Primary sclerosing cholangitis
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Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown origin that is strongly associated with inflammatory bowel disease (IBD). It is characterized by progressive destruction of bile ducts, which may result in the development of biliary cirrhosis. Initially thought to be a rare disorder, PSC is currently one of the more common indications for liver transplantation.

Epidemiology, natural history, and prognosis

The true incidence and prevalence of PSC is not well determined. Only a few population-based studies have looked at the incidence and prevalence of PSC. In Western populations, the estimated prevalence of PSC is 6 to 8 cases per 100,000 persons [1–3]. Unpublished data from a population-based study performed in The Mayo Clinic and Foundation looking at the incidence of PSC in Olmsted County, Minnesota, showed a significant increase in the incidence of PSC in the period of 1991 through 2000, compared with 1976 through 1990 (1.48 versus 0.37 per 100,000 person-years). It was thought that this change might indicate a true increase in the incidence of this disease.

The initial diagnosis is usually made within the third and fourth decades of life. PSC has a male predominance, with a male:female ratio of 3:1.

As many as 80% of the patients with PSC have IBD. There are data suggesting that PSC is the most common chronic liver disease in patients with IBD [4,5]. No correlation exists between the activity of IBD and the occurrence of PSC.

Some studies have shown smoking to be a protective factor against PSC [6–8], although the risk factors for developing PSC aside from IBD are unknown.

At the time of diagnosis, as many as 44% of the patients are asymptomatic; however the condition tends to progress over time [9]. There is a suggestion that survival is better in asymptomatic patients, but this possibility is controversial. In
the three larger independent studies looking at the natural history of PSC, the median survival time was approximately 12 years [9–11].

Several prognostic survival models have been developed in an attempt to determine the rate of disease progression and the optimal timing for liver transplantation [9–12]. Most of these models are limited because they require liver biopsy and use somewhat subjective variables. Most recently Kim et al [13] proposed a new model that uses patient age, levels of serum bilirubin, albumin, and aspartate aminotransferase, and history of variceal bleeding in assessing the risk of patients with PSC. This model has not been prospectively validated, however.

Etiology and pathogenesis

Several causative mechanisms have been proposed to explain the pathogenesis of PSC; however it still remains poorly understood. It seems that immunologic mechanisms as well as nonimmunologic factors (eg, infection, toxins, and ischemia) could be responsible for the development of this disease in genetically susceptible individuals.

Genetic predisposition

The concept of genetic susceptibility to PSC is supported by reports of familial occurrence of this disorder [14], as well as by HLA associations.

Early studies described an increased frequency of HLA B8 and DR3 in patients with PSC [15–17]. These antigens are known to be associated with several autoimmune diseases. Subsequent studies also showed susceptibility to be linked to the presence of HLA DRw52a, HLA DR2, and HLA DR4, which may be a marker of rapid disease progression [18–20].

More recent data suggest that genetic susceptibility to PSC may be related to polymorphisms of the tumor necrosis factor (TNF) gene, also found in chromosome 6, near the HLA genes [21]. Non-MHC genes may also be implicated.

Further work is required to aid in the understanding of the complex mechanisms of genetic susceptibility in PSC.

Immunologic factors

Several humoral and cellular immunologic alterations have been described in patients with PSC, suggesting that immune-mediated mechanisms play a significant role in the pathogenesis of this disorder.

A Swedish study found an increased frequency of autoimmune disorders among PSC patients compared with IBD patients without liver disease [22]. Patients with PSC have a decrease in total number of circulating T cells, and an increased number of T cells in liver infiltrates; elevated circulating immune complexes [23], and complement activation [24], but these changes have not been demonstrated to be linked to the disease pathogenesis.
Angulo et al [25] reported that 97% of patients with PSC were positive for at least one autoantibody, whereas 81% were positive for three or more. Anti-neutrophil cytoplasmic antibodies (ANCA) have been detected in approximately 85% of PSC patients [26]; however, this antibody is not thought to play a pathogenic role. The presence of ANCA antibodies correlates with extensive involvement of the biliary tree but not with other clinical parameters [27]. Efforts have been made to identify whether antigenic specificities of ANCA correlate with distinct clinical features. Antibodies to bactericidal or permeability-increasing protein and cathepsin G were associated with the presence of cirrhosis, whereas anti-lactoferrin antibodies were more frequent in patients with concomitant ulcerative colitis [28]. Autoantibodies that react against a common epitope shared by colon and biliary epithelial cells have been described [29], and more recently, autoantibodies against biliary epithelial cells that induce expression of CD44 and interleukin 6 have been found, suggesting that they may have a role in the inflammatory process [30].

Other factors

A number of other potential origins for PSC have been proposed. The close association between PSC and ulcerative colitis led to the hypothesis that intestinal bacteria or toxic substances might transmigrate from inflamed colonic mucosa, causing chronic inflammation and cholangitis [31]. One study showed strong immunostaining for endotoxin in biliary epithelial cells of PSC patients [32].

Bacterial or viral infections of the biliary tree have also been implicated as a cause of PSC; however, there is no direct evidence to support this hypothesis. A study performed in explanted livers showed a high positivity rate for bacterial isolates in patients with PSC, but that finding seemed to be related to recently performed endoscopic retrograde cholangiopancreatography (ERCP) [33]. More recently Ponsioen et al [34] found increased prevalence of chlamydial lipopolysaccharide antibodies in PSC patients.

Ischemic damage to the bile duct was proposed because of the similar findings encountered in PSC and abnormalities after intra-arterial injection of the chemotherapeutic agent floxuridine [31]. Vascular injury could potentially be immune-mediated, because many of the antibodies present in PSC are markers of vascular damage in others diseases.

Clinical manifestations and complications

As mentioned previously, as many as 44% of patients may be asymptomatic at presentation, but symptoms may develop over time. The main symptoms include pruritus, jaundice, abdominal pain, and fatigue. Pruritus is usually treated with bile acid–binding resins; in patients who do not respond to this treatment, other strategies that may be helpful include rifampin, naltrexone, and ondasetron. At
later stages of the disease, PSC presents with complications of cirrhosis and portal hypertension.

Patients with PSC are susceptible to repeated episodes of bacterial cholangitis and are also prone to develop pigmented biliary stones [35]. Steatorrhea and malabsorption of fat-soluble vitamins can occur, mainly because of the decreased availability of conjugated bile acids in the small intestine. Patients with advanced PSC have significantly lower bone mineral density compared with controls [36]. In one study 8.6% of the PSC patients had bone mineral densities below the fracture thresholds [37].

Cholangiocarcinoma is the most feared complication of PSC, with a reported lifetime prevalence ranging between 10% and 30%. The study involving largest cohort of patients with PSC found the incidence of hepatobiliary carcinoma to be 1.5% per year after the first year following diagnosis of PSC [38]. Risk factors for the development of cholangiocarcinoma are not well defined. Older age, IBD, smoking, and alcohol consumption have been implicated as risk factors, but these associations are not confirmed [39,40]. The diagnosis of cholangiocarcinoma in the setting of PSC can be difficult. Methods for early detection have been studied, using tumor markers (CA 19-9, CEA), cytologic brushings during ERCP, and positron emission tomography, but they have not been evaluated prospectively.

In one study 2% of the 134 patients with PSC who were evaluated for liver transplantation had hepatocellular carcinoma, suggesting that patients with advanced PSC are at increased risk for hepatocellular carcinoma and should be screened for it as well as for cholangiocarcinoma before liver transplantation [41]. Bergquist et al [38] found a 14-fold increase in the risk of pancreatic cancer in PSC patients, when compared with the general Swedish population.

Most patients with PSC suffer from IBD. Chronic ulcerative colitis is most commonly associated with PSC, but patients with Crohn’s colitis also have a higher risk of developing PSC than the general population. Four percent of the patients with ulcerative colitis will develop PSC at some point [4]. No correlation exists between the activity of IBD and PSC.

Several studies have demonstrated that patients with PSC and ulcerative colitis have a higher risk of developing colorectal neoplasia than patients with ulcerative colitis alone [42–44]. In a recent study, 25% of patients with PSC and ulcerative colitis developed colorectal cancer or dysplasia, as opposed to 5.6% of patients with isolated ulcerative colitis. Colorectal cancer associated with PSC seemed more likely to be proximal, to be diagnosed at a more advanced stage, and to be fatal [45]. Aggressive colonoscopic surveillance is advocated.

**Diagnosis**

The diagnosis of PSC is based on characteristic cholangiographic findings in combination with clinical, biochemical, and histologic features. It is important to exclude secondary causes of sclerosing cholangitis, such as biliary neoplasms,
previous biliary surgeries, choledocholithiasis, medication-induced bile duct damage, and chronic bacterial cholangitis.

**Cholangiographic findings**

ERCP is considered the standard method for diagnosis of PSC. When ERCP is unsuccessful, transhepatic cholangiography can be used to visualize the biliary tree.

The typical cholangiographic findings of PSC include multifocal strictures and dilatations that have a classic beaded appearance and may form diverticular outpouchings (Fig. 1). In most cases, these findings affect both intrahepatic and extrahepatic bile ducts, but they can involve either alone.

**Noninvasive imaging**

Recent studies show that magnetic resonance cholangiopancreatography (MRCP) is a valuable technique in the diagnosis and follow-up of patients with PSC [46,47]. Angulo et al [46] reported a diagnostic accuracy greater than 90% in the diagnosis of PSC. There is some suggestion that MRCP may be superior to ERCP for intrahepatic visualization [48,49].

Other abdominal imaging studies, such as CT and ultrasonography, may suggest the diagnosis but are nonspecific.

Fig. 1. ERCP with balloon of a patient with PSC, showing features of multiple strictures and dilatations, involving mainly the intrahepatic biliary tree (9 × R).
Histologic features

Liver biopsy in this condition is more useful for staging purposes than for diagnosis itself. The typical onionskin fibrosis may occur in only 10% of biopsies of PSC patients.

Ludwig et al described a staging system for PSC [31]. Stage I is characterized by portal hepatitis, in stage II fibrosis or hepatitis involves the periportal area, in stage III septal fibrosis or bridging necrosis occur, and stage IV is characterized by biliary cirrhosis. Angulo et al [50] evaluated the rate of histologic progression in patients with PSC. Of the patients with stage II PSC, 42%, 66%, and 93% progressed over 1, 2, and 5 years, respectively; 14%, 25%, and 52% of the patients with stage III PSC progressed over 1, 2, and 5 years, respectively. Regression of the histologic stage was noted in 15% of the total observations, suggesting that there is significant sample variability, which may limit the use of serial liver biopsies for follow-up of these patients [50].

Typical findings on liver biopsy, in the absence of cholangiographic evidence of PSC characterize an entity termed small duct PSC, which accounts for less than 5% of PSC patients.

Laboratory tests

Patients with PSC typically present with a cholestatic pattern of abnormal liver enzymes. Alkaline phosphatase is usually three to five times above normal, whereas aminotransferase levels are only mildly elevated. Hyperbilirubinemia may suggest advanced disease or the development of complications such as dominant strictures, cholangiocarcinoma, biliary stones, and bacterial cholangitis but may also occur in the absence of any of these conditions. Hypergamma-globulinemia, autoantibodies, and abnormal copper accumulation are also common laboratory findings.

Management

Several therapeutic modalities have been investigated for the treatment of PSC in an attempt to avoid disease progression. Unfortunately none except liver transplantation has been proven to alter the course of the disease significantly.

Pharmacologic management

A number of drugs have been studied in PSC patients. Many of the studies were performed in an uncontrolled fashion with a small number of patients. A summary of the published placebo-controlled trials, using different medications for the treatment of PSC is shown in Table 1. A list of the drugs evaluated in pilot studies and their therapeutic benefits is presented in Table 2.
Table 1
Placebo-controlled trials for the treatment of primary sclerosing cholangitis

<table>
<thead>
<tr>
<th>Drug (dosage)</th>
<th>Study</th>
<th>Number in study</th>
<th>Period</th>
<th>Biochemical response</th>
<th>Histologic response</th>
<th>Radiologic response</th>
<th>Symptoms response</th>
<th>Mayo risk score or survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDCA (13–15 mg/kg/day)</td>
<td>Beuers et al, 1992 [53]</td>
<td>14</td>
<td>1 year</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>UDCA (750 mg/day)</td>
<td>Stiehl et al, 1994 [95]</td>
<td>20</td>
<td>1 year</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Trend</td>
<td>NA</td>
</tr>
<tr>
<td>UDCA (600 mg/day)</td>
<td>De Maria et al, 1996 [96]</td>
<td>59</td>
<td>2 years</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>UDCA (13–15 mg/kg/day)</td>
<td>Lindor et al, 1997 [54]</td>
<td>105</td>
<td>2.2 years</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>Not improved</td>
</tr>
<tr>
<td>UDCA (25–30 mg/kg/day)</td>
<td>Harnois et al, 2001 [55]</td>
<td>30</td>
<td>1 year</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Improved</td>
</tr>
<tr>
<td>UDCA (20 mg/kg/day)</td>
<td>Mitchell et al, 2001 [56]</td>
<td>26</td>
<td>2 years</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Penicillamine (750 mg/day)</td>
<td>LaRusso et al, 1988 [65]</td>
<td>70</td>
<td>3 years</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Methotrexate (15 mg/wk)</td>
<td>Knox et al, 1994 [59]</td>
<td>24</td>
<td>2 years</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Colchicine (1 mg/day)</td>
<td>Olsson et al, 1995 [64]</td>
<td>84</td>
<td>3 years</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Nicotine (15 mg/day)</td>
<td>Vleggaar et al, 2001 [67]</td>
<td>12</td>
<td>8 weeks</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
</tr>
</tbody>
</table>
There is evidence suggesting that ursodeoxycholic acid (UDCA) has several beneficial effects in cholestatic disorders. It is cytoprotective, by inhibiting bile acid–induced cytolysis and apoptosis, and it has antioxidant and immunomodulatory effects as well. This drug has been the most extensively studied in patients with PSC.

Uncontrolled studies have observed improvement of liver enzymes in PSC patients treated with UDCA [51,52]. Beuers et al [53] performed the first double-blind, placebo-controlled trial in 14 patients with PSC and documented significant biochemical and histologic improvements. There was no beneficial effect on symptoms or impact in the Mayo risk score, however.

In contrast to these promising results, Lindor [54], in a larger multicenter prospective trial that included 105 patients randomly assigned to receive treatment with 13 to 15 mg/kg per day of UDCA or placebo for a median follow-up of 2.2 years, found no clinical benefit with respect to time to treatment failure or histologic findings in the treatment arm, even though there was significant biochemical improvement [54].

Because of discouraging results with standard doses of UDCA, two groups have evaluated the use of high-dose UDCA to treat PSC [55,56]. Mitchell et al [56], in a preliminary study, treated 26 patients with either UDCA, 20 mg/kg, or placebo for 2 years and demonstrated significant biochemical, histologic, and cholangiographic improvements without significant side effects. No impact on symptoms was noted, however. Harnois et al [55] reported similar results in an open study of 30 patients treated with high-dose (25–30 mg/kg) UDCA for 1 year. When Mayo risk scores of these patients were compared with those observed in a previous study, the projected 4-year mortality was significantly greater in patients treated with placebo than in those receiving high-dose UDCA.

Recent studies have suggested that the use of UDCA reduces the risk for developing colorectal cancer in patients with ulcerative colitis and PSC [57,58].

### Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>No of patients</th>
<th>Therapeutic benefit</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>10</td>
<td>Biochemical</td>
<td>Van Thiel et al, 1995 [60]</td>
</tr>
<tr>
<td>Nicotine</td>
<td>8</td>
<td>None</td>
<td>Angulo et al, 1999 [68]</td>
</tr>
<tr>
<td>Cladribine</td>
<td>4</td>
<td>Histological</td>
<td>Duchini et al, 2000 [61]</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>20</td>
<td>None</td>
<td>Bharucha et al 2000 [62]</td>
</tr>
<tr>
<td>Budesonide</td>
<td>21</td>
<td>Biochemical</td>
<td>Angulo et al, 2000 [63]</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>24</td>
<td>None</td>
<td>Angulo et al, 2002 [66]</td>
</tr>
<tr>
<td>Prednisone + colchicine</td>
<td>12</td>
<td>None</td>
<td>Linder et al, 1991 [69]</td>
</tr>
<tr>
<td>UDCA + methotrexate</td>
<td>19</td>
<td>None</td>
<td>Linder et al, 1996 [70]</td>
</tr>
<tr>
<td>UDCA + prednisolone +</td>
<td>15</td>
<td>Biochemical and histologic</td>
<td>Schramm et al, 1999 [71]</td>
</tr>
<tr>
<td>azathioprine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UDCA + budesonide or</td>
<td>18</td>
<td>Symptomatic&lt;sup&gt;a&lt;/sup&gt;</td>
<td>van Hoogstraten et al 2000 [72]</td>
</tr>
<tr>
<td>prednisone</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<sup>a</sup> minor benefits with prednisone.
Immunosuppressants

Given the immunologic basis for the pathogenesis of PSC, a few trials have looked into immunosuppressive and anti-inflammatory agents as a form of therapy for this condition.

In the one prospective, controlled trial that studied the use of methotrexate in PSC, 12 patients were treated with methotrexate and were compared with 12 patients treated with placebo. No differences in outcome or in biochemical, histologic, or cholangiographic findings were observed [59].

In a small pilot study, tacrolimus (FK-506) improved liver enzymes, but this improvement was not associated with improvement in ERCP finding, hepatic volume, or histologic features [60].

Cladribine, which has antilymphocytic activity, was studied in four patients, treated for 6 months and followed for 2 years. There was a significant decrease in portal inflammation and T-lymphocyte CD4 infiltrate, but no improvement in symptoms, liver enzymes, or degree of biliary stenosis was documented [61]. Randomized, controlled trials with larger follow-up are required to confirm these results.

Pentoxifylline, which inhibits TNF-α, has been shown to prevent and reverse hepatobiliary lesions similar to PSC in rats with experimental small bowel bacterial overgrowth. In a pilot study of 20 patients with PSC treated for up to 1 year, no biochemical or symptomatic improvement was seen with pentoxifylline therapy [62].

Corticosteroids

No long-term controlled studies have investigated corticosteroids in the treatment of PSC. Most of the small, uncontrolled trials showed no significant benefit with the use of oral steroids. This lack of demonstrated benefit in conjunction with the systemic side effects, especially bone loss, has limited their use in treating these patients. Most recently Angulo et al [63] have investigated the use of budesonide in 21 patients treated for 1 year; only minimal improvement was noted in alkaline phosphatase and aspartate aminotransferase levels and in the degree of portal inflammation. No significant changes in the Mayo risk score, degree of fibrosis, or histologic staging were reported. There was, however, marked bone loss compared with matched controls [63].

Antifibrogenic and other agents

Colchicine was studied in a multicenter trial motivated by its antifibrogenic property and promising effects on survival in primary biliary cirrhosis. Over a 3-year period, 44 patients were treated with colchicine and compared with 40 patients treated with placebo, in a randomized, double-blind fashion. The treatment group did not show any difference in mortality or liver transplantation rates, symptoms, or biochemical or histologic findings [64].

In patients with PSC, as in other cholestatic liver diseases, there is an increase in hepatic copper concentration. Penicillamine has cupruretic antifibrogenic, and immunosuppressive effects. La Russo et al [65] have tested it in a double-blind,
placebo-controlled trial with 70 patients, showing no clinical benefit and significant toxicity. A study using pirfenidone, a new antifibrotic agent, led to disappointing results as well [66].

Nicotine was evaluated as a potential treatment for PSC, based on the reported association of PSC with nonsmoking status and on positive effects of nicotine in treatment of ulcerative colitis. No benefit was seen with oral or transdermal nicotine [67,68].

Combination therapy

The combination of prednisone and colchicine was evaluated in an open-label study performed in 12 patients with PSC compared with historical controls. No significant difference in biochemical tests or liver biopsies were noted, but there was a trend toward less clinical deterioration and improved survival [69]. UDCA in combination with methotrexate showed no benefits [70]. A German study assessed UDCA in combination with prednisolone and azathioprine in 15 patients with PSC. This study showed promising results, with significant decrease in liver enzymes and histologic improvement in 6 of 10 patients who had repeat liver biopsies. In 7 patients who were initially treated with UDCA alone, liver enzymes improved only after addition of immunotherapy [71]. No randomized trial has been performed using this combination. UDCA plus budesonide or prednisone did not significantly improve symptoms or liver enzymes in a short-term trial [72]. A study using UDCA and endoscopic dilatation of major stenosis suggested improvement in survival rates compared with the Mayo model [73].

Endoscopic management

Several attempts have been made to change the progressive course of PSC by endoscopic methods, including endoscopic sphincterotomy, nasobiliary lavage, stent placement, and balloon dilatation. Endoscopic therapy seems most advantageous for patients with dominant strictures. Biliary lavage with steroids was evaluated in a randomized, placebo-controlled trial and proved not to be effective [74]. Several reports have shown beneficial effects of balloon dilatation or temporary stenting on clinical, biochemical, and cholangiographic findings in patients with PSC [75–79]. A retrospective study comparing balloon dilatation with stenting of dominant stricture showed no obvious benefit from stenting, and stenting was associated with more complications than seen with dilatation alone [80].

Some reports suggest that survival is positively influenced by endoscopic therapy. Stiehl et al [81], for example, prospectively studied 106 patients treated for up to 13 years with UDCA. Fifty-two of these patients were treated endoscopically for dominant stenosis. The actuarial survival free of orthotopic liver transplantation at 3, 5, and 7 years was significantly better than predicted with the Mayo multicenter survival model [81]. Similar results were observed by Baluyut et al [82], who demonstrated a significantly higher 5-year survival rate in 63 patients undergoing endoscopic therapy when compared with the estimated
rate using the Mayo Clinic survival model (83% versus 65%) [82]. One criticism of this study is that the bilirubin values used in the calculation of the Mayo risk score were determined before dilatation and may have overestimated the underlying liver disease.

Endoscopic intervention is usually preferred to percutaneous biliary drainage because it seems to be safer and is technically easier to perform.

Surgical management

Surgical resection of dominant biliary strictures with choledocojejunostomy or hepaticojejunostomy was favored by some centers. Ahrendt et al [83] found that the 5-year survival and survival free of liver transplantation rates were significantly higher in noncirrhotic patients treated with biliary resection than in those treated with nonoperative dilatation (85% versus 59% and 82% versus 46%, respectively) [83]. Surgical treatment is now less commonly performed because of the advances in endoscopic techniques and the possibility that it may adversely affect outcome after liver transplantation.

Liver transplantation

As discussed previously, medical, endoscopic, and surgical therapies do not convincingly alter disease progression in PSC patients. Liver transplantation remains the only form of therapy that positively affects survival [84], and it also seems to improve quality of life in up to 80% of the patients [85,86].

Graziadei et al [87] reported excellent long-term results in 150 patients with PSC, who underwent liver transplantation. In this study the 1-, 2-, 5-, and 10-year actuarial survival was 93.7%, 92.2%, 86.4%, and 69.8%, respectively, and graft survival was 83.4%, 83.4%, 79%, and 60.5%, respectively [87]. These findings were in accordance with previous observations [88,89].

The optimal timing for liver transplantation in patients with PSC is still uncertain. The presence of cholangiocarcinoma seems to be one of the most important factors adversely impacting outcome after transplant. Nashan et al [90] tried to apply the original Mayo survival model to assess the ideal timing for liver transplantation. In patients with Mayo model risk scores greater than 4.4, the incidence of biliary malignancy was markedly increased, whereas no tumors were found in patients with scores less than 4. They suggested that early timing of liver transplantation should be considered at scores greater than 4 to prevent formation of biliary malignancies.

Other predictive factors reportedly associated with poor outcome after transplantation in cholestatic liver diseases include age, renal failure, Child’s classification, and United Network for Organ Sharing (UNOS) status [91]. Whether previous biliary tract surgery adversely affects survival is still controversial. IBD does not seem to have an impact on liver transplantation in patients with PSC.
Recurrent PSC after liver transplantation has been reported to develop in approximately 4% of patients per year [92]. Risk factors for recurrence are not well defined. One retrospective study found that an intact colon before liver transplantation and male gender were significantly associated with recurrence; however, the sample size was small, and the confidence intervals were broad [93].

Apparently the risk of colorectal malignancy increases after liver transplantation and immunosuppression, but this increased risk is yet to be proven. A recent study in 303 patients undergoing liver transplantation for PSC observed accelerated progression of IBD but found no significant increase in the risk of colorectal cancer [94].

Summary

Primary sclerosing cholangitis is a cholestatic liver disease strongly associated with IBD. Considerable advances in the understanding of its pathogenesis have been made. The idea of autoimmunity affecting genetically susceptible individuals is largely accepted; however, much remains to be explained about the origin of this disease. Despite active investigation of different therapeutic modalities with the goal of modifying disease progression, liver transplantation continues to be the only option to provide survival benefit in these patients.

References


