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TOPIC HIGHLIGHT

Pietro Invernizzi, MD; Ian R Mackay, MD, *Series Editors*

Clinical features and management of primary biliary cirrhosis

Andrea Crosignani, Pier Maria Battezzati, Pietro Invernizzi, Carlo Selmi, Elena Prina, Mauro Podda

Andrea Crosignani, Pier Maria Battezzati, Pietro Invernizzi, Carlo Selmi, Elena Prina, Mauro Podda, Division of Internal Medicine and Liver Unit, San Paolo Hospital School of Medicine, University of Milan, Milano 20142, Italy
Pietro Invernizzi, Carlo Selmi, Division of Rheumatology, Allergy, and Clinical Immunology, University of California at Davis, Davis, CA 95616, United States
Correspondence to: Andrea Crosignani, MD, Dipartimento di Medicina Interna, Polo Universitario, Ospedale San Paolo, Via di Rudinì 8, Milano 20142, Italy. crosihsp@unimi.it
Telephone: +39-2-50323088 Fax: +39-2-50323089
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Abstract

Primary biliary cirrhosis (PBC), which is characterized by progressive destruction of intrahepatic bile ducts, is not a rare disease since both prevalence and incidence are increasing during the last years mainly due to the improvement of case finding strategies. The prognosis of the disease has improved due to both the recognition of earlier and indolent cases, and to the wide use of ursodeoxycholic acid (UDCA). New indicators of prognosis are available that will be useful especially for the growing number of patients with less severe disease. Most patients are asymptomatic at presentation. Pruritus may represent the most distressing symptom and, when UDCA is ineffective, cholestyramine represents the mainstay of treatment. Complications of long-standing cholestasis may be clinically relevant only in very advanced stages. Available data on the effects of UDCA on clinically relevant end points clearly indicate that the drug is able to slow but not to halt the progression of the disease while, in advanced stages, the only therapeutic option remains liver transplantation.

Key words: Primary biliary cirrhosis; Epidemiology; Clinical course; Natural history; Treatment

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INTRODUCTION

Primary biliary cirrhosis (PBC) is an autoimmune liver disease characterized by progressive destruction of intrahepatic bile ducts with cholestasis, portal inflammation, and fibrosis which may lead to cirrhosis, to its complications, and eventually to liver transplantation or death. Thus, primary biliary cirrhosis is indeed a historically-based misnomer, since currently a substantial proportion of patients may not develop cirrhosis as the final event. The disease predominantly affects women who are usually diagnosed in their fifties mainly in an asymptomatic stage. The loss of bile ducts leads to the retention within the liver of detergent bile acids which contribute to parenchymal damage through interaction with cell membranes and cellular organelles. The derangement of the entero-hepatic circulation of bile acids may also induce important pathophysiological changes which may determine, if untreated, some of the extra-hepatic alterations characteristic of established disease. It is well known that both clinical features and natural history vary greatly among individual patients ranging from asymptomatic and stable or only slowly progressive to symptomatic and rapidly progressive disease. The clinical presentation has progressively changed from one characterized by a serious outcome to that of a slowly evolving disease since natural history and outcome have improved, during the last few decades, due to the recognition of earlier more indolent cases and, likely, to widespread use of ursodeoxycholic acid (UDCA).

Since aetiology and immunological aspects are reviewed separately in this series, the aim here is to review the evidence on epidemiology, diagnosis, clinical features, and treatment. Both management of the consequences of long-standing cholestasis and specific therapy for PBC will be discussed.

EPIDEMIOLOGY

Descriptive epidemiology of a particular disease is important in order to establish the magnitude of the problem and to find clues for aetiopathogenesis. There are a number of epidemiologic studies reported among patients affected by PBC[1]. The key issue involving all these studies is that they rely upon the number of diagnoses recorded in a defined location rather than on the screening of the entire population at risk. Obviously, this latter approach

Table 1 Epidemiology of primary biliary cirrhosis: Results from the most relevant studies[2-9]

Area	Patients (No.)	Prevalence (per million)	Incidence (per million/yr)	Age (yr)	Gender (M:F)
Europe (1984)	569	23	54	54	1:10
Northern Sweden (1990)	111	151[1]	13.3	55	1:6
North East England (1990)	347	129[1]	19	58	1:9
Ontario, Canada (1990)	225	22	3.3	59	1:13
Victoria, Australia (1995)	84	19	-	-	1:11
Newcastle, England (1997)	160	240[1]	22	66	1:10
Olmsted County, MN (2000)	46	402[1]	27	-	1:8
Victoria, Australia (2004)	249	51[1]	-	61	1:9

[1]Data include survey of laboratories for antimitochondrial antibodies.

would be particularly expensive in view of the relatively low prevalence of the disease thus requiring large populations to be screened. At present, we must consider the prevalence indicated by case-finding studies as underestimates, to a degree inversely related to the accuracy of the methodology employed to identify the potential diagnoses made in the area under consideration. In Table 1, relevant data from the available epidemiologic studies are reported in chronological order[2-9].

Several difficulties however exist when attempting to compare results of these studies among each other, and over time. Heterogeneity in the methodology of case finding and, to a lesser extent, the criteria used for the diagnosis represent the most problematic issue. In particular, only a few studies used multiple strategies to reduce selection bias by capturing the entire spectrum of illness associated with PBC, especially cases at the preclinical stage[10]. Ascertainment from laboratory determination of anti-mitochondrial antibodies (AMA), which are highly sensitive and specific markers of the disease, has been a valuable approach. Differences in estimates of incidence and prevalence of PBC among populations, coming from the earlier studies[2,11-15], may be due to differences in diagnostic criteria and study design, as well as to the different disease awareness among physicians, and to the differing degrees of access to health care systems. Similarly the same limits may explain the lack of confirmation of preliminary observations of associations between the occurrence of PBC and environmental factors[12,16].

The methodological quality of reported investigations has improved over time which allows some capacity to compare incidence and prevalence rates by geographic areas. Initial studies published between 1974 and 1986 described annual incidence rate of PBC ranging from 0.6 to 13.7 cases per million[2,11,13-15]. Prevalence rates from these studies varied between 23 and 128 cases per million[2,11,13-15]. The majority of data originated from the United Kingdom and Sweden. Since 1989 a larger number of studies have been reported, mainly performed in Europe but also coming from Asia, North America, and Australia[3-10,16-31]. From these more recent studies, both the annual incidence rates and prevalence of PBC have increased[3-10,16-31]. In particular, from the United Kingdom the annual incidence rates increased from 5.8 to 20.5 cases per million between 1980 and 1999 among residents of Sheffield[12,28] and from 11 to 32 cases in Newcastle-upon-Tyne between 1976 and 1994[4,7,27]. A parallel increase of the prevalence rate occurred reaching the number of more than 200 cases per million in the middle-late nineties[4,7,27]. A similar picture has been reported by very recent studies coming from Europe[30,31]. These data may be explained by the progressively higher proportion of asymptomatic cases with early-stage disease, resulting in growing prevalence rates, and the increased use of biochemical and serologic testing leading to the increasing diagnosis of new cases per year. Interestingly the mean age at diagnosis did not change from initial to more recent studies (Table 1), thus indicating that the increasing prevalence and incidence reported by the literature is more related to wider rather than to earlier diagnoses.

Only recently, several epidemiological data are available also from the USA in full indicating an annual incidence rate of 27 cases per million with prevalence rates ranging between 160 and 402 cases per million, thus leading to an estimate of 3500 new cases each year with 47 000 prevalent cases among the white population[8]. However, these data come from specific regions and difficulties in obtaining more complete epidemiological evaluations are mainly due to two reasons: (1) the lack of an universal health care system; and (2) the large number of patients followed in secondary and tertiary centres. Lower prevalence and incidence have been reported in Canada and Australia[5,6,9,18,22].

For PBC there is a well known high prevalence of female gender (F/M 9 to 1), and based on this observation several studies provided greater insight into the aetiopathogenesis of the disease[32]. Little information is available regarding the influence of race or ethnicity on the descriptive epidemiology of PBC[1] indicating that host susceptibility plays a significant role in the development of the disease. PBC occurs more commonly among individuals with a family history of either PBC itself or other autoimmune disorders[33-35] and there is a high concordance rate (63%) *versus* that in other autoimmune diseases in monozygotic twins[36]. Taken altogether, these observations point towards the relevance of genetic factors in the occurrence of PBC. On the other hand, the recent finding of several clusters of PBC within defined spatial boundaries suggests that also environmental factors, such as pollution, may contribute to the development of the disease[37,38]. These associations are statistically extremely weak and may be flawed by quite a high number of biases of different types[39]. The role of a previous infection as the triggering factor for the development of PBC by the mechanism of molecular mimicry has been repeatedly suggested, in analogy with other autoimmune diseases, but data are inconsistent[40-42].

In conclusion, data coming from more recent surveys of diagnoses performed in different geographical areas

indicate that PBC is not a rare disease and its prevalence and incidence are apparently increasing in recent years mainly due to easier recognition of the disease and improved case finding strategies. No firm suggestion on the aetiologic role of any specific environmental factors has come from epidemiology, whereas familial clustering indicates a major role for genetic background.

DIAGNOSIS

The diagnosis of PBC is currently based on three criteria: the presence of AMA in serum which is highly specific for the disease, elevation of biochemical indices of cholestasis for more than 6 mo, and histological features in the liver that are indicative of the diagnosis. The presence of two of these criteria allows a probable diagnosis but for a definite diagnosis the occurrence of all criteria is needed[43]. However, alternative diagnoses of liver disease should be ruled out and particularly in the absence of detectable AMA, a nuclear magnetic resonance cholangiography is necessary to exclude a primary sclerosing cholangitis.

Determination of AMA using routine methods, however may lead to underestimation of their presence[44]. Up to 5% to 10% of patients have no detectable antimitochondrial antibodies, but their disease appears to be identical to that in AMA positive patients[45].

Serum liver enzymes are the earliest biochemical indices to increase in serum: gamma glutamyl transpeptidase, alkaline phosphatase, and aminotransferases in descending order of sensitivity, but each lacks specificity, except, to some extent, alkaline phosphatase, if bone disease can be ruled out. On the other hand, serum bilirubin concentrations increase only in advanced stages of the disease, and accurate measure of serum bile acid concentrations requires state of the art methods, like gas chromatography-mass spectrometry (GC-MS), which are not available routinely[46]. In addition, serum bile acids are extremely sensitive but poorly specific and their detection by GC-MS is more useful to study derangement of the bile acid circulation or the effects of therapeutic bile acids[47].

The utility of liver biopsy in the diagnosis of PBC has been questioned by several hepatologists[43] and even for staging purposes it is scarcely justified in patients who have obvious features of cirrhosis by clinical evaluation including imaging techniques.

HISTOLOGICAL FEATURES

The pathological lesion typical for PBC is a chronic non-suppurative destructive cholangitis involving interlobular bile ducts of 40-80 μm in diameter[48]. Overall, coexistence of portal inflammatory infiltrate with bile duct paucity is needed for diagnosis. PBC is divided into four histological stages but the liver is not affected uniformly and even a single biopsy sample may demonstrate the presence of different stages of the disease. If this is the case, the most advanced stage of those present is assigned, according to convention[43]. Stage 1 is characterized by localization of inflammation to portal triads. Stage 2 entails extension of inflammation beyond the portal triads into the lobular parenchyma and reduction in number of normal bile ducts. Stage 3 entails fibrous septa linking adjacent portal tracts. Stage 4 is the most advanced histological stage in which liver cirrhosis has occurred[49].

Table 2 Modifications during time of the clinical spectrum of primary biliary cirrhosis at presentation[50-52]

	Sherlock 1973 (*n* = 100)	James 1981 (*n* = 93)	Nyberg 1989 (*n* = 80)
Jaundice (%)	28	16	3
Pruritus (%)	57	14	26
Complications (%)	4	9	1
Asymptomatics (%)	11	61	70
Mean age (yr)	50	57	58

CLINICAL FEATURES

Symptoms

Asymptomatic disease: PBC is now diagnosed earlier in its clinical course and most cases are only slowly progressive in comparison with the past, and the large majority of patients are asymptomatic at diagnosis (Table 2)[50-52]. It has been suggested that symptoms develop within five years in most asymptomatic patients, although one third of patients may remain symptom-free for many years[53,54]. Pruritus and fatigue are early symptoms and occur in about 20% of the patients[53,55].

Fatigue: This is reported in up to 78% of PBC patients overall and is suggested to be a significant cause of disability from numerous studies[56-59]. However, a well-preserved quality of life has been recently reported in a very large cohort of patients with PBC in the USA thus arguing against the clinical relevance of fatigue in such a population[60]. Several studies have explored the pathogenesis of this symptom and indicated heterogeneous mechanisms ranging from autonomic dysfunction[59,61,62], to excessive daytime somnolence[63], and to altered manganese homeostasis within the central nervous system[64], while concomitant depression could not be ruled out[65-67]. In addition, studies aimed at demonstrating the clinical relevance of fatigue in PBC are affected by significant flaws, since the correlation of inaccurate quantification of the symptom with both scores related to quality of life and clinically relevant events appears to be inappropriate, and a possible role of concomitant diseases could not be excluded[56-59]. Therefore fatigue seems a poorly specific symptom and a predominant psychogenic component is likely, as usually occurs in carriers of a chronic progressive illness who are aware of the potential impact on their future life.

Pruritus: This appears to be the most typical symptom of PBC. It was reported to occur in 20% to 70% of patients and occasionally is quite distressing[68]. In latter years its frequency in PBC has been decreasing because

the disease is increasingly recognized in its asymptomatic stage. The availability of therapeutic options such as UDCA which has been widely administered during the last two decades, seems to have also modified the occurrence and intensity of this symptom. The onset of pruritus generally precedes the onset of jaundice by months to years. The cause of pruritus remains unknown. However there is consensus that in the course of cholestasis biliary excretion of several compounds is impaired, thus leading to increased systemic concentrations of a putative "pruritogenic" compound. The occurrence of pruritus would result from the interaction between these substances and nervous terminations at the skin level. The extreme variability of the degree of pruritus between patients, or even in the same patient, may have two explanations: (1) inter-individual or time variability of the systemic concentrations of the "pruritogenic" compounds, which are generally confined within the enterohepatic circulation; and (2) subjective variability of the perception of pruritus, mainly due to psycho-emotional factors. Increased serum concentrations of bile acids are associated with cholestasis by definition, and a direct causative relationship between increased bile acid concentrations and the occurrence of pruritus has been suggested[69]. Several observations support this hypothesis, including: (1) the presence of bile acids in the skin in cholestatic patients[70]; (2) the capability of bile acids to produce pruritus when injected subcutaneously[71,72]; (3) the relief of pruritus by external biliary drainage, and by cholestyramine which can bind bile acids and thus favours their fecal elimination[73-75]. However, this hypothesis has never been proven since no relationship was found between degree of pruritus and bile acid levels measured in cutaneous interstitial fluid[76-78]. In addition, it is possible that many other substances are eliminated during both biliary drainage and cholestyramine administration.

The hypothesis that pruritus in cholestatic liver disease may have a central origin has been suggested by the observation of an increased opioidergic activity in both experimental models of cholestasis[79-82] and in cholestatic patients[79-81,83], and by the observation that opioid receptor ligands with agonist properties (morphine for example) mediate pruritus[84-86]. Therefore, there have been studies using opioid antagonists for the treatment of pruritus in cholestatic conditions with positive results[87-89], thus confirming the hypothesis that an increased opioidergic activity plays a role in the occurrence of pruritus associated with cholestasis. In cholestatic conditions high concentrations of bile acids in the systemic circulation may alter several central regulatory systems such as the opioid-mediated system.

Portal hypertension: This may occur even before cirrhosis develops. However, usually, ascites, variceal bleeding, and hepatic encephalopathy complicate the course of PBC only in advanced stages. Similarly, the incidence of hepatocellular carcinoma is elevated among patients with long-standing histologically advanced PBC[90].

Consequences of long-standing cholestasis

Other common findings in advanced PBC include the consequences of long-standing cholestasis that can lead to hyperlipidemia, fat malabsorption, renal tubular acidosis, and osteopenia. However, the clinical relevance of hyperlipidemia in patients with PBC remains questionable since neither cardiovascular risk[91] nor more precocious signs of atherosclerosis[92] are associated with alterations of lipid metabolism in PBC. In addition, the wide use of therapeutic bile acids in the last decade may have modified the metabolic pattern of plasma lipids in PBC[93,94].

Metabolic bone disease described in patients with PBC is the result of two different pathological processes: osteomalacia and osteoporosis. Osteomalacia which is a consequence of lipid malabsorption may be easily corrected by supplementation with calcium and vitamin D[95-97]. The changing spectrum of bone disease associated with cholestasis with a progressive disappearance of osteomalacic features over time may be due to the increasingly wide use of vitamin D and calcium supplementation in clinical practice[97,98]. Therefore, at present, osteoporosis is the predominant component of metabolic bone disease[98]. During end-stage liver disease, which is characterized by reduced physical activity, malnutrition, and, possibly, infectious complications, bone loss is a major clinical issue[99]. On the other hand there is no consensus on the clinical relevance of cholestasis in inducing bone loss at less advanced stages of liver disease[100]. In a recent longitudinal controlled study, we demonstrated that cholestasis was not an additional risk factor for bone demineralization in women with well-compensated PBC if adequate calcium and vitamin D supplementation had been provided[101]. These data are in accordance with several studies[102-104] but in contrast with others[105-107]. Different results may be due to: (1) the cross-sectional nature of many studies; (2) the lack of an adequate control group in the majority of the published studies so precluding the protection against confounding factors such as menopausal status, which is important in a population wherein perimenopausal women are largely represented; (3) the lack of adequate vitamin D and calcium supplementation in most of the published studies; and (4) the confounding effects of other concomitant medications.

Malabsorption, deficiencies of fat-soluble vitamins, and steatorrhea are uncommon except in the late stages of the disease[108]. Finally, the occurrence of renal tubular acidosis which was once thought to be quite frequent[109] was not found in a large population of PBC in the absence of complication of liver cirrhosis[110], thus indicating that such a complication, if present at all, may be restricted to very late stages of the disease in association with multiorgan dysfunction.

Associated diseases of autoimmune type

Symptoms of coexisting autoimmune diseases including Sjogren syndrome, scleroderma, rheumatoid arthritis autoimmune thrombocytopenia, and haemolytic anaemia may be present. Interestingly, liver disease was recently shown to have a slower progression when systemic

sclerosis is associated with PBC compared with matched patients with PBC alone[111]. Overlap syndromes with autoimmune hepatitis are described in another article in this issue.

NATURAL HISTORY AND PROGNOSTIC MODELS

The natural history and prognosis of PBC have become more difficult to characterize given the rising number of asymptomatic cases which require long-term follow-up[1,43,109,112]. Furthermore, patients are more likely than in the past to be asymptomatic at diagnosis[1,43,112] and to receive medical treatment as soon as diagnosis is made. Hence, estimated survival has significantly improved compared to the past. Earlier data on survival suggesting a poor outcome were obtained from patients in whom the disease had been diagnosed many years ago when no effective treatment existed[1,43,112]. In addition, most of these patients were symptomatic[1,43,112].

A different outcome of the disease has been reported for symptomatic *versus* asymptomatic patients. In 1983, the reported survival of asymptomatic PBC patients was similar to that of a normal U.S. population matched for age and sex[113], but, when their survival data were extended for a longer duration, the asymptomatic patients had a shortened survival compared with controls[114]. In this latter study, 279 patients from the USA were observed for up to 24 years, and the median survival of asymptomatic PBC patients was significantly longer than symptomatic patients at presentation[114]. Additional studies confirmed that initially asymptomatic patients had a longer survival than symptomatic ones[109,115]. In one of these studies from Canada, asymptomatic PBC patients had a shortened survival compared with a healthy population[115]. The results described in a community-based study from the UK are at variance with all of the other reports[54]. Here 770 patients (61% asymptomatic) living in England were diagnosed between 1987 and 1994 and observed until death, transplantation, or until data were censored in January 2000. The median survival was similar in asymptomatic and symptomatic patients, and symptom development was not associated with shorter survival. However, the design of this study, in which patients were followed by regular interview and by examination of their medical records may be not as informative as a single centre cohort study to assess the natural history of PBC, even though it is sufficient for epidemiological purposes. In fact, these UK results are confounded by the fact that 45% of the deaths in asymptomatic patients occurred while these patients were remained asymptomatic, suggesting that many of these patients would have been died of non-hepatic causes and that age at diagnosis was a major determinant of survival. Since the prognostic relevance of the presence of symptoms is well documented, the higher proportions of asymptomatic patients enrolled in the more recent cohort studies explain, partly at least, the observed improvement in the natural history of PBC since 1980s.

Table 3 Parameters independently associated with bad prognosis in different prognostic models based on a single point observation[16,113,119,121-123]

Parameters	Yale	European	Mayo	Glasgow	Oslo	London
Increase in serum bilirubin	+	+	+	+	+	+
Decrease in serum albumin		+	+			+
Increase in PT (INR)			+			
Advanced age	+	+	+	+		+
Hepatomegaly	+					+
Ascites, fluid retention			+	+		+
Esophageal varices						+
Gastrointestinal bleeding				+	+	
Cirrhosis	+	+		+		+
Cholestatic picture at histology		+		+		
Mallory bodies				+		

Most patients with PBC are now treated with UDCA[43] and the widely used administration of this drug has greatly changed the natural history of the disease[43,112]. At least 20% of patients treated with UDCA will have no histologic progression over four years, and some will have no progression over a decade or longer[116]. In a recent study, the survival rate of patients with stage 1 or 2 disease given UDCA long-term was similar to that of a healthy control population[117]. In the above-mentioned community-based study from the UK no improvement in survival was found in UDCA-treated patients[54]. We reiterate that such a study design albeit excellent for epidemiological purposes, is not adequate for the evaluation of the effects of medical treatment. In addition, there is sufficient evidence that UDCA treatment does prevent the development of esophageal varices[118]. Therefore, sufficient information is now available to indicate that, among the reasons for the improving prognosis of PBC, is the wide use of bile acid therapy. Detailed information on the effects of UDCA therapy on survival is described below.

Cox proportional hazards regression analysis has been used to develop prognostic models. There are different prognostic models for predicting survival for PBC patients. Of these models, the Mayo survival model is the most popular. The Mayo model was based on combined data from more than 400 patients who were observed at the Mayo Clinic and was then externally cross-validated using PBC patients from other medical centers[119,120]. The Mayo model uses five independent prognostic variables: age, total serum bilirubin, serum albumin, prothrombin time, and the severity of fluid retention. Serum bilirubin is the most heavily weighted among these variables, consistent with the presence of this index in all the proposed prognostic models[16,113,119,121-123] (Table 3). All these models are based on a single assessment but several have been modified to include repeated measures of prognostic indices[121,124,125]. The Mayo model has been widely used to assess the efficacy of medical treatment in clinical trials, but also serum bilirubin concentrations

have been similarly used as surrogate markers of disease improvement, due to the prognostic value of this index in PBC patients with more advanced disease[126].

Recently, also an immune marker was shown to be of prognostic value since a particular specificity of antinuclear antibodies that directed against nuclear pore complex, identified patients destined to experience more rapid disease progression[127].

TREATMENT OF SYMPTOMS AND COMPLICATIONS

Fatigue

No therapy that has been evaluated for the treatment of PBC has proven able to ameliorate fatigue[128-130]. However, this symptom is not specific, only indirect quantitative measurement is available, and there are no convincing data to support any organic pathophysiological mechanism with even a psychological basis possible in some cases[65-67].

Pruritus

Pruritus in several, albeit very rare, cases may severely affect the quality of life, leading to sleep disturbance and major depression. This is the reason why intractable pruritus has been considered an indication for orthotopic liver transplantation (OLT). A large number of pharmacological approaches have been tested on the basis of both pathophysiologic considerations and serendipitous observations. The heterogeneity of the treatments suggested reflects the difficulties in treating this symptom which is extremely variable in severity and type, influenced by subjective factors and not easily quantifiable. The administration of UDCA, the only approved treatment for PBC, was not associated with a consistent improvement of pruritus in most controlled clinical trials; however, since the majority of them were not designed specifically to test the effects of this drug on pruritus, no definite conclusion can be drawn. In addition, as reported above, epidemiological data indicate that the disease expression has changed during the last two decades towards less symptomatic disease[1,43,112], and a possible effect of the widely administered UDCA in decreasing pruritus certainly cannot be ruled out.

The oral anion exchange resin cholestyramine has been the mainstay of therapy for pruritus associated with cholestasis[73-75]. The mechanism of action is related to binding of bile acids and other biliary molecules, with their subsequent fecal excretion. Dose of cholestyramine should start from 4 g daily and should be increased, in case of therapeutic failure, until a maximum of 16 g. The timing of administration is before meals. The drug is more effective in those patients with an intact gallbladder when taken before and after breakfast, because the greatest amount of bile is likely to be available for binding at this time. Since cholestyramine binds also other medications, notably UDCA, oral contraceptive hormones, digoxin and thyroxin, it is advisable that at least 4 h should elapse between the administration of cholestyramine and other medications. In the majority of cases this drug is effective within a few days from starting treatment, but in about 10% to 20% of the patients it is ineffective. In addition, many patients find cholestyramine unpleasant to take and complain of dyspeptic symptoms or diarrhea or, alternatively, constipation so leading to poor compliance with treatment.

Table 4 Pharmacological characteristics of the opiate antagonists investigated in clinical studies

	Pharmacological characteristics
Naloxone	Very short half life Intravenous continuous infusion Dose: 0.2-0.4 μg/kg per minute
Nalmefene	Longer half life Oral administration 2 mg twice/d with a gradual increase until 20 mg twice/d
Naltrexone	Longer half life Oral administration 50 mg/d (in two divided doses the first day and subsequently in a unique dose)

Rifampicin is an enzyme-inducing antibiotic which was serendipitously identified as an agent that improves pruritus in cholestasis[131]. A subsequent crossover trial indicated that the drug provided good control of pruritus in PBC at doses of 150 mg twice per day or three times per day[132]. In subsequent studies higher doses were used up to 600 mg/d[133] and 10 mg/kg per day[134]. Its mechanism of action remains unknown but it may alter bile acid composition[135,136] and stimulate the hepatobiliary transport systems[137,138]. When given long-term, rifampicin was shown to improve also the biochemical expression of PBC[139]. However, it is not effective in all patients and may cause side effects[140]. Two cases of acute hepatitis were reported (12.5% of treated patients) during long-term administration[139], but this spontaneously resolved after discontinuation of treatment. In any case, the potential hepatotoxicity of rifampicin precludes long-term administration of this drug to patients with PBC.

Many studies endorse the use of opioid antagonists, given intravenously or orally, for the treatment of cholestasis-related pruritus[87-89]. The main pharmacological characteristics of the three compounds investigated clinically are reported in Table 4. Each compound was shown to be highly effective in improving pruritus, but the main limit on their use was the occurrence of withdrawal-like symptoms in several patients. In addition, after initial enthusiasm following elegant studies supporting the intriguing hypothesis of an increased opioidergic activity in cholestatic patients[79-82], opioid antagonists have lapsed for the treatment of pruritus. Larger and longer studies are needed to fully assess the actual clinical value of opioid antagonists in controlling pruritus in PBC.

Since the serotoninergic system participates in the mediation of nociception, it appears rational to use drugs acting on this system. Several studies suggested that a possible beneficial effect may be exerted by ondansetron a type Ⅲ serotonin antagonist[141-143], but subsequent studies showed only limited or no effects on pruritus[144-146]. Surprisingly, the results of a recently published small randomized, double-blind, placebo-controlled trial based

on a heterogeneous group of patients with pruritus and liver disease suggested a beneficial effect of sertraline, a serotonin reuptake inhibitor[147]. Finally, since the cannabioidergic system plays a role in the mediation of nociception, uncontrolled observations on the effects of dronabinol, a cannabinoid B1 receptor, suggested relief of pruritus in course of cholestasis[148].

In conclusion, since UDCA is the only accepted therapy for PBC, this bile acid represents the treatment of choice for pruritus. If the symptom persists, cholestyramine be initiated. Only in the case of a lack of response to maximal doses of cholestyramine a therapeutic approach with rifampicin or opioid antagonists should be considered.

Metabolic bone disease

Osteomalacia may be easily corrected by parenteral supplementation of vitamin D (vitamin D_3 100 000 UI intramuscular monthly). Supplementation with calcium carbonate (1 g/d) has been largely recommended based on pathophysiological considerations and on data coming from experience in postmenopausal osteoporosis whereas only indirect evidence is available in PBC patients[97,149].

As reported above, it is highly questionable whether osteoporosis during cholestatic conditions represents a separate clinical entity[100,101]. Therefore the available data on treatment of metabolic bone disease in PBC are similar to those reported for postmenopausal osteoporosis noting that most patients with PBC are females at a menopausal age. Various data indicate that hormone replacement therapy is effective and safe, contrary to previous beliefs[150-154]. Etidronate was suggested to be effective[155,156], but not all studies reported positive results[157], while alendronate was shown to be superior[158,159]. Calcitonin failed to improve bone mineral density in female patients with PBC[149]. The negligible improvement observed in one study[160], is perhaps attributable to concomitant vitamin D and calcium supplementation. Several indications for the clinical management of metabolic bone disease associated with PBC are reported in Table 5. Finally it should be highlighted that UDCA, the specific treatment for PBC was shown to have no effects on the occurrence of bone loss[161].

Table 5 Clinical management of metabolic bone disease associated with primary biliary cirrhosis

Clinical management	Efficacy	
	Moderate efficacy	Mild efficacy, insufficient data
Prevention		
1 Parenteral vitamin D3 supplementation 2 Calcium carbonate supplementation	Indicated for all patients to prevent osteomalacic lesions	
Treatment		
1 Estrogen		Few data but effective and safe
2 Etidronate		Conflicting data Indicated in case of concomitant corticosteroid administration
3 Alendronate		Few data but effective and safe
4 Calcitonin		Probably ineffective

Hyperlipidemia

It is still questionable if hypercholesterolaemia associated with PBC should be treated, and which patients need pharmacological treatment. Since increased cholesterol concentrations associated with cholestasis do not increase the atherosclerotic risk, it seems reasonable to treat hypercholesterolaemia only when hyperlipidemia of familial and nutritional origin probably coexists[162]. The extent of cholesterol reduction by UDCA administration[93] may be insufficient to protect this group of patients from cardiovascular risk. These patients probably would benefit from dietary modifications, weight loss, and the administration of specific lipid-lowering drugs. Cholestyramine may be indicated for its cholesterol lowering capacity in hypercholesterolaemic patients, especially if there is associated pruritus, while HMGCoA-reductase inhibitors should be limited to hypercholesterolaemic patients in whom serum levels of HDL are below the protective range, or if additional risk factors for cardiovascular disease are present[162]. In pilot studies, both simvastatin and atorvastatin proved to be safe and effective in reducing serum cholesterol levels in patients with PBC[163-165].

Malnutrition

During severe cholestasis, which occurs only at very advanced stages of PBC when liver transplantation is precluded, lipid malabsorption occurs with steatorrhoea and weight loss. In such cases a reduction to 40 mg of the daily dietary fat intake is indicated and the same amount should be administered as medium chain triglycerides, which are digested and absorbed in the intestine even in the presence of low bile acid concentrations. In several cases administration of cholestyramine has to be discontinued.

Since malabsorption of lipophilic vitamins occurs even in the absence of clinically evident steatorrhoea, preventive supplementation with vitamin D may be advisable in case of significant alterations of biochemical markers of cholestasis. Parenteral vitamin K supplementation should be given if prothrombin time is increased.

SPECIFIC TREATMENT FOR PBC

Many therapeutic agents have been tested for PBC but difficulties have been encountered in establishing statistically significant long-term benefits for a disease with such a variable natural history. In addition, PBC surrogate markers of prognosis have several limitations: impairment of indices of liver synthetic function occurs only at very advanced phases of the disease, and the likelihood of sampling errors limits the value of liver histology. The only index which may be useful to assess prognosis is serum bilirubin, and this only in late phases of the disease. Randomized, controlled trials, recently

Table 6 Efficacy and toxicity of the principal drugs investigated for the medical treatment of primary biliary cirrhosis

	Efficacy	Toxicity
D-penicillamine	-	+
Chlorambucil	+/-	+
Cyclosporine	+/-	+
Azathioprine	+/-	+
Methotrexate	+/-	+
Colchicine	+/-	-
Glucocorticoids	+/-	+/-
UDCA	+	-

re-evaluated by a meta-analysis[166], have endorsed the failure of penicillamine. The only accepted treatment for PBC is UDCA that may delay but not halt the progression of the disease[167]. For several other agents, mainly immunosuppressive components, some interesting possibilities have been revealed but mainly in terms of combination treatment with UDCA. Data are summarised in Table 6. Regarding corticosteroid drugs, data are scanty mainly because bone demineralization represents a big concern in a population of female patients at postmenopausal age[168,169]. Corticosteroid monotherapy does not seem to offer a sufficient benefit *versus* side effects ratio for most PBC patients and its use should be limited to patients with other concomitant autoimmune diseases or with a PBC-autoimmune hepatitis overlap syndrome[170]. In such cases, co-administration of etidronate may prevent bone loss[156].

Azathioprine administration should not be recommended on the ground of a limited efficacy and the substantial risk of side effects[121,171,172]. For chlorambucil, the frequency and potential severity of side effects outweighs potential benefits of this immunosuppressive drug, thus contraindicating its use in PBC[173]. After preliminary encouraging data coming from a pilot study[174], Kaplan and colleagues have repeatedly reported biochemical and histological improvement after the administration of low dose of methotrexate (15 mg/wk), but no data on survival have been presented[175,176]. Aside from potentially serious complications[177], the beneficial effects of methotrexate in the treatment of PBC, alone or in combination with UDCA, could not be confirmed by randomized, controlled trials performed by other groups[178-180]. There is no indication for the clinical use of cyclosporine in PBC, given the limited efficacy and known side effects[181].

Available information indicates that colchicine with its anti-inflammatory and antifibrotic properties may exert limited beneficial effects on the natural history of PBC but without relevant side effects[182-185]. This is the reason why it has been largely tested in association with UDCA but showing no additional benefit in terms of clinically relevant end-points in comparison with UDCA monotherapy[186,187].

UDCA for the therapy of PBC

The rationale for the use of UDCA in the treatment of PBC depends on its ability in displacing and/or diluting detergent and hepatotoxic bile acids from the bile acid pool. It is well known that in cholestatic conditions, endogenous bile acids are retained within hepatocytes, thus leading to the progressive deterioration of liver function. The beneficial effects of UDCA on indices of liver dysfunction have been attributed to its physicochemical properties, since UDCA is very hydrophilic and therefore non-toxic to biological membranes[188,189]. However, experimental data failed to support this hypothesis since a substantial shift towards hydrophilicity of the bile acid pool was not observed during UDCA administration[47]. It has been suggested that UDCA has a direct cytoprotective effect, and different molecular mechanisms may be responsible, such as regulation of cellular signalling systems and protection against apoptosis[190]. Immunomodulatory effects of UDCA have been also described[190], although it is not conventionally used as an immunosuppressive drug in non-hepatic diseases.

A number of randomized controlled studies have been conducted to evaluate UDCA efficacy[43]. In all studies UDCA was well tolerated since no relevant side effects were reported. In all studies a significant improvement of serum liver enzymes markers of cholestasis and cytolysis occurred. Serum concentrations of bilirubin, the most important prognostic marker of the disease, were reduced by UDCA administration. A consistent reduction of IgM, which is an immunological marker of PBC was also reported.

Results of randomized placebo-controlled trials with a duration long enough to evaluate the effects on histology and on survival are summarized in Table 7[191-197]. Among the six studies that evaluated the effects of UDCA on pruritus[191-196], an improvement was described in only three[191,194,196], but these studies were not specifically designed to assess pruritus. In four studies a significant improvement of several histological indices was reported[191,192,194,196]. The Mayo Clinic group did not report any improvement of liver histology, but have suggested in a separate paper that UDCA delays the occurrence of esophageal varices[118], thus indicating a positive effect on the progression of the disease.

To evaluate the effectiveness of a specific therapy for a severe life-threatening disease, the effects on survival should be explored. However, since PBC is a relatively uncommon disease with a long and variable natural history, a very large sample size and a very long follow-up are needed to obtain reliable data. No effect on survival was observed in any of the single studies reported in Table 7, and only after an extension of follow up was a positive effect on survival without OLT reported by the French and the Mayo Clinic studies[198,199]. During the 2-year extension of the French study all patients administered placebo were switched to UDCA, while in the Mayo Clinic study, UDCA was offered to all patients but, for the analysis, follow-up was censored at the end of the randomized phase for patients initially assigned to the placebo group, thus avoiding the limits of a switch-over design.

A combined analysis of three studies[167] and two meta-

Table 7 Randomized, double-blind, placebo-controlled trials on ursodeoxycholic acid administration to patients with primary biliary cirrhosis

First author	No. of patients	Study design and duration of follow up	UDCA effects on		
			Pruritus	Histology	Survival
Poupon[191]	146	2 yr	Improved	Improved	No effect
Heathcote[192]	222	2 yr	No effect	Improved	No effect
Lindor[193]	180	Mean follow up: 2 yr	No effect	No effect	No effect
Combes[194]	151	2 yr	Improved	Improved (early stages)	No effect
Eriksson[195]	116	2 yr + 2 yr as open trial (UDCA)	No effect	No effect	No effect
Pares[196]	192	Mean follow up: 3.4 yr	Improved	Improved	No effect
Papatheodoritis[197]	86	Mean follow up 7.3 yr for UDCA 8.1 yr for controls	Not evaluated	No effect	No effect

analyses[200,201] have been performed, since the majority of the published studies had insufficient statistical power to explore the effects of UDCA on survival. The combined analysis was obtained by pooling of results from three trials with similar designs but dissimilar results. The analysis included 548 patients and a significant improvement of survival free from OLT was reported with the relative risk of death being 0.53 (0.36-0.77; 95% CI). A significant improvement of survival could be recorded only in patients with serum bilirubin higher than 1.4 mg/dL at baseline. The lack of an effect on survival in patients with less severe disease may well indicate that the time of observation was not sufficient to detect effects of UDCA in a population with a low probability of developing clinically relevant events. On the other hand, results of the two meta-analyses indicate no effects of UDCA on the natural history of the disease. Formal meta-analysis includes consideration of all relevant trials, justifies eventual exclusion of trials from the analysis, and explores heterogeneity between trials and the reason for variation in results. The main limit of a meta-analysis is that trials evaluated may be too different in their designs to be truly comparable. The reason for the opposite results reported by the combined analysis[167] and by the two meta-analyses[200,201] remains unclear. The main criticisms directed against the combined analysis were the limits of the switching over design, but the "intention to treat" basis of the analysis is protective against type I error, thus reducing the probability of demonstrating benefits of UDCA in the absence of a true beneficial effect. Conversely, the inclusion in the meta-analyses of studies using low doses of UDCA, and with a follow-up too short for assessment of effects on clinically relevant end-points, has been strongly criticized. The effects on surrogate markers of clinical outcome, such as serum bilirubin concentration, do indicate that UDCA may positively affect survival in PBC. In addition, the UDCA safety and its relatively low cost permit a wide scale use of this therapeutic bile acid.

So, in conclusion, our opinion is that UDCA does exert a favourable effect on the natural history of PBC, but since many studies had been characterized by an insufficient number of patients, insufficiently long follow-up periods, heterogeneity of evaluated indices, and inadequate study designs, an absolutely clear-cut demonstration of benefit was precluded. Indirect data on the beneficial effects of UDCA also in patients at the initial stages of the disease are now available[117,202]. An excellent long-term survival, comparable to that observed in a control population, has been recently reported in patients with PBC showing biochemical response to UDCA[202]. These data were obtained by studying a cohort of 192 patients, mainly with stage 1 and 2 of the disease, who had been treated for a mean period of more than 6 years. In addition, in a recent study of 262 patients with PBC who received UDCA for a mean of 8 years, the survival rate of patients with stage 1 or 2 disease was similar to that of a healthy control population[117]. However, not all patients have a response to treatment, since in the same study, the probability of death or undergoing OLT in patients with stage 3 or 4 of PBC was significantly increased compared with a healthy population, despite UDCA treatment. Therefore strategies aimed at improving therapeutic agents for PBC are still needed, mainly by the use of associated treatments.

Several drugs have been tested in association with UDCA. The results obtained with colchicine, and budesonide are the more promising but none of the drugs studied was shown to provide any additional benefit, in terms of clinically relevant events, compared to UDCA monotherapy[186,187,203-205].

OLT for the therapy of PBC

Finally, OLT has greatly improved survival in patients with PBC since this is the only effective treatment in patients with very advanced disease. 'The survival rates are 92% and 85% at 1 year and 5 years, respectively[206]. While the recurrence rate is 30% at 10 years[207]. Note that OLT is considered in detail in another article in this series.

CONCLUSION

Data coming from the more recent epidemiological studies indicate that PBC is not a rare disease and its prevalence and incidence are apparently increasing. In addition, the clinical presentation of PBC has progressively changed from a highly symptomatic disorder with a bad prognosis to a slowly evolving disease. The changing methods used for the diagnosis, with an increasingly wide assessment of laboratory indices related to both cholestasis and immunology, together with improved case finding strategies, may explain these observations.

As a result, the recognition of earlier more indolent

cases led to the presence of a substantial proportion of asymptomatic patients within PBC cohorts. Therefore development of early prognostic indices may be useful to predict which patients are destined to develop a progressive disease thus requiring a more intensive follow-up.

UDCA does not act on the aetiology of the disease but reverses the detrimental effects of the retention of endogenous bile acids within the liver. Although several flaws of the available studies prevented a clear-cut demonstration of its efficacy, many indirect observations suggest that a beneficial effect occurs and we cannot exclude that the wide use of UDCA may have significantly changed the clinical course of the disease. However, UDCA is able to slow but not to halt the progression of the disease and, in advanced stages, when the large majority of bile ducts have been destroyed, OLT remains the only therapeutic option.

In the future, reliable epidemiological data to be obtained by screening the entire population at risk, will provide both a correct measurement of the real prevalence and incidence of PBC and a greater insight into aetiology and pathogenesis, thus leading to the possibility of a specifically targeted therapy.

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