients who develop a dominant stricture commonly present with symptoms of progressive cholestasis, *i.e.* jaundice, pruritus, or cholangitis. Eventually, PSC leads to biliary cirrhosis, which can give rise to symptoms of decompensation such as ascites, encephalopathy, coagulopathy, and variceal bleeding. At present, terminal liver failure can be averted effectively by orthotopic liver transplantation (OLT) (41, 42).

Suppurative cholangitis is a well-known complication of PSC and should prompt clinicians to perform ERCP to look for dominant extrahepatic strictures or stone disease. As mentioned earlier, biliary calculi can occur in a substantial part of PSC patients.

Procedure-related suppurative cholangitis can be prevented effectively by the use of broad-spectrum antibiotics before and in the first 24 h after ERCP. Since the introduction of this regimen several years ago, we have encountered this complication only once in our clinic.

A very disturbing complication of PSC is the development of cholangiocarcinoma. In the three larger studies mentioned earlier, this occurred in 6-8% of patients. It is
possible that this may be an underestimation of the true incidence, inasmuch as not all patients that die from liver failure are autopsied. Also, long-standing duration of liver disease is not a prerequisite for the development of cholangiocarcinoma (43). Clinically as well as cholangiographically, cholangiocarcinoma can have a presentation similar to that of a dominant stricture. After diagnosis, the overall median survival is reported to be only 5 months (44).

Detection of cholangiocarcinoma prior to OLT is important, because approximately 70% of patients with this complication, even when it is found incidentally in the resected liver, die within 1 year after OLT (31, 43, 45). Abu-Elmagd et al. found in their group of 169 transplanted PSC patients 18 cholangiocarcinomas (10.6%), for which the 5-year survival rate was 26.7% (46). Most transplant centres will reject PSC patients with cholangiocarcinoma because of these poor outcomes. In The Netherlands, a negative brush cytology of a suspicious stricture is a prerequisite for transplantation.

The reliability of brush cytology for the detection of cholangiocarcinoma in general is however doubtful. In our experience, false negative and especially after stenting-false positive results are possible. The sensitivity is reported to range from 20 to 100% (47-50). Because of the presence of thin-walled sacculations, we regard biopsy as too hazardous. In addition, the often-required sphincterotomy is unattractive in PSC patients, because the natural barrier against enteric pathogens is then destroyed.

Recently, p53 protein overexpression was reported to be found in most cholangiocarcinoma specimens of PSC patients and not in liver tissue of PSC patients without cholangiocarcinoma (51). K-ras oncogene mutations have also been demonstrated in cholangiocarcinoma (52). Perhaps it will be possible in the future to detect cholangiocarcinoma in an earlier -still curatively resectable- stage with the help of such tumor markers, or at least with more reliability, so that the serious decision to perform an OLT can be based on more solid information.

ETIOLOGY AND PATHOGENESIS

The etiology of PSC is essentially unknown. What are the hypothetical options and the evidence to support or discard them? For convenience in this discussion, we have divided the possible causes in non-immune versus immune mechanisms.
Non-immune mechanisms

These mechanisms can be subdivided in infectious, toxic, ischemic, and genetic.

Infectious mechanisms. Several viruses have been implicated in the etiology of PSC. In immunocompromised hosts, CMV has been found to be a cause of sclerosing cholangitis (22). However, a recent study from Mehal et al. ruled out CMV in immunocompetent PSC patients (53). Reovirus type 3, which also displays tropism for bile duct epithelium, has been detected in neonatal biliary atresia with a histologic picture of fibrous obliteratorive cholangitis (54). However, an attempt to associate this virus to PSC cases was negative (55). Therefore, the hypothesis of a viral origin as the cause of PSC has not been substantiated, although extensive viral screening, to our knowledge, has not been performed.

The close association between PSC and IBD led Boden et al. in 1959 to believe that the pericholangitis they observed in UC patients, was the result of portal bacteremia (56). In a subsequent paper, they reported benefit from long term tetracycline therapy (57). In time, their hypothesis was refuted for the following reasons: Portal bacteremia was not reproduced in patients with UC who were submitted for surgery (58); portal vein phlebitis, a typical feature of portal bacteremia was not found in PSC (59, 60); the reported effect of long term tetracycline could not be reproduced (61); the portal infiltrate is not very consistent with pyemia, in that neutrophils are rather inconspicuous; liver abscesses are quite uncommon; and the reticuloendothelial system within the liver is regarded as an effective means of clearing enteric bacteria.

Toxic mechanisms. What about toxic substances such as formylated peptides of bacterial endotoxins permeating through an inflamed colon lining? In a rat model, administration of these substances caused periportal inflammation with neutrophils and eosinophils (62). A strong argument against the role of bacterial metabolites and the portal bacteremia hypothesis is the natural history of PSC in relation to UC. PSC can occur without UC, can precede it by several years, and can develop years after proctocolectomy (63).

Hepatotoxic bile acid metabolites such as lithocholic acid generated by the gut flora have also been implicated (64). However, the composition and concentration of bile acids in bile and portal blood were not found to be significantly abnormal in PSC or IBD patients (65). Furthermore, in contrast to animals, the human body can rapidly sulphate and thereby detoxify lithocholic acid (66).

MDR2 gene knock-out mice lack the P-glycoprotein canalicular transporter for biliary phospholipids and develop a non-suppurative cholangitis, which resembles human chronic cholestatic liver diseases such as PSC (67). Although van Nieuwkerk
et al. could not demonstrate impaired phospholipid content of bile in PSC patients, this animal model may prove useful for intervention studies (68).

**Ischemic mechanisms.** The bile ducts are supplied by the hepatic arterial tree. Accidental damage occurring during surgery or as a complication of cytotoxic drug infusion in the hepatic artery can lead to a form of sclerosing cholangitis (23, 24). However, no major vascular abnormalities were found in a study of peribiliary arteries and arterioles of 20 explanted livers from PSC patients who underwent OLT (69).

**Genetic mechanisms.** There are incidental reports of familial occurrence of PSC (70-73). Certain HLA haplotypes are found with increased prevalence in PSC. Several investigators found a correlation of PSC with the HLA B8 and DR3 haplotype (74, 75). Prochazka et al. reported a 100 % association in 29 PSC patients with end-stage disease with the HLA DRw52a allele, using serological HLA typing (76). This finding was not confirmed by a Swedish study of 21 patients (11). The association with the HLA DRw52a allele was only 52 % and was not statistically different from the 28 % prevalence in a healthy control group. Farrant et al. found comparable prevalences in 71 British PSC patients (77). The discrepancy was explained by the study methods used. In the former report, indirect serological criteria were applied, which overestimate the frequency of this allele. In our own series of 96 Dutch PSC patients, using very specific PCR-SSP techniques, HLA DRw52a was present in 42 %. Overall, although the correlation is not very strong, these findings point to a certain degree of genetic susceptibility.

As mentioned previously, pANCAs have been found in PSC in 60-86 % (13-16). In our own PSC population, pANCA was found in 74 % of patients. To determine whether this feature represented a genetic marker for disease susceptibility, Bansi et al. performed a screening for ANCA in unaffected first degree relatives of PSC and UC patients (15). Only 3 % had ANCA, which was attributable to UC, rheumatoid arthritis, and systemic lupus erythematosus, respectively. They concluded that ANCA is not a genetic marker for increased disease susceptibility to PSC or UC in the British population.

**Immune mechanisms**

Cellular immune factors seem to play a prominent role. This may be inferred from the composition of the portal infiltrate, which is composed mainly of T-lymphocytes, the majority of which are CD4-positive (78, 79), whereas neutrophils are scanty. Normal bile duct epithelium expresses HLA class-I antigens but not HLA class-II
antigens (80). In two studies, HLA DR expression was shown on biliary epithelial cells from PSC patients (81, 82). Evidence of activation of some of the T-cells surrounding the bile ducts, indicated by expression of interleukin-2 receptors or HLA DR, has been reported (79). The finding of HLA class-II expression however, is not unique, inasmuch as HLA DR is found also on bile duct epithelium in patients with extrahepatic obstruction (82, 83). Nevertheless, the presence of HLA class-II molecules on biliary epithelium is an interesting feature. Potentially, these molecules can present a putative allo- or autoantigen to class-II restricted T-lymphocytes, thus initiating an inflammatory response.

Ueno et al. reported the development of immune-mediated cholangitis in rats after immunization with rodent bile duct cells (84). The histology showed similarities with human cholangiopathies. Das et al. found epitopes on extrahepatic biliary epithelia that cross-reacted with a monoclonal antibody developed against a 40 kD protein on colonic epithelial cells (85). Later, this group demonstrated that circulating IgG antibodies against this shared peptide were present in about two thirds of 16 PSC patients, and not in patients with other liver disorders such as primary biliary cirrhosis, secondary extrahepatic biliary stricture, or alcoholic liver cirrhosis (86). The putative pathophysiologic role of these antibodies has not been settled so far.

These cellular and humoral immune abnormalities, the previously mentioned association with certain HLA haplotypes, the high prevalence of pANCA, and the close connection with inflammatory bowel disease all support the contention of an immunological disturbance as the underlying cause of PSC.

**TREATMENT**

**Medical treatment**

At present, there is no medical treatment that has been proven to halt disease progression. An important drawback in medical intervention studies is the slow progression of PSC, with spontaneous fluctuations. Especially in the early phase of the disease, when medical intervention may be most beneficial, many patients are asymptomatic and their disease remains unnoticed.

Several immunosuppressive agents such as prednisone, azathioprine, methotrexate, and penicillamine have been employed in PSC patients, all with limited beneficial effect (87-93). Other than a few small, uncontrolled reports of corticosteroid efficacy (94, 95), there are no prospective controlled trials evaluating its effect in PSC. Lindor et al. treated 12 PSC patients with prednisone 10 mg daily in
Combination with colchicine 0.6 mg b.i.d. and compared the results with those of a historical control group (87). After 2 years, the authors concluded that this combination did not inhibit the long-term clinical or biochemical progression of PSC. A multicenter trial of corticosteroid therapy is currently underway in The Netherlands.

So far, there are only a few case reports regarding the use of azathioprine in PSC (89, 90).

Two papers from Kaplan and associates suggested a favourable effect of methotrexate (91, 96). Subsequently, these and other investigators could not confirm these results (92, 97). Penicillamine was tested in the Mayo Clinic in a randomised, placebo controlled trial including 70 PSC patients (93). After 3 years of follow-up, no beneficial effect on symptoms, biochemistry, histology, disease progression, or survival could be detected, whereas toxicity was appreciable.

Considerable interest has arisen into the use of ursodeoxycholic acid (UDCA) in patients with PSC. Several small, controlled trials showed substantial improvements in standard liver function tests (98-101). Many clinicians currently treat their PSC patients with UDCA, despite the lack of convincing proof that this drug significantly reduces symptoms and improves patient survival. In The Netherlands, UDCA is not formally registered for the indication PSC.

To our knowledge, there are only two randomised studies to date that evaluated the medium long term effect of UDCA treatment on clinical parameters, histology, and time until treatment failure (102, 103). They concluded that UDCA so far does not seem to have obvious clinical benefit. In all, in spite of some beneficial features, UDCA is probably not the drug that can halt disease progression in PSC. So far, its long term use is justified, in our view, only in patients who report amelioration of complaints upon UDCA therapy.

**Endoscopic treatment**

In the management of symptomatic dominant strictures, several approaches have been employed.

Percutaneous transhepatic cholangiography with balloon dilatation and temporary stenting has been reported to improve clinical, laboratory, and radiological parameters (104). However, it can be a technically difficult procedure, particularly because the intrahepatic bile ducts are often not conveniently dilated.

With the advent of endoscopic retrograde cholangiography, several series have been published, employing bougienage, balloon-dilatation and/or placement of an endoprosthesis (105-108).
Several authors have reported favourable results with endoscopic dilation (105, 106, 109).

Recurrent stricture formation is a well recognised problem, although the precise incidence has not been documented. Some investigators prefer to insert an endoprosthesis afterward, which is then left in place for several months (107). It is unknown how long an endoprosthesis should ideally be left in situ to achieve optimal dilatory effect, with a minimum of complications such as stent clogging or suppurative cholangitis (108). Because of the problem of stent clogging, we performed a trial in which the efficacy of short-term stent placement for symptomatic dominant strictures in PSC patients was evaluated (110).

Sixteen patients received one or two stents for cholangitis, jaundice, or progressive cholestasis. The mean duration of stent placement was 9 (7-23) days. The median follow-up was 19 months (range 7-27). All patients showed a substantial decrease in cholestatic parameters, and 13 patients became asymptomatic and remained so during the follow-up period. No complications were noted. These results compare quite favourably with those of a historical control group in which 2-3 months of stenting was applied (108). We have adopted 1-week stenting as the standard treatment of symptomatic dominant strictures in PSC.

Surgical treatment

Surgical treatment of dominant strictures has not been very effective and may actually hamper future liver transplantation (111, 112). Orthotopic liver transplantation is, at present, the ultimate therapy for PSC and should be considered in patients with signs of decompensating liver cirrhosis, recurrent cholangitis caused by inaccessible strictures, or intractable pruritus. The 5-year survival rate in the largest combined series is reported to be 78 %, which is comparable with survival rates in series from Europe (42, 113).

In recent years, some concern has arisen over the possible recurrence of PSC in the graft. Harrison et al. found significantly more histologic features suggestive of PSC in post-transplant liver biopsies ≥ 6 months after OLT in patients receiving transplants for end-stage PSC compared with other indications (114). This difference did not disappear when case-controls were matched for Roux-Y anastomosis. Non-anastomotic biliary strictures occur more frequently after OLT for PSC than for other liver diseases (115, 116). Recently, Sheng and colleagues found PSC-like cholangiographic features in 25 % of 32 grafts in PSC patients versus 6 % of 32 grafts of matched controls (117).
FUTURE PROSPECTS AND CONCLUSIONS

The enormous possibilities of modern molecular biology will provide investigators with refined techniques to further unravel the pathophysiologic mechanisms involved in PSC. Detailed characterisation of the inflammatory response and the interactions between its cellular components may give important clues as to the pathogenesis of the disease. Identification of the antigenic targets to which the p-ANCAs are directed, and confirmation of the results of the studies with the antibodies against the 40 kD protein, may be of particular importance.

In a few years, viral screening techniques using random PCRs will become available, and the question of a viral etiology may be resolved. Given the immune imbalance hypothesis, these developments may yield targets for specific anti-inflammatory therapies, analogous to those that are currently being developed for IBD.

In the coming years more results of long term studies investigating the benefits of UDCA will become available, so that its value can definitively be determined. Comparative studies regarding the efficacy and safety of the various endoscopic treatment modalities for dominant strictures are awaited.

The value of possible markers of early malignant degeneration such as mutations of p53 and K-ras must be studied. When early detection becomes feasible, the next step should be to investigate the role of OLT in these cases.

In conclusion, despite a relative abundance of studies -given the rarity of PSC- in the past 25 years, the main issues are still unresolved. We do not know what causes the disease and there is no effective therapy other than expensive and burdensome OLT. However, evidence indicating that PSC reflects an autoimmune or immune imbalance disease is accumulating. Progress in immunology is developing rapidly, and major breakthroughs are to be expected.

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