

Current management of primary biliary cirrhosis and primary sclerosing cholangitis

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1. Primary biliary cirrhosis

1.1. Background

Primary biliary cirrhosis (PBC) is a chronic, cholestatic autoimmune liver disease characterized by inflammation and progressive destruction of interlobular bile ducts, ultimately leading to biliary cirrhosis. Population based studies have estimated the incidence of PBC as 19.1–251/1 000 000 in the general population [1,2].

The etiology of PBC is attributed to autoimmunity mainly due to the association with antimicrobial antibodies, present in 95% of PBC patients, but genetic and environmental factors are thought to contribute as well. In a large epidemiologic study conducted in the United States a survey was sent to 241 patients with PBC using standardized questions drawn from the National Health and Nutrition Examination Survey in an attempt to identify risk factors for the disease; 83.3% of the patients returned the questionnaires [3]. Surveys were also sent to siblings and friends of the cases. The female-to-male ratio among cases was 10:1, and the mean age of respondents was 53 years, accurately reflecting the general knowledge on epidemiology of PBC. The investigators identified that autoimmune diseases (Sjogren's syndrome, Raynaud's syndrome, autoimmune thyroid disease) were 3–15 times more frequent among PBC cases than their siblings or cases and there was a 6% prevalence of PBC in first degree relatives of cases. In addition, several illnesses were seen in association with PBC, such as urinary tract infection, tonsillectomy, cholecystectomy and shingles, raising the possibility that an infectious agent may also be involved in the pathogenesis of PBC.

Symptoms begin insidiously. Fatigue is the most common symptom, present in up to 70% of patients [4], followed by pruritus, which can be quite distressing for the patient. Jaundice develops later, usually associated with progression of the

disease. Other symptoms are related to portal hypertension and other sequelae of advanced cholestatic liver disease.

There are several prognostic models for predicting survival, with the serum bilirubin level being the only variable common to all of them. The prognosis is noticeably different for asymptomatic or symptomatic patients, but it is clearly documented that even asymptomatic patients have a shorter survival compared to the general population [5]. The overall survival rate ranged from 5.5 to 11.9 years in the pre-transplant era [6]. A Kaplan–Meier graphic of the estimated survival in PBC is shown in Fig. 1.

Therapy is aimed at preventing disease progression as well as treating or preventing its complications, namely osteoporosis, fat-soluble vitamin deficiencies, pruritus and portal hypertension.

1.2. Drugs to modify survival

1.2.1. Immunosuppressants

Given the autoimmune nature of PBC, immunosuppressants were among the first drugs to be studied in this patient population. Table 1 lists all controlled trials performed with immunosuppressants in patients with PBC [7–14]. Despite some apparent benefits, the use of these drugs has been limited mostly by their extensive side effects and, therefore, cannot be recommended as monotherapy in these patients.

1.2.2. Colchicine

Colchicine is an anti-inflammatory drug used for gout and familial Mediterranean fever that is also known to inhibit microtubule assembly within cells. Therefore, colchicine has antimetabolic effects and can interfere with the secretion of collagen, being considered an antifibrotic agent. Early reports of colchicine improving levels of serum alkaline phosphatase and alanine aminotransferase in five patients with PBC [15] prompted the development of clinical trials to assess its efficacy in this setting.

Three randomized controlled trials have been reported [16–18]. The studies were limited by small sample sizes,

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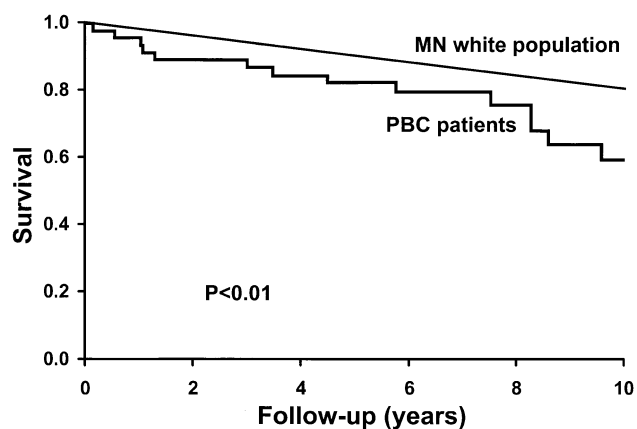


Fig. 1. Kaplan–Meier estimated survival curves of patients with PBC compared with age- and sex-matched Minnesota white population, indicating that PBC patients have shorter survival when compared to the control population ($P < 0.01$). Reproduced with permission from Kim et al. [136].

failure to use intention-to-treat principle, and high drop-out rates. Overall, there was improvement of liver biochemistries in the colchicine treated patients, but histological progression was not different in placebo and colchicine-treated groups. In 1991, Zifroni et al. published the results of a prolonged follow-up period of four more years for patients formerly evaluated in one prospective, randomized, double-blind controlled trial of colchicine compared to placebo [19]. Their results showed that colchicine did not prevent complications such as cirrhosis, deaths or transplantation. The only study that formally evaluated survival failed to definitely demonstrate that cumulative mortality differed in the two groups [16].

The improvement in biochemical markers noted with this drug stimulated further studies involving the combination of colchicine and UDCA, which will be discussed later in this review.

The efficacy of colchicine was compared to that of UDCA in a placebo-controlled trial involving 90 patients, with follow-up period of 2 years [20]. UDCA was noted to be superior to colchicine and especially to placebo. Serum bilirubin and the carboxyterminal propeptide of type I procollagen levels were decreased only by ursodeoxycholic acid. Based on the above studies, the use of colchicine as monotherapy cannot be recommended.

1.2.3. Ursodeoxycholic acid (UDCA)

UDCA is a hydrophilic bile acid with known beneficial hepatic effects. Multiple mechanisms of action have been postulated, based on in vitro and in vivo studies, mostly through three major pathways that probably interact, covered in details by two recent reviews [21,22]. The first mechanism proposed was that of expansion of the hydrophilic bile acid pool by enrichment of bile with UDCA. This more hydrophilic bile is less toxic to the cholangiocytes. However, UDCA has been shown to improve liver tests in

patients with cholestatic liver diseases without any apparent change in the bile acid pool or in the serum levels of the most important hydrophobic bile acids [23], suggesting that other mechanisms are probably involved as well. Two other properties of UDCA came into play: the so-called anti-cholestatic and the anti-apoptotic actions. By promoting apical exocytosis and improving the canalicular transport, UDCA and its taurine conjugate (TUDCA) may stimulate secretion of potentially toxic bile acids or other compounds [24–26]. Furthermore, UDCA has been shown to inhibit hepatocyte apoptosis, probably by stabilizing the mitochondrial membrane and preventing the increase in permeability that usually precedes mitochondrial dysfunction [27].

In 1987, Poupon et al. conducted a landmark pilot study utilizing UDCA to treat 15 patients with PBC for 2 years and demonstrated effectiveness of this drug in lowering standard liver tests and improving symptoms [28]. Several randomized, double-blinded controlled trials were carried out after that confirming the better outcome of patients treated with UDCA, as reflected by fewer deaths and/or referrals for liver transplantation. The largest study to date is a Canadian multicentric double-blinded randomized controlled trial conducted by Heathcote et al., which included 222 patients with PBC [29]. UDCA was used at 13–15 mg/kg per day given once daily. In this trial, the rise in serum bilirubin was prevented by UDCA. Transaminases, alkaline phosphatase, total cholesterol and IgM also improved compared to the placebo group. However, despite some improvement observed in paired biopsies (pre- and post-treatment), treatment with UDCA did not delay or prevent the need for liver transplantation. The authors remark that the trial was not powered to observe a difference in the need for liver transplantation and/or death. In addition, no differences were seen regarding symptoms (pruritus, fatigue, ascites or encephalopathy) between the two treatment groups.

Survival free of transplantation was further evaluated in a combined analysis of data from the three largest trials [29,34,35]. The researchers performed a subgroup analysis according to the severity of disease and it was determined that UDCA increases the probability of survival free of transplantation for patients with bilirubin > 1.4 mg/dl [30]. The greatest effect of UDCA was seen in patients with stage IV disease, likely because of the slow rate of progression of PBC and the relatively short follow-up period. Also, four independent prognostic factors were identified in primary biliary cirrhosis: high serum bilirubin level, low serum albumin level, advanced histological stage and high Mayo Risk Score. The risk of liver transplantation was 2.7 times higher in patients with cirrhosis. In 1999, a meta-analysis failed to demonstrate any difference between placebo and UDCA in the incidence of death, liver-related death or liver transplantation [31]. Limitations of that study were mainly related to the fact that trials with non-homogeneous methodologies were included in the same analysis, blending together studies utilizing different doses of UDCA and with different lengths of follow-up [32,33]. A combined

analysis of the five studies with long-term follow-up [29,34–37] was subsequently performed (Fig. 2), definitely showing that the risk of death or liver transplantation is lower in the UDCA-treated patients, corresponding to a 32% reduction in the risk of dying or receiving a liver transplantation [33].

More recently, it was demonstrated that UDCA therapy could significantly delay progression of liver fibrosis in early stage PBC [38]. The probability of remaining free of extensive fibrosis or cirrhosis for UDCA-treated patients was 76% at 4 years and 61% at 8 years, compared to 29 and 13%, respectively, for placebo-treated patients. These results were in agreement with a previous case-control study showing delayed onset of cirrhosis in UDCA-treated patients [39] and with a double-blind controlled multicentric study involving 192 patients with a mean time between biopsies of almost 5 years [40]. The latter also showed marked effects of UDCA, with significantly lower histological stage and piecemeal necrosis in the UDCA-treated patients. Bile duct paucity was higher in patients receiving placebo. Corpechot et al. identified serum bilirubin greater than 17 (mol/l, albumin less than 38 g/l and the presence of severe lymphocytic piecemeal necrosis as independent factors predictive of cirrhosis development in UDCA-treated patients [38].

The Mayo Risk Score was recalculated for patients on UDCA for 6 months and was found to be the only risk factor predictive of esophageal varices in a multivariate analysis ($P < 0.001$) [41]. Ninety-three percent of the patients who developed varices had a Mayo Risk Score ≥ 4 , making that score an established surrogate marker in PBC. Similarly, the serum alkaline phosphatase level measured after 6 months of therapy had prognostic value, possibly due to improvement of cholestasis by UDCA secondary to its anticholestatic function. Therefore, the alkaline phosphatase level after treatment can be used as a marker of response to UDCA, especially if combined therapy is planned [41]. Such a finding is in concordance with results published a year later by Leuschner et al., who evaluated markers of response to long term UDCA therapy and found that high

serum baseline alkaline phosphatase levels would imply higher likelihood of treatment failure [42].

Because of the delay in referral for liver transplantation induced by administration of UDCA, it was thought that these patients might have a poorer outcome after transplant. This issue was further evaluated in a retrospective trial comparing post transplant survival, infection rates and rejection episodes in patients who had received UDCA as opposed to patients who received placebo [43]. It was clear that UDCA did not increase the risk of death, infection or rejection within the first year of transplantation.

UDCA has been shown to decrease the rate of development of esophageal varices [44]. It has a well-known cholesterol lowering effect that is directly related to the improvement of serum bilirubin during therapy and inversely related to the magnitude of initial serum cholesterol [45]. Periorbital and palmar xanthomas may resolve after 1–2 years of therapy. In contrast, no beneficial effect has been observed on the autoimmune diseases associated with primary biliary cirrhosis [46].

The issue of appropriate dose of UDCA has been addressed by several randomized trials [47–49]. Trials using low dose UDCA [36,37] were not successful in terms of preventing histological progression over the 2-year period of the studies. Although there is evidence to suggest that there is better response with a greater proportion of UDCA in the bile acid pool [50], that does not seem to be the only determinant of UDCA effectiveness in PBC. Different doses of the drug may cause a similar degree of bile acid enrichment. Angulo et al. studied the effects of three different doses of UDCA in PBC: 5–7, 13–15 and 23–25 mg/kg per day [48]. The authors found that a dose of 13–15 mg/kg per day elicits the same biochemical and Mayo Risk Score improvement as a dose of 23–25 mg/kg per day. Both these doses were significantly better than 5–7 mg/kg per day. UDCA is very well tolerated and most of the side effects occurred in the low-dose group, implying that the adverse effects are not dose-related. The same authors performed a pilot study using 28–32 mg/kg per day UDCA for patients who had had incomplete response to the usual 13–15 mg/kg per day and the results were discouraging, not showing any additional benefit for the majority of patients [51]. Therefore, the recommended dose of choice is 13–15 mg/kg per day.

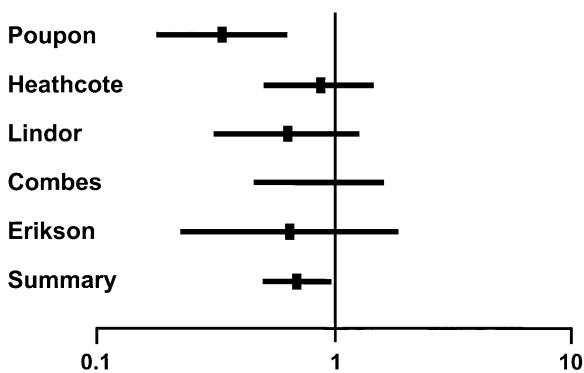


Fig. 2. Liver transplantation or death in clinical trials of UDCA versus placebo for patients with PBC: meta-analysis of the five largest trials. Reproduced with permission from Poupon et al. [32].

1.2.4. Combination therapy

Several controlled trials utilizing immunosuppressants or colchicine in addition to UDCA have been published to date. An outline of their results is shown in Table 2 [52–60]. Overall, little if any incremental benefit is noted when any of such drugs is added to UDCA and in fact unwanted effects such as worsening of bone disease (with the use of corticosteroids) or pulmonary toxicity (seen with methotrexate) may offset these benefits.

Case reports and uncontrolled studies involving combination with UDCA are described below.

Table 1
Controlled trials of immunosuppressants in PBC

Drug	Authors, year	No. of patients	Pruritus	Serum bilirubin level	Histology	Survival/Mayo Risk Score	Duration
Prednisolone	Mitchison et al., 1992 [13]	36	Mild improvement	Mild improvement	Mild improvement	No difference	3 years
Azathioprine	Heathcote et al., 1976 [8]	45	Mild improvement	No improvement	No improvement	No difference	5 years
	Christensen et al., 1985 [7]	236	No improvement	No improvement	No improvement	Trend toward improvement	5 years
Methotrexate	Hendrickse et al., 1997 [10]	60	Not evaluated	No improvement	No improvement	Worse in the treatment group	6 years
Chlorambucil	Hoofnagle et al., 1986 [9]	24	Not evaluated	Significantly improved	Inflammation improved	No difference	4 years
Cyclosporin A	Minuk et al., 1988 [12]	12	No improvement	No improvement	No improvement	No difference	1 year
	Wiesner et al., 1990 [14]	29	Significantly improved	Significantly improved	Absence of histologic progression	Not evaluated	2 years
	Lombard et al., 1993 [11]	349	Significantly improved	Significantly improved	Trend toward delayed progression	No difference	2 years

Table 2
Controlled trials involving drug combinations compared to UDCA alone for patients with PBC^a

Drug combination	Authors, year	No. of patients	Pruritus	Serum liver biochemistries	Histology	Survival/Mayo Risk Score
Aza + Prednisone + UDCA vs. UDCA	Wolfhagen et al., 1998 [58]	50	Improved	Improved	Minimal improvement	Not evaluated
MTX + UDCA vs. UDCA	Buscher et al., 1993 [53]	32	Improved	improved	Not evaluated	Not evaluated
	Lindor et al., 1995 [57]	32	No improvement	No improvement	No improvement	Not evaluated
	Gonzalez-Koch et al., 1997 [54]	25	No improvement	No improvement	No improvement	Not evaluated
	Leuschner et al., 1996 [55]	30	Not evaluated	No improvement	Improved	Not evaluated
Prednisolone + UDCA vs. UDCA	Leuschner et al., 1999 [56]	39	Not evaluated	Improved	Improved	Not evaluated
Budesonide + UDCA vs. UDCA	Angulo et al., 2000 [52]	22	Not evaluated	Transiently Improved	Not evaluated	Worse Mayo Risk Score
Colchicine + UDCA vs. UDCA	Poupon et al., 1996 [59]	74	No improvement	No improvement	Inflammation improved	Not evaluated
	Ikeda et al., 1996 [60]	22	Not evaluated	Improved	Not evaluated	Not evaluated
	Goddard et al., 1994 [133]	57	Not evaluated	Improved	Not evaluated	Not evaluated
	Almasio et al., 2000 [134]	90	No improvement	No improvement	Inflammation improved	Mayo Risk Score increased less in the combination group
	Battezzati et al., 2001 [135] ^b	44	No improvement	No improvement	Not evaluated	Both Mayo Risk Score and actuarial survival similar in the 2 groups

^a Aza, azathioprine; MTX, methotrexate; UDCA, ursodeoxycholic acid.

^b Extended follow-up of 44 out of 90 patients previously reported by Almasio et al. [134].

1.2.4.1. Mycophenolate mofetil (MMF) and UDCA. In 1999 Jones et al. published case reports of two patients who had incomplete response to UDCA (500 mg BID) after 10 and 34 months of therapy, respectively [61]. After starting MMF (1 g BID) there was substantial further decrease of serum alkaline phosphatase to levels near the upper limit of normal. Moreover, repeat liver biopsies also showed further improvement of the inflammatory activity with combined therapy. There was no change in the histological stage, though. Patients were treated for 12 months and no significant side effect developed. Such encouraging results suggest that the combination of UDCA with MMF can possibly become an alternative for patients who respond insufficiently to UDCA. Larger trials with long term follow up and formal survival evaluation would be necessary to confirm this hypothesis.

1.2.4.2. Silymarin and UDCA. Silymarin 140 mg TID was added to the treatment of 27 women who had persistent elevation of alkaline phosphatase levels despite having been on UDCA for 7–221 months [62]. The combination therapy continued for 1 year. No added benefit was noted in serum alkaline phosphatase, bilirubin, albumin, and aminotransferases or in the Mayo Risk Score.

1.2.4.3. Bezafibrate and UDCA. Small pilot studies have evaluated the efficacy of bezafibrate addition to UDCA therapy [63–65]. Overall, patients with the combined therapy tended to have a higher degree of improvement of serum alkaline phosphatase and alanine aminotransferase levels, but no significant difference in the serum bilirubin drop.

Bezafibrate was compared to UDCA in 24 patients and found to significantly decrease the liver biochemistries and serum IgM levels [66]. However, the effect of bezafibrate on histology was not evaluated and the follow up period was short (1 year), hence not allowing further interpretation of these results. The same authors reported the effect of bezafibrate monotherapy on three patients [67] in whom there was no improvement of histological stage after 2–4 years of treatment.

In summary, there is no optimal combination therapy for PBC as of yet. Based on current results, we cannot recommend combination with any immunosuppressant nor with colchicine. We believe that the combination bezafibrate + UDCA should be evaluated in a prospective trial and in fact, there is an ongoing project in our institution with this purpose. The combination mycophenolate mofetil/UDCA has been evaluated in a small pilot study at the Mayo Clinic and preliminary results showed moderate improvement of serum liver biochemistries, of unclear significance in the long term management of these patients.

1.3. Liver transplantation for PBC

Orthotopic liver transplantation (OLT) prevents death in patients with PBC. The indications for transplant are liver

failure and poor quality of life in selected patients with intractable pruritus or severe osteoporosis. In 1989, Markus et al. showed an increased survival for PBC patients treated with liver transplantation (from 31 to 74% at 2 years) [68]. Since then, UDCA has been proved to slow progression of PBC. Accordingly, the most recent series evaluating the efficacy of liver transplantation for PBC have shown that patients are being transplanted at an older age, and with lower serum bilirubin levels and Mayo Risk Score, perhaps indicating an earlier disease stage [69]. The post-transplant outcome, if anything, is enhanced by pre-transplantation UDCA therapy [43].

In a single-center report of 400 patients transplanted for PBC between 1982 and 1999, the overall patient survival at 1, 5 and 10 years were 83, 78 and 67% [69]. When results were broken down to transplant before and after 1990, the 1, 3 and 5 year survival rates were 72, 70 and 66% for patients transplanted in the 1980s and 87, 83 and 80% for those transplanted in the 1990s. Recurrence of PBC was noted in as many as 17% of the allografts in this series.

Kim et al., using the Mayo Risk Score to analyze patients transplanted for PBC between 1987 and 1994, has addressed the optimal timing of liver transplantation [70]. The authors observed that those with a score greater than 7.8 had higher post-transplant mortality. Others have documented a positive correlation between the Mayo Risk Score greater than 7.8 and a higher utilization of resources such as intraoperative blood requirements, length of mechanical ventilation, and duration of hospital stay [71].

1.4. Summary statement

In brief, the currently accepted standard therapy for PBC is UDCA 13–15 mg/kg per day, as it has been proven to delay progression of disease and increase survival free of liver transplantation. The indications for liver transplantation include development of end stage liver disease with liver failure or extremely poor quality of life related to intractable pruritus or osteoporosis. The management of these complications is discussed later in this review.

2. Primary sclerosing cholangitis

2.1. Background

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disorder characterized by diffuse inflammation, obliteration and fibrosis of the extra- and intrahepatic bile ducts which eventually leads to the development of biliary cirrhosis. Although its etiology remains largely unknown, there are growing indications that immune mechanisms are involved in the pathogenesis. In agreement with that hypothesis, hypergammaglobulinemia is frequently seen, associated with a high prevalence of pANCA positivity [72]. About 75% of patients with PSC also have chronic ulcerative colitis (CUC); however, only approximately

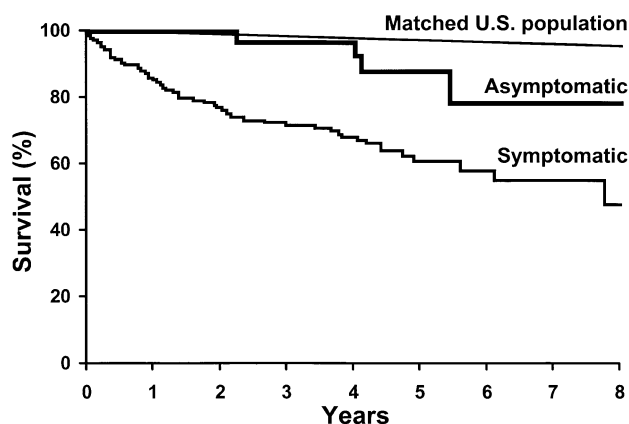


Fig. 3. Survival of symptomatic and asymptomatic patients with PSC compared with age-, sex- and race-matched US population. Difference in survival of controls vs. asymptomatic patients is statistically significant ($P < 0.0001$), as well as difference between symptomatic and asymptomatic patients ($P < 0.003$). Reproduced with permission from Wiesner et al. [74].

2.5–7.5% of patients with CUC will develop PSC. Over two thirds of patients with PSC are men.

PSC patients have a higher risk of developing cholangiocarcinoma than the general population, with prevalence rates reported between 10 and 30%. A recent large study in Sweden involving a cohort of 604 patients with PSC followed for a median of 5.7 years revealed that the frequency of hepatobiliary cancers (cholangiocarcinoma, gallbladder cancer and hepatocellular carcinoma) was 13.3% [73]. Interestingly, the risk of pancreatic cancer was increased 14 times and that of colon cancer increased ten times compared with the normal population.

Prior to the advent of liver transplantation as a treatment possibility for patients with PSC, the median survival from the time of diagnosis was 11.9 years, or seen another way, the 9-year survival rate was 75% [74]. Fig. 3 illustrates estimated survival in PSC. To date, there is no effective treatment to prolong survival other than liver transplantation, which increases overall 5-year survival to up to 90%. Several trials directed at finding effective medical therapy for PSC have been unsuccessful; most recently, high-dose UDCA treatment has shown some promise.

2.2. Drugs to modify survival

Previous randomized controlled trials or pilot studies failed to demonstrate a beneficial effect of d-penicillamine [75], immunosuppressants (methotrexate [76], budesonide [77], cyclosporin [78]), antifibrotic agents (colchicine [79], pirfenidone [80]), nicotine [81,82], or pentoxifylline (anti-TNF, antifibrotic drug) in patients with PSC [83]. Cladribine, an antilymphocytic agent, was used in four patients with PSC and found to decrease periportal inflammation [84]. However, no improvement was observed in serum liver biochemistry levels, cholangiograms or symptom scores.

2.2.1. Ursodeoxycholic acid (UDCA)

As mentioned before, UDCA is a hydrophilic bile acid with choleric, hepatoprotective and immunomodulatory properties. Given the successful treatment of PBC with UDCA and the mechanisms by which UDCA exerts its beneficial effects, several researchers have investigated the efficacy and safety of this drug in patients with PSC. A list of all controlled trials with UDCA in PSC to date is shown in Table 3 [85–91].

We have evaluated the effect of UDCA (13–15-mg/kg daily) in a randomized, placebo controlled trial involving 105 patients with PSC [90]. The mean follow-up period in that study was 2.2 years. Despite a statistically significant improvement in serum alkaline phosphatase, bilirubin, albumin and aspartate aminotransferase levels noted in the UDCA-treated group, prevention of histological progression could not be demonstrated. The time to treatment failure or time to liver transplantation was not different between the treatment groups. Such biochemical response was consistent with that shown in other smaller trials. The lack of clinical effect might have been related to patient selection, with a large percentage of patients having advanced histological stage, short duration of follow-up or inadequate dosage of UDCA.

In 1998, Van Hoogstraten et al. performed a randomized controlled trial comparing single dose versus multiple daily doses of UDCA and found no significant difference [91]. Both drug administration schedules resulted in similar decreases of the serum alkaline phosphatase and had no effect on serum total bilirubin and IgG levels. There was a trend towards decreased inflammatory activity in the group of patients receiving single daily dose, but the authors could not observe a definite histological improvement in either group. Also, symptoms such as pruritus and fatigue were not improved by treatment.

Two studies have evaluated the use of high-dose UDCA for patients with PSC (Table 4). Mitchell et al. randomized 26 patients to UDCA (20 mg/kg per day) or placebo and followed them for 2 years [92]. Results show a statistically significant drop in serum alkaline phosphatase and GGT levels, less progression in disease stage and improvement in cholangiographic appearance in the UDCA-treated group. In the second study, 30 patients received UDCA 25–30 mg/kg per day, with 1-year follow up. Treatment with UDCA caused a statistically significant decrease in serum alkaline phosphatase, AST, albumin and total bilirubin levels [93]. When the Mayo prognostic model was utilized, the expected mortality at 4 years was considerably improved in patients treated with high-dose UDCA compared to those who received placebo in a previous study (11 versus 17%) [90].

Furthermore, a recent cross-sectional study evaluating the prevalence of colonic dysplasia in patients with PSC and ulcerative colitis who were undergoing surveillance colonoscopies found that the use of UDCA was associated with a lower prevalence of high grade dysplasia, possibly suggesting a protective effect of UDCA [94].

Presently, high-dose UDCA is being evaluated in a large scale randomized controlled multicenter trial.

2.2.2. Tacrolimus

This macrolide antibiotic with strong immunosuppressive properties has been studied in a pilot study involving 10 patients with PSC [95]. Despite significant biochemical improvement after 1 year of therapy, no histologic or radiologic regression could be demonstrated. However, none of the enrolled patients had histologic progression of disease either, suggesting that perhaps a longer treatment period is required in order for us to identify long term benefits. No significant side effects were noted. A pilot study of Tacrolimus in PSC is currently underway in our institution.

2.2.3. Combination therapy

2.2.3.1. Colchicine and prednisone. In one of the earliest combination studies, Lindor et al. treated 12 patients for 2 years with colchicine and prednisone [96]. No significant difference could be appreciated in the serum biochemistries or in liver biopsies between treated and untreated patients. There was a trend toward improved survival in the treated group.

2.2.3.2. Azathioprine, prednisolone and UDCA. The suggestion that PSC has an autoimmune nature and the incomplete response to UDCA has prompted researchers to study the addition of corticosteroids and/or other immunosuppressants to UDCA. Schramm et al. evaluated the use of a combination of azathioprine (1–1.5 mg/kg per day), prednisolone (1 mg/kg per day initially, tapering 5–10 mg/day) and UDCA (mean 650 mg/day) in a pilot study with 15 patients, who were treated for 3–81 months [97]. Although a drop in the serum levels of alkaline phosphatase, alanine aminotransferase and total bilirubin has been demonstrated, it is important to note that the dose of UDCA in this study was suboptimal and therefore it is not clear whether the additional benefits can really be attributed to the immunosuppressants.

2.2.3.3. Budesonide or prednisone and UDCA. Following the same line of thought, van Hoogstraten et al. performed a

double blinded randomized trial comparing UDCA (12 mg/kg per day) + prednisone (10 mg/day) versus UDCA + budesonide (3 or 9 mg/day). Eighteen patients were studied [98]. They had been receiving UDCA for at least 5 months and subsequently had the corticosteroid added for another 8 weeks. No major short-term benefit was observed with additional therapy.

2.3. Other medical therapy

Bezafibrate is a fibric acid derivative largely used for hypertriglyceridemia, which was recently found to cause a decrease in serum levels of alkaline phosphatase, gamma-glutamyl transferase and IgM in patients with PBC. It has been studied in PBC in combination with UDCA, and thought to elicit a biochemical response, although its histologic effects are yet unknown. Kita et al. described three patients with PSC who had incomplete response to UDCA and to who bezafibrate was added [99]. An additional benefit was seen in terms of further reduction of the serum alkaline phosphatase levels. Nevertheless, the follow up period was excessively short and biopsy samples were not available for comparison. Also, these patients were not on high-dose UDCA. Further trials are warranted for better evaluation of this treatment possibility.

2.4. Endoscopic therapy

Before the current refined endoscopic techniques of bile duct dilatation and stenting for dominant strictures in PSC were developed, attempts were made at lavaging the biliary tree with corticosteroids through nasobiliary irrigation. A randomized placebo-controlled trial proved not to be beneficial but set the stage for newer endoscopic approaches [100].

Up to 15–20% of patients with PSC will develop a dominant stricture in the extrahepatic bile ducts, and 30% may form small intrahepatic stones or pigmented debris. There is, however, evidence that the use of UDCA may lead to an increase in the proportion of patients who develop dominant strictures. Stiehl et al. prospectively followed 106 patients with PSC for a mean of 5.2 years and found that dominant stenosis developed in 39% of patients during treatment with

Table 3
Placebo-controlled trials of UDCA in PSC^a

Authors, year	No. of patients	Biochemical response	Histological response	Mayo Risk Score or survival	Dose (mean duration)
Beuers et al., 1992 [85]	14	Yes	Yes	No improvement	13–15 mg/kg/day (1 year)
Lo et al., 1992 [86]	18	Trend	No	NA	10 mg/kg/day (2 years)
Van Thiel et al., 1992 [87]	48	Yes	NA	NA	600 mg/day (18 months)
Stiehl et al., 1994 [88]	20	Yes	Yes	NA	750 mg/day (1 year)
De Maria et al., 1996 [89]	59	No	No	NA	600 mg/day (2 years)
Lindor, 1997 [90]	105	Yes	No	No improvement	13–15 mg/kg/day (2.2 years)
Van Hoogstraten et al., 1998 [91]	48	Yes	Trend	No improvement	10 mg/kg/day (2 years)

^a NA, not available.

Table 4
High-dose UDCA trials in PSC

Authors, year	No. of patients	Biochemical response	Histological response	Mayo Risk Score or survival	Dose (mean duration)
Mitchell et al., 2001 [92]	26	Yes	Yes	NA	20 mg/kg/day (2 years)
Harnois et al., 2001 [93]	30	Yes	NA	Improved	25–30 mg/kg/day (1 year)

UDCA (8.8–17.4 mg/kg per day) [88]. Endoscopic therapy may involve sphincterotomy, balloon/graduated catheter dilatation, stenting and/or nasobiliary drainage (Fig. 4). An endoscopic approach is indicated for selected patients with dominant strictures that can be reached with the guidewire, usually within 2 cm of the bifurcation, but only in experienced centers. Complications occur in 7–45% of patients and are usually mild [80–82]. Nevertheless, one of the greatest concerns with the use of endoscopic therapy is that it may delay the diagnosis of a bile duct malignancy, therefore jeopardizing timing for surgical intervention. On the other hand, 75–80% of patients show biochemical improvement after endoscopic intervention [101,102], and there is indirect evidence of increased survival free of liver transplantation for patients with dominant strictures treated endoscopically, especially for those with advanced stages of disease. Baluyut et al. evaluated survival of 63 consecutive patients with PSC who underwent endoscopic therapy and were followed for a median of 34 months [103]. Observed survival was compared to that predicted by the Mayo Risk Score and found to be significantly higher (83 vs. 65%). This study was criticized for using serum bilirubin values obtained prior to dilatation to calculate the Mayo Risk Score, therefore overestimating the severity of the underlying liver disease. These results, however, are in line with findings from Stiehl et al. in 1997 that the association of UDCA and endoscopic therapy led to better survival than UDCA alone [104]. The actuarial survival rates 5 years after the first endoscopic intervention in this population was 100% for patients with stage 2 disease, 72% for those with stage 3 and 50% for patients with stage 4 disease, which is very good considering that patients with major strictures become candidates for OLT if the obstruction cannot be relieved.

2.5. Surgical treatment

Ahrendt et al. reported a series of all patients with PSC managed at The Johns Hopkins Hospital between 1980 and 1995, with emphasis on results of endoscopic and surgical treatments, including liver transplantation [105]. Fifty patients with PSC underwent resection of the extrahepatic biliary tract, 40 of those with resection of the hepatic duct bifurcation as well. Forty patients were noncirrhotic and had an operative mortality of 2.5%. The overall 1-, 3- and 5-year survival rates were 86, 84 and 76%, respectively. A subgroup analysis of noncirrhotic patients only revealed 1-, 3- and 5-year survival rates of 95, 92 and 85%, respectively, which was also better than noncirrhotic patients treated with endoscopic therapy. Transplant-free survival for low and moderate risk patients (stratified according to their multicenter risk score) was longer

for those treated with operative modalities when compared to patients managed nonoperatively.

In Ahrendt's series, nine of 25 patients diagnosed with cholangiocarcinoma underwent surgical exploration and resection. Four received OLT and five had resection of the extrahepatic biliary tract and hepatic duct bifurcation with or without hepatectomy or left hepatic lobectomy. Sixteen patients had palliative procedures. The 1-, 3- and 5-year survival rates for the nine patients who underwent resection were 56, 30 and 15%, respectively.

2.6. Liver transplantation for PSC

OLT remains the ultimate treatment for PSC. Indications may relate to end-stage liver disease (advanced cholestasis, complications of portal hypertension, spontaneous bacterial peritonitis) or quality-of-life, that is, intractable pruritus and osteoporosis. There is no evidence that medical therapy can affect the timing for OLT in patients with PSC, although use of the endoscopic approach to dominant strictures may cause immediate relief of cholestasis and temporarily delay referral [106]. The outcome of OLT for PSC has been extremely satisfactory, with 5 year-survival rates of 73–100% [107]. Results are significantly worse in patients with cholangiocarcinoma diagnosed pre-transplant with survival rates at 1 and 6 years of 30 and 0%, respectively [108]. However, the outcome of patients with cholangiocarcinomas detected incidentally during liver transplantation is still debatable, with some series reporting results similar to patients with known cholangiocarcinomas and other reporting survival rates as high as those for patients without cancer [109], [110]. With the understanding that biliary malignancies happen more often in patients with PSC (prevalence of 10–30%), Nashan et al. attempted to identify an optimal timing for OLT in patients with PSC by applying the Mayo Survival Model to 48 patients receiving transplant for that indication [108]. All ten patients with biliary malignancies had a Mayo Score greater than 4 and there was a marked increase in the incidence of biliary tumors at scores greater than 4.4. The authors suggest that consideration should be given to OLT for all patients with PSC whose Mayo Scores are above 4. Of interest, previous abdominal surgery (except for cholecystectomy) appears to be associated with increased post-transplant in-hospital mortality rate [111]. This information underlies the importance of a priori identification of optimal transplant candidates and overall early consideration of referral for OLT.

Recurrence of PSC in the transplanted liver has been reported in 8–20% of patients. A study in our institution

looked at possible risk factors for recurrence of PSC and failed to demonstrate any convincing relation with age, sex, previous biliary surgery, surgical technique, number of episodes of rejection, CMV infection or lymphocytotoxic mismatch [112]. Among patients with recurrence of PSC, 92% had ulcerative colitis, while this disease was only present in 76% of the patients without recurrence. This difference did not reach statistical significance.

2.7. Summary statement

Unfortunately, there is no standard therapy for PSC. High-dose UDCA appears promising and is being evaluated in a randomized controlled trial, but cannot be recommended outside of clinical trials. As of today, treatment of PSC is mostly symptomatic and involves endoscopic therapy or surgery when appropriate.

3. Therapy to improve the quality of life: PBC and PSC

3.1. Pruritus

Pruritus, defined as ‘the need to scratch’, can be a very distressing symptom. It is seen more often in patients with PBC but can also occur in PSC. The pathogenesis of this very common complication of cholestasis is not entirely understood, but the increased production of endogenous opioids has been implicated, associated with an increased opioidergic tone in the central nervous system [113]. A potential role for serotonergic neurotransmitters is also entertained.

The bile acid binding resin cholestyramine is usually the first choice therapy for pruritus, given that it has almost no side effects. The starting dose is 4g daily. It should be empha-

sized that this resin also binds several other drugs, including UDCA, and needs to be taken 2–4 h prior to the other medications. The dose can be escalated to a maximum of 16 g daily. If an incomplete or no response is seen with cholestyramine, rifampin can be given at 150–300 mg twice a day.

The treatment of pruritus with opiate antagonists has been evaluated in two randomized controlled trials through measurement of scratching activity and visual analogue scales [113,114]. Both showed that naloxone infusions (0.2 mg/kg per min) significantly ameliorated the perception of pruritus as well as decreased the scratching activity. This response was later corroborated by the efficacy of oral naltrexone (50 mg daily) and oral nalmefene (2 mg twice a day) in patients with refractory pruritus in placebo controlled trials [115,116]. Symptoms of opioid withdrawal may occur during initial treatment with opioid antagonists, possibly as a consequence of the increased opioidergic tone in the central nervous system.

Ondansetron (a 5-HT₃ antagonist) given intravenously effectively relieved pruritus in one patient with PBC [117] and in a placebo-controlled trial with ten cholestatic patients [118]. Nevertheless, the study was limited by its methodology: the investigators were not blinded, the sample size was small and itching was only assessed subjectively. The scientific evidence on the efficacy of ondansetron is still very limited, but it indicates a potential role for the serotonergic neurotransmitters in the pathogenesis of pruritus.

3.2. Osteoporosis

Bone disease has long been recognized as a complication of cholestatic liver diseases [119]. The pathogenesis of osteoporosis in PBC patients is unknown, but there is

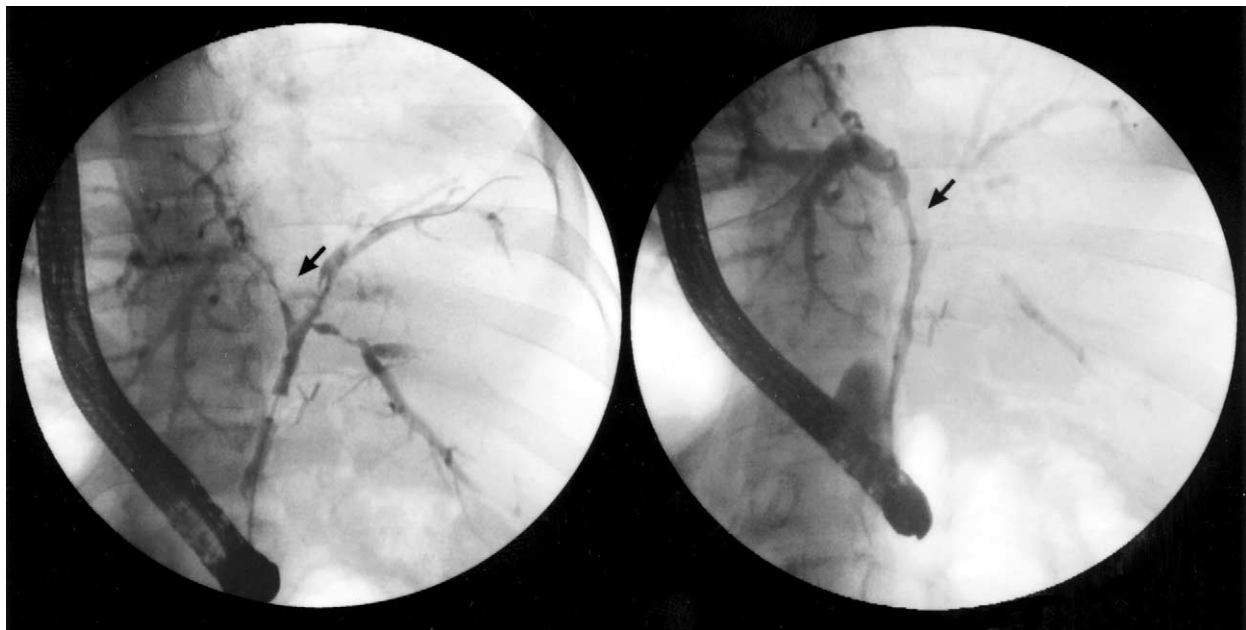


Fig. 4. Dominant stricture in the left hepatic duct (arrow) of a patient with PSC, pre- and post-dilatation with 7-F balloon. Contrast opacification is significantly better after dilatation. Photograph from Mayo archives.

evidence that bilirubin inhibits osteoblast function in vitro [120]. Accordingly, a low bone formation rate is seen in PBC. Other possible explanations involve increased bone resorption [121] and vitamin K deficiency, as this vitamin is known to participate in the synthesis of several bone proteins, including osteocalcin [122].

In our institution, 20% of PBC patients had established osteoporosis at the time of their first visit and the risk of osteoporosis was > 30-fold higher than expected [123]. Independent risk factors for the development of osteoporosis were advanced age, body mass index < 24 and histologic stages 3 and 4. The only variable correlating with rate of bone loss was serum bilirubin level. Based on these findings, the authors suggest that a screening bone densitometry measurement be performed in PBC patients with the above mentioned risk factors, perhaps more frequently in patients with advanced histologic stage.

The results of the Mayo study conflict with those from a British group who retrospectively evaluated 272 patients with PBC and at least one bone densitometry measurement [124]. No significant difference was found in the prevalence of severe osteoporosis in the population studied than would have been expected in a normal population based on z-scores, although the data were not evaluated through statistical analysis.

As for PSC, 8.6% of patients entered in a therapeutic trial and 40% of pre-transplant patients with PSC evaluated in our institution were found to have severe osteoporosis, which was also more likely to happen in patients with longer duration of inflammatory bowel disease [125].

The use of hormone replacement therapy to prevent osteoporosis can no longer be recommended. The HERS II trial (heart and estrogen/progestin replacement study follow-up) showed an increased risk of hip fractures in women on hormone therapy (6.8 years observation period, relative hazard 1.61) [126]. In addition, estrogen therapy also led to increased risk of venous thromboembolism and biliary tract surgery without any cardioprotective effects.

Bisphosphonate compounds inhibit bone resorption and are effective in treating osteoporosis in postmenopausal women. A randomized trial involving 67 patients with PBC could not demonstrate any difference in bone mineral density results in patients receiving etidronate compared to placebo [127]. When compared to fluoride, etidronate is more effective in preventing bone loss in PBC [128]. Fluoride is thought to increase the fragility of newly formed bone, though, and it was only tested in a small number of patients. Calcitonin was also found to be ineffective [129].

Vitamin K2 increases bone mineral density (BMD) and prevents bone fractures in patients with osteoporosis [130]. It is known to modulate a protein termed osteocalcin, very important in bone metabolism. In a pilot study, 30 women with PBC with low BMD were randomized to vitamin K2 (45 mg/day) or placebo. Results pointed to a considerably higher BMD in the vitamin K2-treated group after 2 years of follow-up. Accordingly, the serum undercarboxylated

osteocalcin level was significantly lowered by vitamin K2 treatment, and adverse effects were not observed. It is not known if fractures can be prevented by vitamin K2 in patients without osteoporosis. Larger randomized controlled trials are warranted.

At present, the standard therapy for established osteoporosis is calcium and vitamin D supplementation. For patients with normal BMD, 1–1.5 g per day calcium and 800 IU/day vitamin D are recommended.

3.3. Fat-soluble vitamin deficiency

In a large patient population with PBC 33.5, 13.2, 1.9 and 7.8% of patients had deficiency of vitamins A, D, E and K, respectively [131]. Deficiency of Vitamin A correlated with a Mayo Risk Score > 5 and advanced histologic stages (3 and 4).

Forty-three of the 56 patients with PSC who entered a study evaluating the use of UDCA for this condition at the Mayo Clinic were tested for fat-soluble vitamin deficiencies [132]. Vitamin A deficiency was seen in 40%, vitamin D deficiency in 14% and vitamin E deficiency in 2% of those tested. Seventy-two of 87 patients with PSC undergoing pretransplant evaluation were also tested, and the deficiencies were even more prominent. It is recommended that patients with PSC and PBC be screened for fat-soluble vitamin deficiencies and treated as appropriate.

Declaration

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