

# Management Of Primary Sclerosing Cholangitis

Bimaljit S. Sandhu, MBBS, MD, DM, and Velimir A. Luketic, MD, FACP, FACC

Dr. Sandhu serves as Assistant Professor of Medicine and Dr. Luketic as Professor of Medicine, both in the Division of Gastroenterology at Virginia Commonwealth University.

Address correspondence to:  
Velimir A. Luketic, MD, Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University Medical Center, PO Box 980341, Richmond, VA 23298-0341; Tel: 804-828-4060; Fax: 804-828-5348; E-mail: vluketic@hsc.vcu.edu

**Abstract:** Management of primary sclerosing cholangitis (PSC) can be divided into endoscopic, medical, and surgical treatments. Whereas endoscopic therapy is primarily used to manage dominant strictures, medical treatment is directed both at modifying course of the disease and at symptomatic relief. Ursodeoxycholic acid is the most promising disease-modifying agent. Corticosteroids and other immunosuppressive agents do not have a proven role. Cholestyramine and rifampicin improve pruritis but response to these agents cannot be reliably predicted. Opioid antagonists are useful in refractory pruritis. All patients with advanced PSC should be offered bone mineral-density measurement and, if needed, treatment for osteoporosis. These approaches are not mutually exclusive and are often used concurrently or in sequence depending on the clinical situation. Liver transplantation is the only therapy that improves survival. In this review, we discuss the various management options for PSC.

**P**rimarily sclerosing cholangitis (PSC) is one of the most common adult chronic cholestatic liver diseases in the United States.<sup>1-3</sup> It is characterized by inflammation and obliterative fibrosis of the extrahepatic and the intrahepatic bile ducts. The subsequent cholestasis, in particular retention of hydrophobic bile acids in the liver, results in hepatocyte injury, development of hepatic fibrosis, and ultimately biliary cirrhosis. Although the course of PSC is unpredictable—bacterial infection and development of a dominant stricture can accelerate disease progression—end-stage liver disease usually develops around 12 years after diagnosis.<sup>4</sup> Cholangiocarcinoma in the setting of PSC reduces life expectancy to less than 1 year.<sup>5</sup>

The causes of bile duct injury and factors responsible for progression of PSC remain largely unknown. Genetic predisposition and immunologic abnormalities are thought to play a key role because of the close association between PSC and inflammatory bowel disease in adults and autoimmune hepatitis in children.<sup>6,7</sup> Other proposed causes of injury to bile ducts include bacterial proteins that leak into the portal blood from an inflamed bowel, toxic bile acid metabolites from the enterohepatic circulation, chronic viral infections, and ischemic injury.<sup>8</sup> As more than one of these factors may contribute

## Keywords

Primary sclerosing cholangitis, ursodeoxycholic acid, immunosuppressives, liver transplant

**Table 1.** Drugs Evaluated for Treatment of Primary Sclerosing Cholangitis

<p>Immunosuppressants:</p> <ul style="list-style-type: none"> <li>• Prednisone</li> <li>• Budesonide</li> <li>• Methotrexate</li> <li>• Azathioprine</li> <li>• Mycophenolate mofetil</li> <li>• Cyclosporine</li> <li>• Tacrolimus</li> <li>• Cladribine</li> <li>• Pentoxifylline</li> </ul> <p>Antifibrotics and Other Agents:</p> <ul style="list-style-type: none"> <li>• Colchicine</li> <li>• D-penicillamine</li> <li>• Pirfenidone</li> <li>• Nicotine</li> </ul> <p>Bile Acids:</p> <ul style="list-style-type: none"> <li>• UDCA 10–15 mg/kg daily</li> <li>• UDCA 20–30 mg/kg daily</li> </ul> <p>Combination Therapy:</p> <ul style="list-style-type: none"> <li>• Prednisone + colchicine</li> <li>• UDCA + methotrexate</li> <li>• UDCA + mycophenolate mofetil</li> <li>• UDCA + prednisolone + azathioprine</li> <li>• UDCA + budesonide or prednisone</li> </ul>
--

to the development of PSC in any one individual, a unified effective treatment for PSC has yet to be established.

In 2006, PSC management can be divided into endoscopic, medical, and surgical treatments. Endoscopic therapy is primarily used to manage dominant strictures. Medical treatment is directed both at modifying the course of the disease and at symptomatic relief. Surgical therapy currently is limited to liver transplantation. These approaches are not mutually exclusive and are often used concurrently or in sequence, depending on the clinical situation. In this review, we discuss the various management options for PSC.

## Medical Management

Drugs used in management of PSC include those that affect the course of the disease (disease-modifying agents) and those aimed at symptomatic relief. Because of the uncertainty regarding the pathogenesis of PSC, drug therapy is often based on treatments that have been shown to be effective in other cholestatic and autoimmune disorders.

### *Disease-modifying Agents*

Injury in PSC is a two-step process: (1) bile duct injury results in an interruption in bile flow and (2) accumulation of bile acids leads to liver injury and ultimately cirrhosis. PSC treatments directed at each of these steps have been evaluated in both controlled and uncontrolled trials (Table 1); none, whether used alone or in combination, has proven satisfactory. The number of patients involved tends to be small and inadequate to provide meaningful survival data and patient characteristics, and study designs are too heterogeneous to allow for meta-analysis. Ursodeoxycholic acid (UDCA) is the most commonly used drug to treat PSC. This is due to its proven ability to improve liver biochemistries in any type of liver disease as well as its effectiveness in primary biliary cirrhosis (PBC).<sup>9-11</sup>

**Ursodeoxycholic Acid** Bile acids are amphipathic molecules that have a steroid nucleus from which hydroxyl groups project into space. The presence of both a hydrophilic (water-soluble) and a hydrophobic (lipid-soluble) surface make bile acids excellent detergents, good at breaking up complex fats so that they can be absorbed. The fewer hydroxyl groups, the more hydrophobic a bile acid, and the stronger are its detergent properties. These detergent-like effects on cellular membranes were thought to be the primary mechanism for bile acid-induced hepatocyte injury.<sup>12</sup> More recent data, however, indicate that more important may be bile acid-induced ligand-independent death receptor pathways that trigger apoptosis in hepatocytes.<sup>13,14</sup>

UDCA is a dihydroxy bile acid with hydroxyl groups pointing to either side of the steroid ring. As a consequence it is the most hydrophilic of bile acids and the least effective detergent.<sup>12</sup> Under normal physiologic circumstances, UDCA makes up approximately 3% of the human bile acid pool. The proportion, however, increases to 50% when it is administered orally at a dose of 13–15 mg/kg daily (the standard dose approved for use in PBC).<sup>15</sup> Historically, enrichment of the bile acid pool with the hydrophilic UDCA was thought to reduce overall cytotoxicity by simple displacement of hydrophobic bile acids.<sup>16</sup> The mechanisms involved in fact are multiple and much more complex.

UDCA has a choleric effect that increases bile flow and thus excretion of potentially toxic bile acids and other metabolites.<sup>17</sup> This effect is due to stimulation of transporter proteins in the hepatocytes, modulation of the intracellular signaling cascades, and modification of the transporter molecules in the apical hepatocyte membrane.<sup>18-20</sup> UDCA also modifies apoptotic threshold via activation of the epidermal growth factor receptor and mitogen-activated protein kinases.<sup>21</sup> UDCA appears to inhibit apoptosis by

preventing cholestasis-induced mitochondrial membrane permeability and release of caspase-activating proteins into the cytosol.<sup>17</sup> In animal experiments, UDCA inhibits bile ductular proliferation via stimulation of the calcium and protein kinase C- $\alpha$ -dependent signaling pathway in the cholangiocytes.<sup>22</sup> Importantly, it also decreases aberrant HLA type I expression on hepatocytes<sup>23</sup> and cytokine secretion by peripheral monocytes.<sup>24</sup>

**Clinical Trials of UDCA in PSC** The earliest trials of UDCA in patients with PSC, both controlled and uncontrolled, involved small groups of patients and used UDCA 10–15 mg/kg daily. In general, these studies showed improvements in liver enzymes, rarely improvement in symptoms, and a mixed picture in histology (when done). For example, an open-label study of 10 mg/kg UDCA once daily showed reductions in alkaline phosphatase (ALP), transaminases, bilirubin, and cholesterol as well as decreases in disabling fatigue and pruritus after 2 years of therapy.<sup>25</sup> In contrast, a controlled pilot study showed no effect on fatigue and pruritus in spite of significant improvement in serum transaminases, ALP, and gamma-glutamyl transferase in those receiving UDCA.<sup>26</sup> The largest study of 105 patients randomized to UDCA or placebo showed no difference in symptom relief or histologic progression between the two groups.<sup>27</sup> After a mean follow-up of 2.9 years UDCA did not significantly change time to development of cirrhosis, death, or liver transplantation. The study did show, however, that the rate of treatment failure was one third lower in those whose transaminases improved to within 1.5 times the upper limit of normal.<sup>27</sup>

Data from studies that used UDCA to treat cholestasis associated with cystic fibrosis have led to evaluation of higher doses of UDCA in patients with PSC. Three recent trials evaluated UDCA doses as high as 30 mg/kg daily. Mitchell and colleagues randomized 26 PSC patients to UDCA 20–25 mg/kg daily or placebo. Although there was no reduction in symptoms, there was a significant improvement in serum ALP and gamma-glutamyl transferase levels ( $P < .05$ ).<sup>28</sup> More importantly after 2 years of therapy there was significant improvement in cholangiographic appearance ( $P < .03$ ) and liver fibrosis ( $P < .05$ ). A shorter open-label pilot study conducted at the Mayo Clinic compared high-dose UDCA (25–30 mg/kg daily) to placebo.<sup>29</sup> This study demonstrated significant improvement in the projected survival using the Mayo risk score, albeit the impact of the high dose of UDCA on liver histology and cholangiographic appearance was not evaluated.

These promising findings were not confirmed by Olson and associates<sup>30</sup> in a large (110 patients) randomized placebo-controlled study utilizing UDCA 17–23 mg/kg

daily for up to 5 years. Although there were fewer deaths, transplantations, and cholangiocarcinomas in the UDCA group, the differences were not significant. Enrollment in the study, however, was stopped after 15 months, with only 63% patient accrual, and the dose of UDCA may have been too low. Rost and colleagues,<sup>31</sup> for example, demonstrated in a small study that in PSC patients biliary enrichment with UDCA increases until a dose of 22–25 mg/kg daily is reached. A National Institutes of Health–sponsored multicenter randomized placebo-controlled study evaluating UDCA 25–30 mg/kg daily is currently in progress. Results will be available in 3 years and hopefully will give final guidance about the effectiveness of UDCA therapy.

**Immunosuppressive Agents** As genetic predisposition and immune dysregulation are thought to play a major role in pathogenesis of PSC, it is not surprising that immunomodulators have been studied as disease-modifying agents in PSC. What is surprising is the paucity of trials, most of which have been small and uncontrolled. To a large extent this is because of investigator concerns regarding toxic side effects. Overall results of these trials have been disappointing.

A few studies have evaluated prednisone. The only controlled trial compared it, in combination with colchicine, to concurrent historical controls.<sup>32</sup> The combination was not found to retard histologic progression after 2 years of therapy. Angulo and colleagues investigated the use of budesonide in PSC patients.<sup>33</sup> After one year there was only minimal improvement in the biochemical parameters and in the degree of portal inflammation and there was no significant change in the Mayo risk score, degree of fibrosis, or histologic staging. Surprisingly, and in contrast to what would be expected of budesonide, there was marked bone loss compared with matched controls at the end of the study. The lack of enthusiasm for corticosteroids is probably also due to the clinical observation that there is no evidence of improvement in the clinical or biochemical parameters of PSC in patients who receive corticosteroids for concurrent inflammatory bowel disease.<sup>34</sup>

Corticosteroids, however, can be beneficial in patients who have been diagnosed as having a PSC/autoimmune hepatitis overlap syndrome. In a retrospective study, a subgroup of PSC patients with features of autoimmune hepatitis seemed to respond favorably to corticosteroid treatment and may obtain improved long-term survival.<sup>34</sup> Approximately 10% of patients with cholangiographically proven PSC also have elevated IgG4 levels. Recently it has been suggested that such patients may have autoimmune sclerosing cholangitis, an entity seen in combination with autoimmune pancreatitis.<sup>35</sup> Corticosteroid therapy may be effective in this setting.

Other immunosuppressive agents tested in patients with PSC, either alone or in combination with UDCA, are methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, and tacrolimus. In a randomized placebo-controlled trial of methotrexate in PSC, no significant changes in liver histology, cholangiographic appearance, or biochemical parameters other than ALP were observed.<sup>36</sup> A pilot study of methotrexate in combination with UDCA did not show any additional benefit when compared to UDCA alone.<sup>37</sup> Similar findings were seen in two open-label trials comparing mycophenolate mofetil in combination with UDCA and standard UDCA.<sup>38-41</sup> There are case reports of azathioprine in PSC but no controlled trials.<sup>38-41</sup> Thus in a case series, a combination of UDCA (500–750 mg/day), prednisolone (1 mg/kg daily), and azathioprine (1.5 mg/kg daily) showed improvement in the liver histology in a good proportion of patients without any significant side effects.<sup>42</sup> Cyclosporine has been evaluated in a controlled trial at Mayo Clinic.<sup>43</sup> Although there was no dramatic improvement in PSC, patients with concurrent UC experienced a moderation in the severity of colitis and had fewer recurrent colitis flares. Two open-label pilot studies of tacrolimus were not promising enough to warrant further testing in randomized trials.<sup>43</sup> Pilot studies of the anti-tumor necrosis factor agents pentoxifylline and etanercept failed to show any clinical improvement.<sup>44-46</sup>

**Other Agents** The antifibrotic agents pirfenidone<sup>47</sup> and colchicine<sup>48</sup> have failed to show any beneficial effects in PSC. In a placebo-controlled trial comparing UDCA 300 mg twice daily to colchicine 0.6 mg twice daily no difference was evident after 2 years in liver injury, liver function, liver size, or hepatic copper content.<sup>49</sup> Further, there was no difference in biliary ductal morphology, and the authors concluded that neither UDCA nor colchicine is effective therapy for PSC. The finding of elevated copper levels in PSC led to a large randomized controlled trial of D-penicillamine. There was no effect on disease progression as measured by clinical, radiographic, or histologic parameters.<sup>50</sup> The finding of an inverse association between PSC and smoking prompted two pilot studies of nicotine; neither showed a benefit and the oral preparation was associated with side effects.<sup>51</sup> Metronidazole used in combination with UDCA to suppress bacterial activity in the gut in PSC was superior to UDCA alone in improving the biochemical parameters.<sup>52</sup>

### **Supportive Therapy**

Common complications of chronic cholestasis are fatigue, pruritus, and osteoporosis. At times these complications can be so disabling that they have been used as indications for liver transplantation. Fatigue and pruritus are present

in as many as 70% and 69%, respectively, of patients with PSC<sup>53</sup> and are often the presenting symptoms. Fatigue remains a poorly understood phenomenon in PSC. Most patients feel well in the morning and become tired as the day progresses. This is not the pattern typical of clinical depression and thus it is not surprising that trials of selective serotonin reuptake inhibitors were not successful.<sup>54</sup>

The agent responsible for pruritus has not yet been identified. It appears, however, to be a gut-derived, liver-metabolized opioid receptor ligand that acts centrally.<sup>55</sup> Traditional empiric therapy has been directed at preventing the absorption and facilitating liver clearance of the pruritogen. Cholestyramine 4–16 g/day in divided doses has been used to accomplish the former, and rifampicin 300–600 mg/day in divided doses the latter.<sup>12</sup> Rifampicin promotes pruritogen metabolism via microsomal enzyme induction,<sup>56</sup> while cholestyramine binding promotes its excretion from the gut. Rifampicin has been shown to help relieve pruritus of cholestasis in most of the randomized trials.<sup>57-59</sup> Response to either cholestyramine or rifampicin is unpredictable. For refractory pruritus there is good evidence that the opioid antagonists nalmefene, naloxone, and naltrexone can be effective.<sup>60-62</sup> Opioid withdrawal can develop, however, with initial use and all patients should be monitored during the first 2 to 3 days of use.

Information on osteoporosis in PSC is limited. However, there is evidence that osteoporosis worsens with PSC progression: although only 7 of 81 relatively healthy patients enrolling in a UDCA trial had bone mineral density of the lumbar spine below the fracture threshold, the proportion had risen to 50% at time of transplantation.<sup>63</sup> The causes are multiple and include prolonged corticosteroid use, vitamin D deficiency due to fat malabsorption, and calcium loss secondary to inflammatory bowel disease and fat binding. Treatment of osteoporosis in PSC is empiric and based on recommendations from other cholestatic diseases.<sup>64</sup> All patients with advanced disease and particularly those on prolonged corticosteroid therapy should be offered bone mineral density measurement. Treatment should consist of calcium and vitamin D supplementation, bisphosphonates, and hormone replacement therapy in postmenopausal women. Based on PBC data, hormone replacement therapy is well tolerated by patients with cholestasis.

### **Endoscopic Therapy in PSC**

In recent years magnetic resonance cholangiography has been the preferred method to confirm the diagnosis of PSC. It is noninvasive, associated with few risks, and, in experienced hands, both highly sensitive (83–88%) and specific (92–99%) for large duct disease seen in PSC.<sup>65-67</sup>

Endoscopic approach, however, remains the mainstay of management of biliary strictures in PSC. Surgery and interventional radiology require a percutaneous approach and are inherently risky. Endoscopy is noninvasive, provides a convenient, rapid access to the biliary tree, and thus allows for repeat interventions with few complications.

### **Dominant Strictures**

The precise definition of dominant stricture remains a matter of debate. Most investigators, however, agree that it involves the narrowing of one of the larger bile ducts to the point that the obstruction worsens the already existing cholestasis. Development of dominant strictures is one of the common complications of PSC: they are present in 35% of patients after 8 years<sup>68</sup> and in more than half after 13 years in spite of UDCA therapy.<sup>69</sup> Presence of biliary obstruction irrespective of cause accelerates the progression of liver disease to end-stage. PSC patients with biliary strictures also tend to have bacterial cholangitis,<sup>70,71</sup> which not only contributes to liver damage but also to overall morbidity as a result of systemic infection.

### **Endoscopic Therapy of Biliary Strictures**

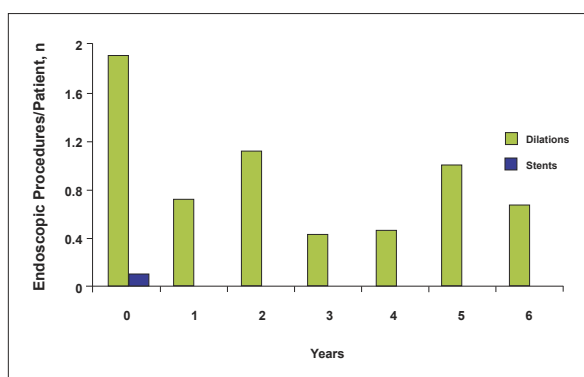
Endoscopic balloon dilatation and/or biliary stenting as treatment for dominant strictures have been evaluated in a number of clinical trials (Table 2). Both modalities require repeat endoscopic interventions to maintain duct patency (Figure 1). After stenting, additional procedures, usually at 2 to 3 month intervals but sometimes within weeks of deployment, are needed to deal with stent occlusion. Stent occlusion is of particular concern because it predisposes patients to bacterial cholangitis.<sup>72</sup> To minimize the risk of biliary tract infection, all endoscopic procedures should be performed under antibiotic prophylaxis,<sup>71</sup> albeit a short-course antibiotic treatment is not effective in eradicating bacteria from the bile ducts.<sup>70</sup> Repeat procedures are also required after most balloon dilatations because the fibrous ring responsible for the development of the stenosis shrinks over time and again occludes the duct.<sup>69</sup> Recently most investigators have recommended balloon dilatation over stent placement for dominant strictures in PSC.<sup>69,73-75</sup> In part, this is in order to avoid the problem of infection, but also because of evidence that the addition of stenting after balloon dilatation of a dominant stricture is ineffective.<sup>74</sup> In cases where stenting is required, for example, drainage of bacterial cholangitis complicated by sepsis, stents are kept in place for as short a time as possible.<sup>72</sup>

Results of endoscopic therapy of biliary strictures in patients with PSC have been mixed.<sup>69,73-79</sup> In general, presence of a dominant stricture, common bile duct stricture and high serum bilirubin levels are all independent predictors of a successful outcome to endoscopic

**Table 2.** Endoscopic Treatment of Patients with Primary Sclerosing Cholangitis with Dominant Stenoses of Major Bile Ducts

Author	Patient, N	Stent, n	Dilatation, n
Johnson, 1987	35	11	24
Gaing, 1993	16	15	6
Lee, 1995	53	22	31
van Milligen, 1996	25	21	0
Wagner, 1996	12	0	12
Kaya, 2001	71	37	34
Baluyut, 2001	63	32	140
Stiehl, 2002	52	5	210

Reproduced from Stiehl A. Primary sclerosing cholangitis: the role of endoscopic therapy. *Semin Liver Dis*, 2006;26:62-68.



**Figure 1.** Endoscopic procedures in patients with PSC with dominant stenoses.

Reproduced from Stiehl et al.<sup>69</sup>

therapy.<sup>80</sup> Importantly, serum bilirubin level is a more sensitive indicator of successful therapeutic intervention than transaminases.<sup>80</sup> In addition, repeated endoscopic treatment of dominant strictures decreases the risk of development of cholangiocarcinoma.<sup>69</sup> The two larger studies published in 2001 and 2002 repeated endoscopic attempts to maintain biliary patency and also improved patient survival when compared to predicted survival.<sup>69,75</sup> In the German study, participants in a UDCA treatment trial underwent endoscopic dilatation when clinically indicated; in the US study, no additional UDCA was provided. The patients who did best were those with early disease, demonstrating the importance of early identification of dominant strictures.<sup>69</sup> Neither study, however, showed that endoscopic therapy in the long run prevented progression to end-stage liver disease or eliminated the need for liver transplantation.

## Liver Transplantation in PSC

Liver transplantation is the only form of therapy that improves survival in PSC patients who develop end-stage liver disease.<sup>81</sup> Excellent long-term survival of 77% and 86% at 5 years and 69% and 70% at 10 years were reported in Europe and the United States, respectively.<sup>82,83</sup> These survival rates compare favorably to those transplanted for other chronic, nonmalignant, nonviral liver diseases.<sup>84</sup> Age, renal failure, Child-Pugh classification, and United Network for Organ Sharing status are among predictive factors associated with poor outcome after transplantation.<sup>85</sup> Recurrence of PSC after liver transplantation has been reported to occur in 4–20% of patients.<sup>82,86,87</sup> The true incidence has been difficult to determine because recurrent PSC is often indistinguishable from biliary strictures due to other (well-established) causes.

## Summary and Treatment Recommendations

Treatment of PSC remains a work in progress. To a large extent this is because of continuing uncertainty about its pathogenesis and the factors that promote progression to end-stage liver disease. Among disease-modifying agents, UDCA is the most promising. It has been shown to improve biochemical abnormalities in patients with PSC and may improve symptoms and histology. Until appropriately powered studies confirm the benefit of high-dose UDCA therapy, it should be administered at a dose of 13–15 mg/kg daily. Corticosteroids can be used to treat PSC/autoimmune hepatitis overlap syndrome but have no role in treatment of uncomplicated PSC. Endoscopic therapy is the approach of choice for dominant strictures. For patients with end-stage liver disease due to PSC, liver transplantation is the only therapy that improves survival. Transplanted patients need to be monitored for recurrent PSC, which may be difficult to distinguish from biliary stenosis due to other causes.

## References

1. Wiesner RH, Larusso NF. Clinicopathologic features of the syndrome of primary sclerosing cholangitis. *Gastroenterology*. 1980;79:200-206.
2. Lee YM, Kaplan MM. Primary sclerosing cholangitis. *N Engl J Med*. 1995;332:924-933.
3. Harnois DM, Lindor KD. Primary sclerosing cholangitis: evolving concepts in diagnosis and treatment. *Dig Dis*. 1997;15:23-41.
4. Broome U, Olsson R, Loof L, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. *Gut*. 1996;38:610-615.
5. Rosen CB, Nagorney DM, Wiesner RH, et al. Cholangiocarcinoma complicating primary sclerosing cholangitis. *Ann Surg*. 1991;213:21-25.
6. Fausa O, Schruppf E, Elgjo K. Relationship of inflammatory bowel disease and primary sclerosing cholangitis. *Semin Liver Dis*. 1991;11:31-39.
7. van Milligen de Wit AW, van Deventer SJ, Tytgat GN. Immunogenetic aspects of primary sclerosing cholangitis: implications for therapeutic strategies. *Am J Gastroenterol*. 1995;90:893-900.
8. O'Mahony CA, Vierling JM. Etiopathogenesis of primary sclerosing cholangitis. *Semin Liver Dis*. 2006;26:3-21.
9. Colombo C, Battezzati PM, Podda M, et al. Ursodeoxycholic acid for liver disease associated with cystic fibrosis: a double-blind multicenter trial. The Italian Group for the Study of Ursodeoxycholic Acid in Cystic Fibrosis. *Hepatology*. 1996;23:1484-1490.
10. Poupon RE, Lindor KD, Cauch-Dudek K, et al. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. *Gastroenterology*. 1997;113:884-890.
11. Lazaridis KN, Gores GJ, Lindor KD. Ursodeoxycholic acid 'mechanisms of action and clinical use in hepatobiliary disorders'. *J Hepatol*. 2001;35:134-146.
12. Luketic VA, Sanyal AJ. The current status of ursodeoxycholate in the treatment of chronic cholestatic liver disease. *Gastroenterologist*. 1994;2:74-79.
13. Guicciardi ME, Gores GJ. Ursodeoxycholic acid cytoprotection: dancing with death receptors and survival pathways. *Hepatology*. 2002;35:971-973.
14. Patel T, Gores GJ. Apoptosis and hepatobiliary disease. *Hepatology*. 1995;21:1725-1741.
15. Crosignani A, Setchell KD, Invernizzi P, et al. Clinical pharmacokinetics of therapeutic bile acids. *Clin Pharmacokinet*. 1996;30:333-358.
16. Heuman DM, Bajaj R. Ursodeoxycholate conjugates protect against disruption of cholesterol-rich membranes by bile salts. *Gastroenterology*. 1994;106:1333-1341.
17. Rodrigues CM, Steer CJ. Mitochondrial membrane perturbations in cholestasis. *J Hepatol*. 2000;32:135-141.
18. Beuers U, Bilzer M, Chittattu A, et al. Tauroursodeoxycholic acid inserts the apical conjugate export pump, Mrp2, into canalicular membranes and stimulates organic anion secretion by protein kinase C-dependent mechanisms in cholestatic rat liver. *Hepatology*. 2001;33:1206-1216.
19. Fickert P, Zollner G, Fuchsichler A, et al. Effects of ursodeoxycholic and cholic acid feeding on hepatocellular transporter expression in mouse liver. *Gastroenterology*. 2001;121:170-183.
20. Kurz AK, Graf D, Schmitt M, et al. Tauroursodeoxycholate-induced cholestasis involves p38(MAPK) activation and translocation of the bile salt export pump in rats. *Gastroenterology*. 2001;121:407-419.
21. Qiao L, Yacoub A, Studer E, et al. Inhibition of the MAPK and PI3K pathways enhances UDCA-induced apoptosis in primary rodent hepatocytes. *Hepatology*. 2002;35:779-789.
22. Alpini G, Baiocchi L, Glaser S, et al. Ursodeoxycholate and tauroursodeoxycholate inhibit cholangiocyte growth and secretion of BDL rats through activation of PKC alpha. *Hepatology*. 2002;35:1041-1052.
23. Hillaire S, Boucher E, Calmus Y, et al. Effects of bile acids and cholestasis on major histocompatibility complex class I in human and rat hepatocytes. *Gastroenterology*. 1994;107:781-788.
24. Yoshikawa M, Tsujii T, Matsumura K, et al. Immunomodulatory effects of ursodeoxycholic acid on immune responses. *Hepatology*. 1992;16:358-364.
25. O'Brien CB, Senior JR, Arora-Mirchandani R, et al. Ursodeoxycholic acid for the treatment of primary sclerosing cholangitis: a 30-month pilot study. *Hepatology*. 1991;14:838-847.
26. Stiehl A, Walker S, Stiehl L, et al. Effect of ursodeoxycholic acid on liver and bile duct disease in primary sclerosing cholangitis. A 3-year pilot study with a placebo-controlled study period. *J Hepatol*. 1994;20:57-64.
27. Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. *N Engl J Med*. 1997;336:691-695.
28. Mitchell SA, Bansi DS, Hunt N, et al. A preliminary trial of high-dose ursodeoxycholic acid in primary sclerosing cholangitis. *Gastroenterology*. 2001;121:900-907.
29. Harnois DM, Angulo P, Jorgensen RA, et al. High-dose ursodeoxycholic acid as a therapy for patients with primary sclerosing cholangitis. *Am J Gastroenterol*. 2001;96:1558-1562.
30. Olsson R, Boberg KM, de Muckadell OS, et al. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. *Gastroenterology*. 2005;129:1464-1472.
31. Rost D, Rudolph G, Kloeters-Plachky P, Stiehl A. Effect of high-dose ursodeoxycholic acid on its biliary enrichment in primary sclerosing cholangitis. *Hepatology*. 2004;40:693-698.
32. Lindor KD, Wiesner RH, Colwell LJ, et al. The combination of prednisone and colchicine in patients with primary sclerosing cholangitis. *Am J Gastroenterol*. 1991;86:57-61.
33. Angulo P, Batts KP, Jorgensen RA, et al. Oral budesonide in the treatment of primary sclerosing cholangitis. *Am J Gastroenterol*. 2000;95:2333-2337.
34. Boberg KM, Egeland T, Schruppf E. Long-term effect of corticosteroid treatment in primary sclerosing cholangitis patients. *Scand J Gastroenterol*. 2003;38:991-995.
35. Nakazawa T, Ohara H, Sano H, et al. Clinical differences between primary

- sclerosing cholangitis and sclerosing cholangitis with autoimmune pancreatitis. *Pancreas*. 2005;30:20-25.
36. Knox TA, Kaplan MM. A double-blind controlled trial of oral-pulse methotrexate therapy in the treatment of primary sclerosing cholangitis. *Gastroenterology*. 1994;106:494-499.
  37. Lindor KD, Jorgensen RA, Anderson ML, et al. Ursodeoxycholic acid and methotrexate for primary sclerosing cholangitis: a pilot study. *Am J Gastroenterol*. 1996;91:511-515.
  38. Van Thiel DH, Carroll P, Abu-Elmagd K, et al. Tacrolimus (FK 506), a treatment for primary sclerosing cholangitis: results of an open-label preliminary trial. *Am J Gastroenterol*. 1995;90:455-459.
  39. Talwalkar JA, Angulo P, Keach JC, et al. Mycophenolate mofetil for the treatment of primary sclerosing cholangitis. *Am J Gastroenterol*. 2005;100:308-312.
  40. Sterling RK, Salvatori JJ, Luketic VA, et al. A prospective, randomized-controlled pilot study of ursodeoxycholic acid combined with mycophenolate mofetil in the treatment of primary sclerosing cholangitis. *Aliment Pharmacol Ther*. 2004;20:943-949.
  41. Wagner A. Azathioprine treatment in primary sclerosing cholangitis. *Lancet*. 1971;2:663-664.
  42. Schramm C, Schirmacher P, Helmreich-Becker I, et al. Combined therapy with azathioprine, prednisolone, and ursodiol in patients with primary sclerosing cholangitis. A case series. *Ann Intern Med*. 1999;131:943-946.
  43. Sandborn WJ, Wiesner RH, Tremaine WJ, Larusso NF. Ulcerative colitis disease activity following treatment of associated primary sclerosing cholangitis with cyclosporin. *Gut*. 1993;34:242-246.
  44. Duchini A, Younossi ZM, Saven A, et al. An open-label pilot trial of cladribine (2-chlorodeoxyadenosine) in patients with primary sclerosing cholangitis. *J Clin Gastroenterol*. 2000;31:292-296.
  45. Bharucha AE, Jorgensen R, Lichtman SN, et al. A pilot study of pentoxifylline for the treatment of primary sclerosing cholangitis. *Am J Gastroenterol*. 2000;95:2338-2342.
  46. Epstein MP, Kaplan MM. A pilot study of etanercept in the treatment of primary sclerosing cholangitis. *Dig Dis Sci*. 2004;49:1-4.
  47. Angulo P, MacCarty RL, Sylvestre PB, et al. Pirfenidone in the treatment of primary sclerosing cholangitis. *Dig Dis Sci*. 2002;47:157-161.
  48. Olsson R, Broome U, Danielsson A, et al. Colchicine treatment of primary sclerosing cholangitis. *Gastroenterology*. 1995;108:1199-1203.
  49. De Maria N, Colantoni A, Rosenbloom E, Van Thiel DH. Ursodeoxycholic acid does not improve the clinical course of primary sclerosing cholangitis over a 2-year period. *Hepatogastroenterology*. 1996;43:1472-1479.
  50. Larusso NF, Wiesner RH, Ludwig J, et al. Prospective trial of penicillamine in primary sclerosing cholangitis. *Gastroenterology*. 1988;95:1036-1042.
  51. Angulo P, Bharucha AE, Jorgensen RA, et al. Oral nicotine in treatment of primary sclerosing cholangitis: a pilot study. *Dig Dis Sci*. 1999;44:602-607.
  52. Farkkila M, Karvonen AL, Nurmi H, et al. Metronidazole and ursodeoxycholic acid for primary sclerosing cholangitis: a randomized placebo-controlled trial. *Hepatology*. 2004;40:1379-1386.
  53. Angulo P, Lindor KD. Primary biliary cirrhosis and primary sclerosing cholangitis. *Clin Liver Dis*. 1999;3:529-570.
  54. Cullen SN, Chapman RW. The medical management of primary sclerosing cholangitis. *Semin Liver Dis*. 2006;26:52-61.
  55. Bergasa NV, Jones EA. The pruritus of cholestasis: potential pathogenic and therapeutic implications of opioids. *Gastroenterology*. 1995;108:1582-1588.
  56. Miguet JP, Mavie P, Soussy CJ, Dhumeaux D. Induction of hepatic microsomal enzymes after brief administration of rifampicin in man. *Gastroenterology*. 1977;72:924-926.
  57. Ghent CN, Carruthers SG. Treatment of pruritus in primary biliary cirrhosis with rifampin. Results of a double-blind, crossover, randomized trial. *Gastroenterology*. 1988;94:488-493.
  58. Podesta A, Lopez P, Terg R, et al. Treatment of pruritus of primary biliary cirrhosis with rifampin. *Dig Dis Sci*. 1991;36:216-220.
  59. Bachs L, Pares A, Elena M, et al. Effects of long-term rifampicin administration in primary biliary cirrhosis. *Gastroenterology*. 1992;102:2077-2080.
  60. Bergasa NV, Talbot TL, Alling DW, et al. A controlled trial of naloxone infusions for the pruritus of chronic cholestasis. *Gastroenterology*. 1992;102:544-549.
  61. Bergasa NV, Schmitt JM, Talbot TL, et al. Open-label trial of oral nalmefene therapy for the pruritus of cholestasis. *Hepatology*. 1998;27:679-684.
  62. Wolfhagen FH, Sternieri E, Hop WC, et al. Oral naltrexone treatment for cholestatic pruritus: a double-blind, placebo-controlled study. *Gastroenterology*. 1997;113:1264-1269.
  63. Angulo P, Therneau TM, Jorgensen A, et al. Bone disease in patients with primary sclerosing cholangitis: prevalence, severity and prediction of progression. *J Hepatol*. 1998;29:729-735.
  64. Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. *Hepatology*. 2000;31:1005-1013.
  65. Fulcher AS, Turner MA, Franklin KJ, et al. Primary sclerosing cholangitis: evaluation with MR cholangiography—a case-control study. *Radiology*. 2000;215:71-80.
  66. Angulo P, Pearce DH, Johnson CD, et al. Magnetic resonance cholangiography in patients with biliary disease: its role in primary sclerosing cholangitis. *J Hepatol*. 2000;33:520-527.
  67. Textor HJ, Flacke S, Pauleit D, et al. Three-dimensional magnetic resonance cholangiopancreatography with respiratory triggering in the diagnosis of primary sclerosing cholangitis: comparison with endoscopic retrograde cholangiography. *Endoscopy*. 2002;34:984-990.
  68. Stiehl A, Rudolph G, Sauer P, et al. Efficacy of ursodeoxycholic acid treatment and endoscopic dilation of major duct stenoses in primary sclerosing cholangitis. An 8-year prospective study. *J Hepatol*. 1997;26:560-566.
  69. Stiehl A, Rudolph G, Kloters-Plachky P, et al. Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. *J Hepatol*. 2002;36:151-156.
  70. Pohl J, Ring A, Stremmel W, Stiehl A. The role of dominant stenoses in bacterial infections of bile ducts in primary sclerosing cholangitis. *Eur J Gastroenterol Hepatol*. 2006;18:69-74.
  71. Olsson R, Björnsson E, Backman L, et al. Bile duct bacterial isolates in primary sclerosing cholangitis: a study of explanted livers. *J Hepatol*. 1998;28:426-432.
  72. Parlak E, Kuran SO, Disibeyaz S, et al. Endoscopic treatment of primary sclerosing cholangitis. *Turk J Gastroenterol*. 2004;15:144-148.
  73. Wagner S, Gebel M, Meier P, et al. Endoscopic management of biliary tract strictures in primary sclerosing cholangitis. *Endoscopy*. 1996;28:546-551.
  74. Kaya M, Petersen BT, Angulo P, et al. Balloon dilation compared to stenting of dominant strictures in primary sclerosing cholangitis. *Am J Gastroenterol*. 2001;96:1059-1066.
  75. Baluyut AR, Sherman S, Lehman GA, et al. Impact of endoscopic therapy on the survival of patients with primary sclerosing cholangitis. *Gastrointest Endosc*. 2001;53:308-312.
  76. Grijm R, Huijbregtse K, Bartelma J, et al. Therapeutic investigations in primary sclerosing cholangitis. *Dig Dis Sci*. 1986;31:792-798.
  77. Johnson GK, Geenen JE, Venu RP, Hogan WJ. Endoscopic treatment of biliary duct strictures in sclerosing cholangitis: follow-up assessment of a new therapeutic approach. *Gastrointest Endosc*. 1987;33:9-12.
  78. Gaing AA, Geders JM, Cohen SA, Siegel JH. Endoscopic management of primary sclerosing cholangitis: review, and report of an open series. *Am J Gastroenterol*. 1993;88:2000-2008.
  79. Lee JG, Leung JW, Baillie J, et al. Benign, dysplastic, or malignant—making sense of endoscopic bile duct brush cytology: results in 149 consecutive patients. *Am J Gastroenterol*. 1995;90:722-726.
  80. Enns R, Eloubeidi MA, Mergener K, et al. Predictors of successful clinical and laboratory outcomes in patients with primary sclerosing cholangitis undergoing endoscopic retrograde cholangiopancreatography. *Can J Gastroenterol*. 2003;17:243-248.
  81. Hay JE. Liver transplantation for primary biliary cirrhosis and primary sclerosing cholangitis: does medical treatment alter timing and selection? *Liver Transpl Surg*. 1998;4:S9-17.
  82. Graziadei IW, Wiesner RH, Marotta PJ, et al. Long-term results of patients undergoing liver transplantation for primary sclerosing cholangitis. *Hepatology*. 1999;30:1121-1127.
  83. MacQuillan GC, Neuberger J. Liver transplantation for primary biliary cirrhosis. *Clin Liver Dis*. 2003;7:941-56, ix.
  84. Bjoro K, Brandsaeter B, Foss A, Schrupf E. Liver transplantation in primary sclerosing cholangitis. *Semin Liver Dis*. 2006;26:69-79.
  85. Ricci P, Therneau TM, Malinchoc M, et al. A prognostic model for the outcome of liver transplantation in patients with cholestatic liver disease. *Hepatology*. 1997;25:672-677.
  86. Goss JA, Shackleton CR, Farmer DG, et al. Orthotopic liver transplantation for primary sclerosing cholangitis. A 12-year single center experience. *Ann Surg*. 1997;225:472-481.
  87. Graziadei IW, Wiesner RH, Batts KP, et al. Recurrence of primary sclerosing cholangitis following liver transplantation. *Hepatology*. 1999;29:1050-1056.
  88. van Milligen de Wit AW, van Bracht J, Rauws EA, et al. Endoscopic stent therapy for dominant extrahepatic bile duct strictures in primary sclerosing cholangitis. *Gastrointest Endosc*. 1996;44:293-299.