Medical Treatment of Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis

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Key Words
Cholestasis · Immunosuppressants · Liver diseases · Primary biliary cirrhosis · Primary sclerosing cholangitis · Ursodeoxycholic acid

Abstract
Treatment of primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) with ursodeoxycholic acid (UDCA) has been in common use since 1985. In PBC, treatment with UDCA improves laboratory data, liver histology, enables a longer transplantation-free interval and prolongs disease survival. Because UDCA is unable to cure the disease newer drugs or combination therapies are still needed. Studies with UDCA and immunosuppressants such as prednisone, budesonide and azathioprine have shown that in selected patients combination therapy may be superior to UDCA monotherapy. PSC is treated successfully with UDCA and endoscopically dilatation of the bile duct strictures. Treatment of extrahepatic manifestations of cholestatic liver disease such as pruritus, fatigue, osteoporosis and steatorrhea can be problematic and time-consuming.

Introduction
Definition. Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are both cholestatic liver diseases. Common features of these disorders are an increase of cholestasis enzymes, bile duct destruction, and finally liver cirrhosis.

Etiology. The etiology and pathogenesis of PBC and PSC are still unknown. PBC is considered to be an autoimmune disease [1]. Immunological mechanisms may also be involved in PSC since clinical studies have reported an association with ulcerative colitis (UC) [2] and autoantibodies [3]. Furthermore, genetic factors seem to play an important role in both diseases [3, 4].

Therapy. Since the pathogenesis of both diseases has not been elucidated yet, there is no definite causal treatment. However, ursodeoxycholic acid (UDCA) has been shown to be highly effective in reducing biochemical cholestasis as well as in improving liver histology and survival. Other drugs which can be used alone or in combination with UDCA are promising and might further improve the outcome of the diseases.

Ursodeoxycholic Acid

In 1981, the first observation that UDCA noticeably improves liver function tests was made in patients with chronic active hepatitis who underwent gallstone dissolution with UDCA [5]. These data were confirmed in 1985 [6]. In the same year, the first results were published on the treatment of 6 patients with PBC and 2 patients with PSC [7]. Since then, numerous clinical observations have been published that support the notion that UDCA is effective in cholestatic disorders, and increasing experimental evidence supports the use of UDCA in these conditions [8].
UDCA is the 7β-epimer of chenodeoxycholic acid and represents a small fraction of the normal bile acid pool in humans [9]. During oral UDCA administration, the bile acid pool shifts to the more hydrophilic side, and the proportion of UDCA increases up to 50% [10]. UDCA is efficiently taken up in the liver, conjugated primarily with glycine (and to a lesser extent with taurine) and secreted into bile with subsequent enterohepatic circulation [10].

**Mechanisms of Action**

The mechanisms of action of UDCA in cholestatic liver diseases are unknown. The favorable effects can be classified into: (1) reduced hydrophobic bile acid concentrations; (2) hepatoprotective effects; (3) stimulation of choleresis; (4) influence on signal transduction and bile acid transporters, and (5) immunomodulatory effects.

**Replacement of Toxic Endogenous Bile Acids and Hepatoprotective Effects**

Under continuous oral treatment, UDCA becomes the predominant bile acid in serum, liver tissue and bile and replaces more hydrophobic and therefore toxic bile acids [11]. This mechanism is supported by an animal model where the mdr2 gene, which encodes a p-glycoprotein, is inactivated. This mdr2 (–/–) knockout mouse is unable to secrete phospholipids into the bile, which normally protects the biliary epithelium against toxic hydrophobic bile acids. In this model, treatment with UDCA ameliorates the bile duct injury presumably by rendering bile more hydrophilic [12]. The cytoprotective effects of UDCA are thought to be mediated through direct membrane-stabilizing and anti-apoptotic effects [9, 13]. Membrane stabilization is due to incorporation of UDCA into the more apolar domain of the membrane [15, 16] and the reduction in mitochondrial membrane permeability [16].

**Stimulation of Choleresis and Influence on Signal Transduction and Bile Acid Transporters**

In 1993 it could be shown that the beneficial effect of UDCA in cholestatic liver diseases is related to the Ca²⁺-dependent stimulation of vesicular exocytosis at least in part by activation of α-protein kinase C [17, 18]. In a recently published trial, the same group demonstrated that taurine-conjugated UDCA stimulates insertion of the conjugate export pump Mrp2 into the canalicular membrane as well as organic anion secretion into bile by a protein-kinase-C-dependent mechanism. [19]. Furthermore, it was shown that UDCA leads to an increase in canalicular transporter expression [20]. The prerogative for these mechanisms is an intact structure of external cell membranes [15, 16]. Furthermore, it has been demonstrated that taurine-conjugated UDCA activates Ras, which is an important molecular switch in cell signaling. This activation is mediated through a phosphoinositide 3 kinase (PI3-kinase)-dependent pathway leading to extracellular-signal-regulated kinase (Erk) activation, which seems to be responsible for the choleric effect of UDCA [21]. It is possible that taurine-conjugated UDCA-induced Ras and Erk-activation are also involved in the anti-apoptotic effect of UDCA [22].

**Immunomodulatory Effects**

Several reports suggest that UDCA has modulatory effects on immune functions. The expression of MHC class I molecules is increased in cholestasis, which may activate cytotoxic T lymphocytes in PSC and PBC. This might be prevented by UDCA since it was shown that UDCA downregulates the expression of aberrant MHC class I molecules on periportal hepatocytes and of MHC class II on cholangiocytes of PBC and PSC patients [9]. However, it is more likely that the effects on MHC class I expression are the result of improved cholestatic liver injury rather than a direct immunosuppressive effect of UDCA [8]. Furthermore, changes in the concentration of circulating IgM, of activated T lymphocytes and of IFN-γ were reported [23]. Taken together, the mode of action of UDCA seems to be multifactorial.

**Treatment of PBC**

Up to now, several trials have been conducted to evaluate drugs with different modes of action but have failed to provide convincing evidence of a benefit. In addition, many drugs exhibited an unacceptable profile of adverse effects.

**UDCA in PBC**

In 1989, the first randomized controlled trial demonstrated the therapeutic value of UDCA [24], which was confirmed by many other studies [25–28]. UDCA slows the progression of the disease, leads to an improvement of survival, and reduces the need for liver transplantation [1]. A recent study demonstrated that patients receiving UDCA had a lower incidence of major complications and lower medical care costs compared to patients receiving
placebo [29]. Based on these studies, UDCA has been established as the treatment of choice for PBC. It is safe and well tolerated at 5–25 mg/kg/day [30]. The recommended daily dose of PBC is 13–15 mg/kg/day [30]. The only significant side effect is diarrhea, which probably occurs in less than 5% of patients. According to biochemical data and the Mayo risk score, no further improvement is achieved when higher doses are administered [30, 31]. Below 10 mg/kg/day, treatment is apparently not effective [32].

Effect on Laboratory Values
In all trials, it was shown that even short-term treatment with UDCA leads to a marked improvement in the biochemical markers of primary biliary cirrhosis [33]. However, only in 30% of the UDCA-treated patients, biochemical tests demonstrated completely normal values, whereas 70% responded incompletely [34]. Recent evidence suggests, that the effects of UDCA are not primarily related to the stage of the disease [35] but to the degree of cholestasis. Thus, a therapeutic approach with a more powerful choleretic compound might be more effective in those subjects. First results of a prospective, controlled pilot study with sulindac support this hypothesis. Sulindac, a nonsteroidal anti-inflammatory drug with choleretic properties [36], was able to further improve biochemical parameters of the liver in incompletely responding patients when given at 100–300 mg/day in combination with UDCA [37].

Effect on Histology
The effect of UDCA on liver histology was less conclusive, and conflicting results have been published. In some trials, a benefit on liver histology was not observed [26, 28, 43, 44], while others saw a positive effect on inflammation but not on liver fibrosis and bile duct alterations [44–47]. However, in a recently published trial, UDCA decreased the progression to extensive fibrosis [48]. This beneficial effect of UDCA is supported by the observed antifibrotic effects in laboratory trials [49].

Effect on Survival
UDCA led to a significant increase in survival in five controlled trials [1]. This effect is especially visible in studies with advanced disease (bilirubin >1.4 mg/dl, and/or histological stage III, IV) [38]. In 1992, patients with PBC treated with UDCA were followed for a maximum of 12 years, and the survival time of these patients exceeded those of previously studied controls [39]. In a recently published long-term trial, the 10-year survival of 225 patients treated with UDCA was higher than that of untreated patients predicted by the Mayo model [40]. One suggests that the real benefit from UDCA may be greater with early onset of therapy than in later stages.

The effects of UDCA in PBC were questioned in a recently published meta-analysis, which failed to show a reduction in the need for transplantations or survival without transplantation [41]. The authors evaluated eleven trials but in eight studies UDCA dosage, stage of the disease, treatment time and definition of treatment failure were not well defined. Therefore, it is not possible to draw any conclusion from this meta-analysis. In a second meta-analysis using the same eleven studies, others demonstrated that the risk of death or liver transplantation in the UDCA group is statistically significantly lower than in untreated patients [42].

Effect on Symptoms and Portal Hypertension
A beneficial effect on pruritus and fatigue was observed by some groups [27, 50–52] but was not confirmed by others [26]. Improvement in liver enzymes is probably not correlated with the amelioration of pruritus [53]. Nevertheless, pruritus improved in patients with a complete normalization of cholestasis [34]. Therapy with UDCA appears to reduce the onset and severity of portal hypertension [54] and to lower the risk of esophageal varices [55].

Summary and Conclusions
UDCA has been extensively evaluated and shown to improve liver biochemistries, liver histology as well as survival in patients with PBC. Although UDCA slows the progression of PBC, it does not cure the disease. Since 70% of patients treated with UDCA respond incompletely to UDCA monotherapy with respect to their laboratory values, there is a need for newer drugs or combination therapies.

Immunosuppressants in PBC
Because PBC is a chronic autoimmune disease, several immunosuppressive drugs have been tested in randomized controlled trials [33]. However, so far none have been shown to be of great benefit and their use is limited due to their side effects.

Steroids in PBC
Although prednisolone was the first immunosuppressant used in PBC, only small controlled trials were published [56–58]. The results were rather disappointing and steroid monotherapy cannot be recommended [57, 58].
Recently, it has been shown that short-term administration of methylprednisolone increases cholic acid synthesis and turnover, as well as intestinal synthesis of toxic deoxycholic acid [59]. This could limit the therapeutic value of steroids. On the other hand, the combination of corticosteroids with UDCA appears to be superior to UDCA monotherapy [60, 61]. Because long-term or even life-long treatment is necessary in patients with PBC, glucocorticoid-induced side effects, such as osteoporosis, are a major problem.

**Budesonide in PBC**

Budesonide is a topical nonhalogenated glucocorticoid with a high first-pass effect of more than 90% resulting in fewer systemic side effects [62]. In a controlled, double-blind trial, the combination therapy with budesonide (3 × 3 mg/day) and UDCA over 2 years improved laboratory values and histology in patients with early stages of the disease [63]. In another trial, budesonide was less effective and had more side effects [64]. However, this was an uncontrolled 1-year study which included patients with late-stage PBC who were incomplete responders to UDCA monotherapy. Furthermore, it is possible that the advantage of the high first-pass effect of budesonide is abolished in patients with liver cirrhosis and portosystemic shunts. Thus, it is too early to conclude whether budesonide is effective or not, especially when subjects with end-stage liver disease are included.

**Azathioprine in PBC**

There are only few trials evaluating azathioprine monotherapy. No improvement in survival was observed [65–67]. However, in one trial azathioprine in combination with prednisolone and UDCA had a beneficial effect on liver biochemistry [68]. Furthermore, azathioprine may facilitate a reduction in the glucocorticoid dose, thus preventing side effects.

**Methotrexate in PBC**

There are contradictory studies concerning the treatment of PBC with methotrexate (MTX). With respect to liver histology, the degree of inflammation and bile duct injury improved in some patients but the degree of liver fibrosis and the histological stage, which are the most important parameters, did not improve or even worsened [69]. Furthermore, the use of MTX is limited due to its toxic side effects. Patients with PBC receiving methotrexate 15 mg/week are more susceptible to interstitial pneumonitis (up to 15%) than patients with psoriasis or rheumatoid arthritis [70]. With a low dose of MTX (7.5 mg/week) side effects were prevented but the treatment was ineffective [71]. The minimal effective dose for MTX in PBC appears to be 12.5–20 mg/week [72]. MTX may have a role in patients with early-stage disease [73, 74], however, in uncontrolled trials only.

In most studies combination therapy of UDCA with MTX did not show any additional benefit to that achieved by UDCA alone [75–77]. Only in one trial, symptoms and laboratory values improved. Histology and the natural cause of the disease were not investigated [78]. At present, MTX cannot be recommended.

**Cyclosporine A in PBC**

Treatment with cyclosporine has been disappointing because of limited efficacy and a marked toxicity [79]. The modest improvement in liver function tests, histology and survival are counterbalanced by the development of hypertension in some and worsening renal function in most patients [80]. Cyclosporin A may be helpful only in selected cases.

**Other Therapies in PBC**

**Colchicine**

An alternative approach to therapy of PBC is the prevention of fibrosis using agents that inhibit collagen formation [81–83]. Colchicine is a safe and inexpensive drug with a long-term effect on the biochemical parameters of disease activity. However, complications of cirrhosis, deaths and transplantations were not reduced [83, 84]. In contrast to other studies [53, 87], combination therapy with UDCA and colchicine led to an additional improvement in laboratory values [85, 86], but the effect on liver histology was not convincing [53, 88]. Combination therapy with colchicine, MTX and UDCA may be beneficial for patients who incompletely respond to UDCA [89]. Colchicine in addition to UDCA was less effective than treatment with MTX plus UDCA [90].

**Bezafibrate**

In a preliminary study, the combination with UDCA and bezafibrate was superior to UDCA alone with respect to alkaline phosphatase and IgM [91]. Side effects were not observed. In another trial monotherapy with bezafibrate showed a significant reduction in laboratory values, being similar to that seen with the UDCA and bezafibrate combination [92]. It is believed that bezafibrate stimulates phospholipid excretion into bile. Phospholipids protect bile duct epithelial cells.
Table 1. Drugs for mono and combination therapy in PBC

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Doses</th>
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<tr>
<td>Treatment of choice</td>
<td>UDCA</td>
</tr>
<tr>
<td></td>
<td>13–15 mg/kg/day</td>
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<tr>
<td></td>
<td>3× daily or in one single dose life long therapy</td>
</tr>
<tr>
<td>Patients with incomplete response to UDCA monotherapy</td>
<td>UDCA + prednisone + or + prednisolone</td>
</tr>
<tr>
<td>or UDCA + budesonide</td>
<td>+ 10–15 mg/day</td>
</tr>
<tr>
<td>or UDCA + azathioprine</td>
<td>+ 3 × 3 mg/day</td>
</tr>
<tr>
<td>or UDCA + azathiopine</td>
<td>+ 50–100 mg/day</td>
</tr>
<tr>
<td>UDCA + MTX&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13–15 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>+ 7.5 mg/week</td>
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</table>

<sup>a</sup> Further evidence still lacking.

**D-Penicillamine and Chlorambucil**

D-Penicillamine is not recommended in PBC since it is not effective at low doses and may lead to major side effects [93, 94]. In a randomized trial with chlorambucil, a benefit on laboratory values, especially on serum bilirubin, was observed [95]. Although the patients were treated with a suboptimal dose, all developed bone marrow suppression. Therefore the drug cannot be recommended.

**Summary**

All patients with PBC should be treated with UDCA at doses between 13–15 mg/kg/day or even higher. Patients with an incomplete response to UDCA monotherapy should be treated with a combination therapy (table 1).

**Treatment of PSC**

**Treatment with UDCA**

Because treatment with UDCA in PBC was effective and well tolerated, several studies were conducted in PSC [96]. Similar to PBC, all studies showed a marked reduction in cholestasis [97–101], and even bilirubin, a strong prognostic marker, improved. Thus, UDCA is considered as the treatment of choice for patients with all stages of PSC. Patients should be treated as early as possible, and prolonged or life-long therapy can be recommended since no major side effects have been observed [96]. The recommended dosage of UDCA is 15–25 mg/kg. Dosages less than 10 mg/kg appear to be without effect [101, 102].

There are only limited data on histological changes during UDCA therapy. In most studies, the cellular infiltrate of the portal triads improved whereas all other changes were not significant [97, 99]. Improvement was more pronounced with higher dosages of UDCA [101]. UDCA did not affect the histological progression when patients with a histologically advanced disease were treated [98, 103]. Up to now, no study had sufficient power to assess the effects of UDCA on survival. Treatment of pruritus, osteoporosis and vitamin deficiencies due to steatorrhea should follow the general guidelines [104]. Improvement in symptoms was observed in some but not all individuals on UDCA therapy [98, 100].

**Other Medical Therapies**

Attempts have been made to treat patients with immunosuppressive, antiinflammatory and antifibrotic agents. None of these drugs could stop the natural course of the disease. On the other hand, treatment may even be harmful because of the high incidence of bacterial cholangitis.

**Steroids in PSC**

Patients with UC who receive steroids can develop PSC or experience progression of the disease. Thus, monotherapy with corticosteroids seems not to be effective [96]. No benefit was seen in a 1-year uncontrolled study in which patients with late-stage PSC were treated with budesonide. Serum alkaline phosphatase and AST levels improved while serum bilirubin concentrations increased. In addition, a significant improvement in portal inflammation was noted, whereas the degree of fibrosis and the stage of the disease were not significantly affected [105]. Minor positive effects were observed with predni-
In addition to UDCA, the combination of budesonide and UDCA [106] produced positive results. These were also obtained with the combination of UDCA, prednisolone, and azathioprine (decrease in liver enzymes) [107]. However, the benefit of such combination therapies has not been confirmed in a long-term trial with a larger group and a more detailed description of the histological status.

### Additional Drugs

Uncontrolled and controlled trials and case reports have demonstrated that azathioprine [108], cyclosporine A [109], MTX [110, 111], tacrolimus [112], colchicine [113, 114] and pentoxifylline [115]. At present, none of these drugs can be recommended as monotherapy. In a recently published trial, cladribine, which is a nucleoside analog with specific antilymphocytic activity, decreased the hepatic lymphocytic inflammation in early-stage PSC [116].

It is very likely that a better understanding of the underlying pathophysiology may enable the introduction of additional new molecules with different modes of action.

### Endoscopic and Surgical Treatment

Dominant stenoses of the bile ducts are common in PSC. In a 12-year prospective trial on the effect of UDCA, 28/96 patients developed a progressive stenosis of major bile ducts [117]. UDCA monotherapy was unable to improve the transplant-free survival over 2 years [98], but UDCA plus endoscopic dilatation of duct stenoses did [118]. This is to be expected since stenoses are not likely to improve on medical treatment. Therefore, frequent endoscopic interventions are necessary to manage this complication [118]. Apart from repeated dilatations, intermittent placement of stents or nasobiliary catheter perfusion represent additional options of the treatment of biliary stenoses. Thus, endoscopic retrograde cholangiography is not only the gold standard for the diagnosis of PSC but also represents an important therapeutic tool for the management of the disease.

Dominant strictures can also be managed surgically by dilatation or cholecodochojjunostomy. However, the procedure is reserved to patients with an early histological stage and symptomatic extrahepatic or perihilar strictures. There is no benefit for patients with more advanced disease [119]. Unwarranted surgical intervention may complicate a future liver transplantation [120].

### Diagnosis and Treatment of Cholangiocarcinoma

Patients with PSC have a significantly increased risk to develop cholangiocarcinoma (CCC) [118]. In a large multicenter study from Sweden, bile duct carcinoma was observed in 8% of patients with PSC followed for 63 months [121]. Furthermore, CCC can be detected in up to 20% of explanted livers [122]. Alcohol consumption is an additional risk factor for developing CCC in PSC. There is no correlation between the course of PSC and the development of CCC [123]. The incidence of CCC was higher in patients with PSC and inflammatory bowel disease than in patients with PSC only [124]. At present, it is unclear whether treatment with UDCA has an influence on the development of bile duct carcinoma [118]. The prognosis for patients with CCC remains poor. The relative 1- and 2-year survival rates following diagnosis were 24.5 and 12.8%, respectively [125]. Generally, survival is less than 1 year [126].

The diagnosis of CCC in PSC can be difficult because endoscopic brush cytology and/or biopsies and imaging studies are often false negative. Furthermore, the serum levels of CA 19-9 can rise temporarily in association with a biochemical relapse of PSC resulting in insufficient sensitivity and specificity [123, 127, 128]. As Ca 19-9 and CEA are not helpful in identifying patients with premalignant changes who would benefit from surgery [129], their prognostic value is limited. The detection of K-ras mutations and p53 dysfunction holds some promise but requires further evaluation [130, 131].

Computed tomography (spiral CT, multislice CT and CT angiography) and magnetic resonance imaging (MRI) have been refined technologically within the last several years [14]. However, those noninvasive imaging studies still have their limitations in diagnosing CCC [132]. Currently, magnetic resonance cholangiopancreatography represents the best noninvasive diagnostic tool for the evaluation of malignant perihilar biliary obstructions with reference to endoscopic retrograde cholangiography [133]. Furthermore, three-dimensional and cine cholangiography might be also adequate in the assessment of the biliary system in patients with hilar CCC [134]. PET can be highly sensitive and specific for the detection and localization of CCC. It is especially helpful for the diagnosis of distant metastases, but it is not suitable for the detection of regional lymph node metastases [135, 136].

With advances in the surgical technique, the number of curative resections of hilar CCC has increased. However, the recurrence rate after curative resection is high. There is no established adjuvant therapy. CCC is a highly resis-
Table 2. Recommendations for the treatment of pruritus

<table>
<thead>
<tr>
<th>Line</th>
<th>Drugs</th>
<th>Doses</th>
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<tbody>
<tr>
<td>First line</td>
<td>UDCA</td>
<td>13–15 mg/day</td>
</tr>
<tr>
<td></td>
<td>cholestyramine</td>
<td>4–16 g/day in increasing dosage</td>
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<tr>
<td></td>
<td>colestipol</td>
<td>5–30 g/day</td>
</tr>
<tr>
<td>Second line</td>
<td>naloxone</td>
<td>2–3 × 0.4 mg/day</td>
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<tr>
<td></td>
<td>naltrexone</td>
<td>50 mg/day orally</td>
</tr>
<tr>
<td></td>
<td>ondansentron</td>
<td>3 × 4 to 3 × 8 mg/day orally</td>
</tr>
<tr>
<td>Third line</td>
<td>rifampicin</td>
<td>300–500 mg/day up to 10 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>metronidazole</td>
<td>3 × 250 mg/day for 1 week</td>
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<tr>
<td></td>
<td>2,6-di-isopropylphenol</td>
<td>up to 15 mg/day</td>
</tr>
<tr>
<td>Fourth line</td>
<td>plasmapheresis</td>
<td>3 ×/week, subsequently once every 2 weeks</td>
</tr>
<tr>
<td></td>
<td>liver transplantation</td>
<td>in cases who are refractory to treatment</td>
</tr>
</tbody>
</table>

PSC and Colorectal Cancer

80% of patients with PSC suffer from UC, which is often mild or even asymptomatic [118]. Interestingly, the severity of UC increases within the first years after liver transplantation [138, 141], and proctocolectomy does not affect the progression of PSC [142]. PSC appears to be an independent risk factor for the development of colonic dysplasia and of colon carcinoma in patients with UC [143]. This risk is further increased in subjects with PSC and UC after liver transplantation. Therefore, repeated colonoscopies are strongly recommended in these patients [144]. Results of a recently published trial showed that UDCA therapy was associated with a decreased prevalence of colonic dysplasia in patients with PSC [145]. Further trials are needed to confirm these interesting results.

Extrahepatic Manifestations of Cholestatic Liver Diseases

Pruritus

Patients with chronic cholestatic liver disease frequently suffer from pruritus. Pruritus reduces the quality of life considerably, and, in severe cases, may serve as an indication for liver transplantation. Because the pathogenesis of pruritus is unknown, treatment is not based on scientific evidence but on empirical knowledge [146] (table 2). The accumulation of toxic bile acids and an increase in pruritogenic substances at present do not appear to be important. More recent findings suggest that an increase in neurotransmission, mediated by endogenous opioid agonists, may be responsible for the development of pruritus [146].

Treatment

Although bile acids appear to be less important in the pathogenesis of pruritus, cholestyramine, a non-absorbable bile-acid-binding anion exchange resin, is effective in 80–90% [147]. Patients who do not tolerate its side effects, e.g. bad taste, bloating, diarrhea and constipation, may be treated with colestipol. Patients in whom cholestyramine is not effective, treatment with enzyme inducers such as rifampicin [148] phenobarbital [149] and S-adenosyl-methionine [150] may be helpful. In addition, the antibiotic effects of rifampicin and metronidazole might ameliorate pruritus. It is possible that this effect is secondary to changes in the intestinal flora, which could influence the metabolism of bile salts and up to now unknown pruritogens [151]. The unsatisfactory effects of
antihistamines are likely to be due to their sedative properties [152].

As mentioned above, disturbances in the neurotransmission/neuromodulation of the central nervous system may be involved in the pathogenesis of pruritus. Potent opiate antagonists, such as naloxone (USA) [153], naltrexone [154], and naloxone [155], are effective in 50–60% of the patients [146]. Other neurotransmitter systems, such as serotonin, might also be involved in the pathogenesis of pruritus. Some authors suggest that the 5HT3 serotonin antagonist ondansetron may ameliorate pruritus [146, 156]. However, further investigation is needed to determine whether specific serotonin receptor subtype ligands have a place in the treatment of pruritus.

**Fatigue**

Fatigue is noted in up to two thirds of the PBC patients, but its etiology remains obscure [157]. It may be centrally mediated like pruritus [146] since increased serotonergic neurotransmission in the CNS contributes to fatigue [158, 159]. There are no convincing data about the efficacy of UDCA [1, 27, 98] or other drugs. A beneficial effect of antioxidant therapy requires further investigation [160].

**Osteoporosis**

Osteoporosis is a frequent complication of cholestatic liver diseases and is present in almost all patients with end-stage liver disease [161]. Its pathogenesis is not well understood. Osteoporosis is more frequently seen in PBC than in PSC [162], although osteoporosis-favoring factors specifically related to PBC have not been defined [163]. Dual-energy X-ray absorptiometry is the method of choice for evaluating and monitoring osteoporosis [164]. Risk factors for the development of osteoporosis in biliary liver diseases are not well defined. The role of disease severity [165], vitamin D receptor genotypes in PBC, cholestasis itself and Sjögren’s syndrome are currently discussed [166]. Inflammatory bowel disease in combination with PSC may or may not be an additional risk factor [162].

**Treatment**

No therapy has been shown to provide satisfactory results in the treatment of metabolic bone disease associated with cholestatic liver disease (table 3). At an early stage, physical exercise and maintenance of adequate serum vitamin D levels and calcium intake may be sufficient. Monitoring of dietary intake of calcium and vitamin D is reasonable, and the threshold for initiating supplementation should be low [167]. The results of treatment with calcitonin monotherapy are still controversial. Whereas some authors were able to show a benefit [168], the majority was unable to demonstrate a significant improvement [169]. Most likely, a combination with vitamin D (1,25-dihydroxyvitamin D) and calcium is effective [170]. UDCA does not appear to have an influence on osteoporosis [162, 171].

In menopausal women with low bone mineral density, estrogens are the standard treatment to prevent osteoporosis [172]. Unfortunately, there are only few data on estrogen therapy and PBC, but estrogens appear to be a safe and effective treatment option [173]. Today, in postmenopausal patients, biphosphonates (alendronate) are the first choice of treatment [172], but with respect to PBC, results are controversial [174]. In a recently pub-
lished trial, cyclical etidronate alternated with calcium was unable to improve bone density [175]. However, PBC patients treated with prednisolone seemed to benefit [176].

**Steatorrhea**

In cholestatic liver disease, steatorrhea can occur for three reasons: When bile acid concentration in the small bowel is below the critical micellar concentration, micelle formation and fat absorption are reduced. In patients with PBC, sicca syndrome is accompanied by the decreased secretion of pancreatic enzymes and in some patients celiac disease develops [177, 178]. During treatment, fat intake should not exceed 20% of the total energy intake. In severe cases middle chain triglycerides can be effective. Deficiencies in fat-soluble vitamins A, D, E and K are seldom but have to be expected in manifest steatorrhea and should be supplemented by intramuscular vitamin injections. Furthermore, pancreatic enzymes can be administered in high doses (table 4).

**New Immunosuppressants**

Over the past 50 years, many immunosuppressive drugs have been described. Eventually the mechanisms of action were found to fall into five groups: (i) regulators of gene expression; (ii) alkylating agents; (iii) inhibitors of purine synthesis; (iv) inhibitors of pyrimidine synthesis, and (v) inhibitors of kinases and phosphatases. Most of the new immunosuppressive drugs have been developed for organ transplantation and more recently for autoimmune diseases [179]. Two of the immunosuppressive drugs which represent interesting candidates for the treatment of PBC and PSC are tacrolimus (FK506) and mycophenolate mofetil (MMF).

In 1987, tacrolimus (FK506), a metabolite of the actinomycete *Streptomyces tsukubaensis*, was shown to be immunologically effective. Adverse effects of the drug include neurotoxicity and nephrotoxicity [180]. Extensive efforts aimed at identifying compounds with an improved therapeutic profile may lead to the design of safer FK506-related immunosuppressants [181]. Sirolimus is structurally related to the immunosuppressive agent tacrolimus, and retains a pharmacokinetic and drug interaction profile similar to cyclosporine and tacrolimus [182]. It is the latest pharmaceutical agent to complete phase III trials, acts to inhibit interleukin-2-driven lymphocyte proliferation and reduces the risk of acute rejection to below 20% [183]. However, the molecule causes severe hyperlipidemia, and the long-term consequences on both the pathogenesis of cardiovascular disease and on lipid-associated renal injury have yet to be determined [184].

MMF was initially derived from cultures of *Penicillium* spp. The drug is currently the leading candidate for the replacement of azathioprine [185]. Based on the experience obtained in clinical trials, the recommended dosage is 2 g/day. Two patients with PBC were treated with a combination of MMF 2 g and UDCA 1 g daily for 12 months. Both were incomplete responders to UDCA monotherapy. A decrease in elevated serum alkaline phosphatase levels to values close to the upper limit of normal, and an almost complete disappearance of the chronic inflammatory cell infiltrate was observed without

| Table 4. Treatment of steatorrhea and vitamin and zinc deficiencies |
|------------------------|------------------|------------------|
| **Steatorrhea**         | Reduction of fat intake to 30–50 g/day |
|                        | Middle chain triglycerides |
|                        | Lowering cholestyramine dosage |
|                        | Pancreatic enzymes |
|                        | Gluten-free diet |
| **Vitamin deficiencies** | vitamin A 25,000–50,000 IU i.m., 3 x/week or 3 x 25,000 IU/week |
|                        | vitamin K 10 mg/month i.m. |
|                        | vitamin E 100–400 mg α-tocopherol/month i.m. or 10–20 mg/day |
|                        | vitamin D₃ 500–5,000 IU/day orally or 100,000 IU/month i.m. |
| **Electrolyte and trace element deficiencies** | calcium 1,000–1,500 mg/day or substitution sometimes necessary |
|                        | zinc |
significant adverse events [186]. However, the lack of severe side effects could be due to the short observation period, and therefore long-term studies have to be performed.

Another approach to improve immunosuppression is the development of targeted monoclonal antibodies. Anti-interleukin-2 antibodies have shown promising results in phase III trials (not PBC). The treatment was well tolerated and had little side effects [185].

In summary, the development of new drugs offers the opportunity to use combinations that block different pathways of immune activation. In addition, drugs with different toxicity profiles can be selected in order to reduce the dosage of each drug.

References


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