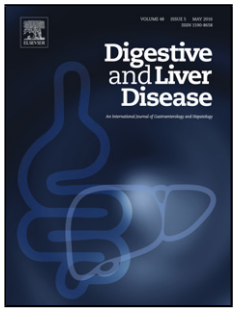

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Primary Biliary Cholangitis: advances in management and treatment of the disease.

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Abstract

Primary Biliary Cholangitis, previously known as Primary Biliary Cirrhosis, is a rare disease, which mainly affects women in their fifth to seventh decades of life. It is a chronic autoimmune disease characterized by a progressive damage of interlobular bile ducts leading to ductopenia, chronic cholestasis and bile acids retention. Even if the disease usually presents a long asymptomatic phase and a slow progression, in many patients it may progress faster toward cirrhosis and its complications. The 10 year mortality is greater than in diseases such as human immunodeficiency virus/Hepatitis C Virus coinfection and breast cancer. Ursodeoxycholic acid is the only treatment available today, but even if effective in counteracting the disease progression for the majority of patients, in approximately 40% is not able to decrease effectively the alkaline phosphatase, a surrogate

marker of disease activity. Recently, obeticholic acid received the European Medicines Agency conditional approval, as add on treatment in patients non responders or intolerant to ursodeoxycholic acid. The present paper illustrates the opinion of a working group, composed by clinical pharmacologists, gastroenterologists/hepatologists with specific expertise on Primary Biliary Cholangitis and patient associations, on the state of the art and future perspectives of the disease management. The agreement on the document was reached through an Expert Meeting.

Keywords: ursodeoxycholic acid, alkaline phosphatase; obeticholic acid, fibrates, budesonide.

Introduction

As its prevalence is below 5 cases out of 10,000, Primary Biliary Cholangitis (PBC) is a rare disease according to the European Union criteria. Its former denomination, Primary Biliary Cirrhosis, was changed into Primary Biliary Cholangitis, leaving the PBC abbreviation unaffected, in the year 2015. The change of nomenclature was made to address the demands from patient organizations and providers in the sector so as to remove the term cirrhosis, which only refers to the end stage of the disease. Indeed, as of today, PBC is generally diagnosed in the earlier phases of the disease and treatments are often capable of blocking progression. For this reason, labeling PBC patients as cirrhotic was frustrating and incoherent as well [1].

PBC is a chronic autoimmune disease electively affecting interlobular bile ducts (cholangitis) leading to retention of bile salts into the liver (cholestasis) and secondary damage of hepatocytes. The onset is often silent and insidious but the disease may progress toward cirrhosis, liver failure and death.

As PBC is a rare disease, the issues related to it concern, among others, diagnosis, care and shared management of the patient not only by specialized centers but also in the local outpatient healthcare setting.

To study this rare condition there has been an international effort to build up a network on centres studying PBC. The Global PBC Group, an international independent working group, was established in 2012 with the aim of setting up a collaboration among centers involved in the scientific research program on PBC. All data collected from patients followed by these centers are merged into a single database which accounts for more than 6,000 patients as of today [2].

The present document is the outcome of the consensus reached within an Italian working group of experts on the disease (physicians, pharmacologists and patients) and its purpose is to establish shared recommendations with regard to disease management and treatment for the benefit of the providers of the sector.

Epidemiology: according to the latest estimates, patients affected by PBC range from 12 to 13,000 in Italy.

Global PBC prevalence and incidence provided in the latest Orphanet report are 2.1/10,000 and 0.3/10,000/year, respectively [3]. Two revisions of the

epidemiological studies conducted in various geographical regions, North America (US and Canada), Northern Europe (Norway, Finland, Sweden, Denmark and UK), Spain, Israel and Australia, were published in 2012 and 2013 [4, 5], showing a marked variability of epidemiological data among the different regions, with prevalence ranging from 0.09 to 4.02/10,000 and incidence ranging from 0.03 to 0.58/10,000/year. As discussed by the authors, such variability is likely due to the varying degree of access to diagnosis and care rather than an actual geographic difference in the epidemiology of the disease.

No specific PBC register is currently in place in Italy. According to the only available Italian epidemiological study conducted by Lleo et al. in 2016 [6] and based on administrative databases in Region Lombardy in the 2000-2009 timeframe, the number of prevalent PBC cases is 2,970 in a population of 9,742,676 inhabitants as of January 1st 2010. The authors estimated a nationwide prevalence of 2.95 PBC cases every 10,000 inhabitants and an incidence of 0.167/10,000/year. As reported in the paper, epidemiological data refer to a population aged over 20 years old. However, the ICD9 (International Classification of the Diseases) code 571.6 used to identify cases of PBC in administrative databases is not specific for PBC as it includes all types of biliary cirrhosis, although the majority of them is certainly represented by PBC. After adjusting data for age (according to ISTAT 2016 data 82% of the Italian population is aged over 20 years old) the total number of PBC cases in Italy equals 14,675, while applying a 10% correction factor due to non PBC-specificity of the ICD9 code 571.6 the estimated number of PBC cases in Italy drops to 13,207.

Data reported by Lleo et al. (2016) [6] are consistent with what has been reported by Orphanet (12,740 prevalent cases applying the 2.1/10,000 global prevalence to the Italian population). Therefore, we can assume that the number of PBC prevalent cases in Italy ranges from 12,740 [3] to 13.207 [6].

Prognostic factors: men, women below 45 years old and patients in advanced stage of disease at the time of the diagnosis have a higher risk of non-response to ursodeoxycholic acid (UDCA). An absent or partial response to UDCA is the strongest predictor of poor outcome.

PBC typically affects women aged from 50 to 60 years old [7-9]. The silent form of PBC is characterized by positivity of anti-mitochondrial antibodies (AMA), while liver biochemistry is normal. The silent form is often found in close relatives or patients who underwent an AMA test requested by another specialist. From 70% to 80% of these patients will develop symptoms of the disease over 20 to 30 years [10, 11]. The asymptomatic form of PBC is characterized by AMA positivity and increase of serum alkaline phosphatase (ALP), although no symptoms are present. Less than 5% of these patients remain asymptomatic over 20 years [12]. Fatigue and pruritus typically appear in the symptom phase. The symptomatic onset has mainly been noticed in young women affected by most biochemically active forms of disease, less responsive to treatment with UDCA and in whom disease progression was faster [13].

UDCA is the recommended first-line agent for treatment of PBC, where the optimum dose is 13–15 mg/kg per day [7]. Biochemical response to UDCA in PBC is highly variable among patients. Response rates are lower in male patients and

in young women (<45 years old) [14]. An absent or partial response to UDCA is the strongest predictor of poor outcome [14].

From the histological point of view, the disease progression occurs through four stages as originally defined by Ludwig (stage 1 defined by portal inflammation; stage 2 corresponding to the extension of this inflammation beyond portal tracts into the surrounding parenchyma, with or without associated duct loss; stage 3 where fibrous septa link adjacent portal triads and, stage 4 representing cirrhosis). A meta-analysis by Ishibashi et al. 2011 [15, 16] showed that 50% of PBC patients with moderate fibrosis localized in the portal area develop cirrhosis within 4 years, compared to 31% of patients where fibrosis is absent. Furthermore, out of 667 PBC patients, 5.9% who were at cirrhotic or pre-cirrhotic stage developed hepatocellular carcinoma (HCC) over 20 years. No PBC patient with moderate or no fibrosis developed HCC over the same timeframe [15, 17].

In addition to UDCA response and histology, the following markers at the time of diagnosis identify patients with a worse prognosis: histological ductopenia, PBC/autoimmune hepatitis overlap syndrome, greater than normal bilirubin levels, low levels of albumin [18, 19].

From a genetic perspective, the DRB1*0801 allele of the Human Leucocyte Antigen (HLA) showed an association with PBC in four distinct cohorts: the Canadian/US cohort (2009), the Italian/Canadian/US cohort (2010), the UK cohort (2011), and the Japanese cohort (2012). However, these are single-center studies and the results should be validated over wider geographical regions [20].

With regard to serum prognostic markers, an association was described [21, 22] between anti-gp210 positivity and the progression of the disease towards liver failure. Furthermore, in patients presenting anti-centromere antibodies, PBC more often progresses towards portal hypertension. This finding is certainly remarkable, but validation studies in European populations are needed before being able to consider it as a patient stratification criterion.

Diagnosis of PBC: diagnosis of PBC is based on the evidence of persistent increase of serum ALP in association with AMA positivity.

Currently, most of the patients are diagnosed in the asymptomatic phase of the disease and symptoms generally appear from 2 to 4 years after diagnosis.

The EASL [7] and AASLD [23] guidelines agree on the following PBC diagnostic criteria:

1. Persistent increase (>6 months) of serum levels of alkaline phosphatase (ALP) in patients with normal results at ultrasound examination of the biliary tract;
2. Positivity of AMA (title >1:40 at IF measurement) or anti-Sp100 and anti gp210 subtypes of anti nuclear antibodies (ANA);
3. Histologic evidence of nonsuppurative obstructive cholangitis involving interlobular bile ducts.

At least two of the criteria listed above must be met for the diagnosis of PBC. Presence of AMA is fundamental, while in case of absence a histologic examination is needed to confirm diagnosis. There is general agreement that AMA

positivity and ALP increase allow definitive diagnosis as the positive predictive value exceeds 95% in this case. Thus, in most of the cases liver biopsy is not required for diagnosis. Biopsy is necessary for diagnostic purposes in the following conditions:

1. Patients with persistent increase of ALP of hepatic origin while negative to AMA, M2 antibodies or for PBC-specific ANA subtypes (anti Sp100 and anti gp210).
2. Patients with PBC with a clinical and laboratory picture suggesting the presence of features of autoimmune hepatitis (serum transaminases >5 times the upper normal limit, IgG >2 times the upper normal limit, ANA+ (>1:320), SMA positivity (>1:80)) or in whom other liver diseases must be excluded.

Another potential indication for liver biopsy that could help the patient management is the lack of response to UDCA. The histologic examination is the reference tool for the assessment of the stage of PBC and fibrosis, but this test is invasive, has non-negligible risks, is not easily accepted by patients and cannot be used for the periodic assessment of disease progression. Alternative non-invasive methods to assess the stage of fibrosis, including unidimensional transient elastography (Fibroscan), which evaluates the elasticity of liver parenchyma (the so called *liver stiffness*), are being evaluated. Recent studies show that liver stiffness values <9.6 kPa identify patients with poor or no disease progression over a six year follow up period. Reversely, about 30% of patients with liver stiffness values >9.6 kPa incur major disease-related events over a six year period. During repeated follow up liver stiffness measurements, an increase equal or superior to 2.1 kPa enables to select patients with the highest risk of incurring

liver disease-related major events, liver failure, liver transplantation, and death [24]. It must be highlighted, however, that there are currently no data proving the predictive ability of liver stiffness with regard to drug treatment efficacy.

Also the APRI index (AST to Platelet Ratio Index) has been proposed as an independent predictor of advanced fibrosis and worse transplant free survival with cutpoint = 0.54 [25].

Identification of surrogate markers able to reliably predict the clinical outcome of patients is demanding [26]. Currently, only the serum levels of ALP, both at the time of diagnosis and during treatment with UDCA, are acknowledged as markers of progression. Indeed, there is wide evidence in medical literature that abnormal serum levels of ALP (especially when two times upper normal limit), are predictive of progressive disease [27, 28].

Managing PBC: managing PBC patients means managing symptoms, outcomes of cholestasis and chronic liver disease.

The approach to a patient affected by PBC is not substantially different from managing a patient affected by another liver disease, although with features related to the management of symptoms and the assessment of disease progression. Obviously, also PBC patients need to be monitored with regard to comorbidities and risk factors (alcohol intake, obesity, viruses, etc.). Liver biochemistry should be checked on a yearly basis in the early stages of the disease, and then every 3 to 6 months in more advanced stages. Above all, attention must be drawn at the potential onset of PBC/autoimmune hepatitis

overlap through monitoring of transaminases and possibly IgG (in case of hypertransaminasemia), as patient's prognosis and treatment course would markedly change in this case. As it was already said, the assessment of liver stiffness at the time of diagnosis via Fibroscan might be useful to identify the progressive forms of the disease, but how to schedule follow up Fibroscan is currently uncertain.

Managing symptoms: pruritus should be treated with cholestyramine (first line), rifampicin (second line) or naltrexone (third line); UDCA and antihistamine drugs are inefficacious. No treatment for fatigue has been reported to be of significant benefit so far [7].

Severe pruritus has an impact on the quality of life of PBC patients, suffice it to say that severe drug resistant pruritus is an indication to liver transplant. Given its remarkable impact on patients' quality of life, this symptom requires particular clinical attention. Neither UDCA nor anti histamine drugs showed efficacy in the treatment of pruritus. The first line drug is cholestyramine, an ion exchange resin able to bind bile acids in the intestinal lumen. The recommended dosage of cholestyramine in treating pruritus is 4g per day up to 4 times daily (from 4 to 16 g per day). Rifampicin (from 150 to 600 mg per day) is considered as a second line drug, but it requires close monitoring because of potential liver toxicity occurring in 10% of patients. The third line drug is naltrexone (50 mg per day), which is recommended to be started at low dose and then increased, with the risk of suspension syndrome requiring medical attention. The use of sertraline, a serotonin reuptake inhibitor, in a crossover study conducted versus placebo (from

50 to 100 mg per day) in patients with cholestasis of various etiology, has been reported to have positive effects on pruritus. This drug is effective in approximately 40% of patients [7, 29].

Fatigue is a poorly specific and generally multifactorial symptom. First of all, common and treatable causes of fatigue (anemia, hypothyroidism, depression, psychotropic drug abuse, etc.) should be excluded in these patients. Fatigue due to PBC is not correlated with the severity or duration of the disease. In some cases it is disabling and prevents the most common daily activities. Eighty percent of patients with PBC present fatigue, often associated with sleep disorders and orthostatic hypotension. No specific drug treatment for fatigue or dedicated guidelines are available as of today; furthermore, drugs that are widespread in the age group who is most affected by PBC, like blood pressure lowering drugs, may exacerbate the condition of fatigue. Results of a recent randomized double-blind study with modanafil for the treatment of PBC patients for 12 weeks compared to placebo showed ineffectiveness of this drug for the management of fatigue in patients with PBC [30]. The results of a clinical trial on the efficacy of rituximab for this indication are not yet available [31].

Managing the outcomes of chronic cholestasis: supplementation with calcium and vitamin D should be considered in perimenopausal women as treatment of osteoporosis. The administration of alendronate or ibandronate might be considered in osteopenic patients in non cirrhotic stage. Hyperlipidemia needs to be treated only in patients with family history of significant cardiovascular events [7].

Due to malabsorption of vitamin D, osteoporosis is often associated with PBC (in 20 to 52% of patients) and progresses along with cholestasis. However, it is important to remind that patients with PBC are mainly women in post-menopausal age, who are per se at risk of developing osteoporosis. Consensus is missing between European and American guidelines with regard to treatment of osteoporosis. Supplementation with calcium (1000 to 1500 mg per day) and Vitamin D (1000 IU per day) should be considered in these patients and in post-menopausal women in particular. Such treatments are routine in the management of osteoporosis and do not depend on the diagnosis of PBC. The administration of alendronate (70 mg weekly) or ibandronate (150 mg monthly) might be considered in osteopenic patients in non cirrhotic stage. Data demonstrating the efficacy of ibandronate once a month in preventing fractures have been reported [32], but further studies are needed to confirm these results.

Hyperlipidemia is a common outcome of chronic cholestasis. However, the absence of an additional cardiovascular risk in these patients has been demonstrated [33]. In patients with family history of significant cardiovascular events, or hypercholesterolemia associated with low levels of HDL, lipid lowering drugs should be considered.

Managing cirrhosis. Managing cirrhosis secondary to PBC is not substantially different from managing cirrhosis of other etiology.

Managing cirrhosis due to PBC is not substantially different from managing cirrhosis of other etiology. The incidence of HCC in PBC patients is estimated at 0.36 per 100 person years where male sex, an advanced histologic stage and

inadequate response to UDCA being associated with higher risk [34]. In order to monitor the onset of HCC, an ultrasound surveillance every 6 months is required [7].

In presence of ultrasound signs of portal hypertension, platelet levels <140,000 or Mayo Risk score >4.1, an endoscopic examination should be performed in order to assess the presence of esophageal varices. [35]. Management of esophageal varices involves the use of non-selective beta-blockers or elastic banding as primary and secondary prevention. Good clinical outcomes of transplantation have been reported, with 80 to 85% survival rate over 5 years and almost universal recurrence of the disease [36]. Patients with PBC should be referred to a transplant center in presence of MELD score >12, Mayo Risk Score ≥ 7.8 or when bilirubin levels get close to 6 mg/dl, given that bilirubin levels are a much more accurate prognostic indicator in PBC than in liver diseases of other etiology. Although the progression of PBC is slow, it is potentially serious: suffice it to mention that the 10 year mortality rate is 59% in PBC patients with greater than normal bilirubin levels and 38% in patients with ALP >2 ULN [37]; markedly higher with respect to diseases like HCV/HIV coinfection (25%) [38] or mammary carcinoma (29%) [39]. For this reason, it is essential to identify the right treatment capable of blocking the progression of the disease in UDCA non responders or intolerants.

Treating PBC: UDCA is the only drug approved as first line treatment of the disease. Consensus is missing with regard to second line or alternative to UDCA treatments for patients who are non responders or intolerant to this drug.

As of today, UDCA is the only drug approved as first line treatment of PBC and the only one recommended by the international guidelines [7, 23]. The drug was proven to be effective in reducing serum biochemical parameters altered in PBC (ALP, bilirubin, GGT, cholesterol, and IgM) and also in slowing the progression of the disease. The main mechanisms of action of UDCA are linked with its choleretic effect and with its effect on the secretion of bicarbonates protecting the biliary epithelium from the detergent activity of hydrophobic biliary salts. A clinical trial demonstrated that the likelihood of transplant or death in PBC patients is reduced by a 4 year treatment with UDCA compared to placebo as early as in 1994 [40]. Following studies demonstrated slower disease progression along with reduced rate of major liver events and need of transplant in patients treated with UDCA compared to control patients [16]. Thus, UDCA is certainly a valid treatment option for patients with PBC; however, in a part of the patient population (around 40%) the drug is ineffective in reducing biochemical markers, ALP in particular. Furthermore, from 3 to 5% of patients are intolerant to UDCA, manifesting adverse events that prevent continuing the drug, for example incoercible or otherwise unexplained diarrhea.

The definition of UDCA non-responder is not completely clear, as different criteria have been reported in medical literature [41]. These criteria (Table 1) are based on the improvement of biochemical markers of the disease (ALP, gamma-GT, albumin, bilirubin) after 6 to 12 months of treatment. All studies agree that the response to UDCA, whatever the definition, represents an independent prognostic factor of disease progression.

Therefore, the percentage of patients who are non-responders to UDCA changes according to the chosen marker; by and large, 40% of patients treated with UDCA need an add-on treatment, while 3 to 5% of patients are intolerant to the drug, that is, they manifest adverse events that de facto prevent them from taking it. All models that have been proposed to define the lack of response to UDCA (table 1) are easy to use but also dichotomous, namely they are able to define only two levels of risk (responder and non-responder). Conversely, these models are not able to provide intermediate levels of risk and, above all, they do not measure risk over time, in other words they do not predict the likelihood that a patient will undergo transplant after 1 to 5 years. In order to drive decisions on patient management, it is necessary to provide continuous models (indices, scores) with the power to measure the level of risk for each single patient in each disease stage and, above all, to quantify risk over time. Two large multicenter studies have recently developed continuous predictive models (UK score, Globe score) that are based on biochemical markers related to stage of disease and response to UDCA, and therefore allow to quantify and stratify the risk of progression in continuous and time related fashion [42, 43]. Using such models is it possible to quantify the risk of developing liver failure requiring transplant or liver and non liver related mortality over a specific timeframe (5,10 and 15 years) in single patients.

Treating PBC patients non responding to UDCA: although randomized clinical trials are lacking, some studies support potential efficacy of budesonide and fibrates

With regard to add on therapies to UDCA, according to published studies budesonide and fibrates (bezafibrate, fenofibrate) are of benefit in patients who do not respond to UDCA. However, these are single center or retrospective studies conducted in very small patient populations and requiring validation [44, 45]. Budesonide might be of more benefit in PBC patients with signs of hepatitis (elevated serum transaminases) in whom the inflammatory component is prevailing, but it cannot be used in patients at cirrhotic stage, with severe osteopenia/osteoporosis, elderly, or who suffer from diabetes or hypertension. Fibrates might be useful in patients with marked hyperlipidemia and high cardiovascular risk, and in patients with pruritus as a prevailing symptom, but they carry potential side effects like muscle damage (myositis and rhabdomyolysis) and renal insufficiency; fibrates may also cause drug induced liver damage.

As of today, OCA is the only drug for which controlled multicenter studies have demonstrated efficacy in the UDCA non-responder or intolerant patient sub group [46].

Obeticholic acid (OCA) might be considered as add on therapy in UDCA non-responders or intolerants.

OCA belongs to the class of bile acids, being an analogue of chenodeoxycholic acid (CDCA), with the addition of an ethyl group providing a strong affinity for the nuclear farnesoid X receptor (FXR). This receptor is involved in the regulation of bile acids homeostasis, inhibiting their production (via the inhibition of CYP7A1 and CYP8A1) [47], increasing their excretion [48] and reducing liver and intestinal reabsorption [49, 50]**.** OCA has a 100 times higher affinity for FXR than CDCA,

and a different mechanism of action from UDCA, whose primary activity is the dilution of the endogenous bile [51].

Based on the results of two phase II studies and one phase III study (POISE), OCA received a conditional approval by EMA [52]. In the phase II 747 202 study, OCA in combination with UDCA was proven to reduce ALP by 20-25% in a non dose-dependent fashion after a 12 week treatment. In these studies the reduction of ALP is clinically and statistically significant as early as after two weeks of treatment, reaches a peak after 6 months and then stabilizes [53].

The POISE study evaluated a composite primary endpoint recommended by FDA and based on the following elements: ALP<1.67 + ALP reduction of at least by 15% from baseline and total bilirubin (TB) lower than or equal to the Upper Limit of Normal (ULN) at 12 months. The secondary endpoints evaluated were the reductions of biochemical markers: ALP, AST, bilirubin and GGT. The study included three treatment arms: OCA 10mg ± UDCA, Titration (OCA 5mg ± UDCA for 6 months with the OCA dose increased to 10mg for the following 6 months) and placebo ± UDCA. Patients were randomized in 1:1:1 ratio. The primary endpoint was reached by 46 to 47% of patients taking OCA, with an earlier effect in the OCA 10mg treatment arm. OCA was proven effective in reducing ALP, AST and GGT, achieving clinically and statistically significant levels after two weeks of treatment. ALP, AST and GGT reached their lowest levels after three months and then remained stable for the whole study period, as it was seen in phase II studies. Furthermore, a reduction of ALP by at least 15% was reported in 77% of patients. Two hundred and sixteen patients, of whom 32 from Italy, were enrolled in the

study. The improvement in the markers of cholestasis was also confirmed by the following 12-month open-label phase [46].

The main adverse event was pruritus, that was the reason for study interruption for 7 out of 73 patients in the OCA 10 mg treatment arm and 1 out of 70 in the titration arm. However, pruritus suffered by patients decreased over time and reached the same level as at baseline after six months [46].

Conclusions

UDCA shows to be effective in a wide range of patients, although 30 to 40% of them are still lacking an adequate response. Globe Score and UK PBC Risk Score seem a very promising support to the decisions that must be made concerning follow-up and indications for second-line drugs. As of today, in theory, at least three drugs can be used as an add-on to UDCA in an individualized fashion according to the characteristics of the patient affected by PBC. Of them, only OCA received conditional approval by EMA. With regard to the other two options, budesonide and fibrates, the current off label utilization still requires further scientific evidence, especially in terms of validation through randomized clinical trials.

Conflict of interest

The authors declare that the working group has been unconditionally supported by Intercept Pharmaceuticals.

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REFERENCES

[1]. Beuers U, Gershwin ME, Gish RG, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Hepatology 2015; 62: 1620-1622.

[2]. http://www.globalpbc.com/philosophy.

[3]. Orphanet Quaderno novembre 2016 http://www.orpha.net/orphacom/cahiers/docs/IT/Prevalenza_delle_malattie_rare_in_ordine_decrescente_o_casi.pdf. in.

[4]. Podda M, Selmi C, Lleo A, et al. The limitations and hidden gems of the epidemiology of primary biliary cirrhosis. Journal of autoimmunity 2013; 46: 81-87.

[5]. Boonstra K, Beuers U, Ponsioen CY Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. Journal of hepatology 2012; 56: 1181-1188.

[6]. Lleo A, Jepsen P, Morenghi E, et al. Evolving Trends in Female to Male Incidence and Male Mortality of Primary Biliary Cholangitis. Scientific reports 2016; 6: 25906.

[7]. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. Journal of Hepatology 2017; http://dx.doi.org/10.1016/j.jhep.2017.03.022.

[8]. Huang YQ Recent advances in the diagnosis and treatment of primary biliary cholangitis. World journal of hepatology 2016; 8: 1419-1441.

[9]. Kumagi T, Heathcote EJ Primary biliary cirrhosis. Orphanet journal of rare diseases 2008; 3: 1.

[10]. Metcalf JV, Mitchison HC, Palmer JM, et al. Natural history of early primary biliary cirrhosis. Lancet 1996; 348: 1399-1402.

[11]. Mitchison HC, Bassendine MF, Hendrick A, et al. Positive antimitochondrial antibody but normal alkaline phosphatase: is this primary biliary cirrhosis? Hepatology 1986; 6: 1279-1284.

[12]. Prince MI, Chetwynd A, Craig WL, et al. Asymptomatic primary biliary cirrhosis: clinical features, prognosis, and symptom progression in a large population based cohort. Gut 2004; 53: 865-870.

[13]. Quarneti C, Muratori P, Lalanne C, et al. Fatigue and pruritus at onset identify a more aggressive subset of primary biliary cirrhosis. Liver international : official journal of the International Association for the Study of the Liver 2015; 35: 636-641.

[14]. Carbone M, Mells GF, Pells G, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. Gastroenterology 2013; 144: 560-569 e567; quiz e513-564.

[15]. Ishibashi H, Komori A, Shimoda S, et al. Risk factors and prediction of long-term outcome in primary biliary cirrhosis. Internal medicine 2011; 50: 1-10.

[16]. Corpechot C, Carrat F, Bonnand AM, et al. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. Hepatology 2000; 32: 1196-1199.

[17]. Jones DE, Metcalf JV, Collier JD, et al. Hepatocellular carcinoma in primary biliary cirrhosis and its impact on outcomes. Hepatology 1997; 26: 1138-1142.

[18]. Carey EJ, Ali AH, Lindor KD Primary biliary cirrhosis. Lancet 2015; 386: 1565-1575.

[19]. Trivedi PJ, Corpechot C, Pares A, et al. Risk stratification in autoimmune cholestatic liver diseases: Opportunities for clinicians and trialists. Hepatology 2016; 63: 644-659.

[20]. Zhang H, Carbone M, Lleo A, et al. Geoepidemiology, Genetic and Environmental Risk Factors for PBC. Digestive diseases 2015; 33 Suppl 2: 94-101.

[21]. Wesierska-Gadek J, Penner E, Battezzati PM, et al. Correlation of initial autoantibody profile and clinical outcome in primary biliary cirrhosis. Hepatology 2006; 43: 1135-1144.

[22]. Nakamura M, Kondo H, Mori T, et al. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. Hepatology 2007; 45: 118-127.

[23]. Lindor KD, Gershwin ME, Poupon R, et al. Primary biliary cirrhosis. Hepatology 2009; 50: 291-308.

[24]. Corpechot C CF, Poujol-Robert A, Gaouar F, Wendum D, Chazouillères O, Poupon R. Noninvasive elastography-based assessment of liver fibrosis progression and prognosis in primary biliary cirrhosis. Hepatology 2012 Jul; 56(1):198-208.

[25]. Trivedi PJ, Bruns T, Cheung A, et al. Optimising risk stratification in primary biliary cirrhosis: AST/platelet ratio index predicts outcome independent of ursodeoxycholic acid response. Journal of hepatology 2014; 60: 1249-1258.

[26]. Silveira MG, Brunt EM, Heathcote J, et al. American Association for the Study of Liver Diseases endpoints conference: design and endpoints for clinical trials in primary biliary cirrhosis. Hepatology 2010; 52: 349-359.

[27]. Lammers WJ, Kowdley KV, van Buuren HR Predicting outcome in primary biliary cirrhosis. Annals of hepatology 2014; 13: 316-326.

[28]. Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology 2014; 147: 1338-1349 e1335; quiz e1315.

[29]. Bergasa NV Pruritus in primary biliary cirrhosis: pathogenesis and therapy. Clinics in liver disease 2008; 12: 385-406; x.

[30]. Silveira MG, Gossard AA, Stahler AC, et al. A Randomized, Placebo-Controlled Clinical Trial of Efficacy and Safety: Modafinil in the Treatment of Fatigue in Patients With Primary Biliary Cirrhosis. American journal of therapeutics 2016.

[31]. Jopson L, Newton JL, Palmer J, et al. RITPBC: B-cell depleting therapy (rituximab) as a treatment for fatigue in primary biliary cirrhosis: study protocol for a randomised controlled trial. BMJ open 2015; 5: e007985.

[32]. Guanabens N, Monegal A, Cerda D, et al. Randomized trial comparing monthly ibandronate and weekly alendronate for osteoporosis in patients with primary biliary cirrhosis. Hepatology 2013; 58: 2070-2078.

[33]. Solaymani-Dodaran M, Aithal GP, Card T, et al. Risk of cardiovascular and cerebrovascular events in primary biliary cirrhosis: a population-based cohort study. The American journal of gastroenterology 2008; 103: 2784-2788.

[34]. EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma. Journal of Hepatology 2012;56:908–943.

[35]. de Franchis R, Baveno VIF Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and

individualizing care for portal hypertension. Journal of hepatology 2015; 63: 743-752.

[36]. Carbone M, Neuberger JM Autoimmune liver disease, autoimmunity and liver transplantation. Journal of hepatology 2014; 60: 210-223.

[37]. Sclair SN, Little E, Levy C Current Concepts in Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis. Clinical and translational gastroenterology 2015; 6: e109.

[38]. Down C MN, Marks K. The Risk of Cardiovascular Disease, Diabetes,Liver-Related Outcomes, and Death Over 10 Years in HIV/HCV-Coinfected Patients With and Without Steatosis. AIDS research and human retroviruses 2016 Sep; Vol. 32(9):868-71.

[39]. Allemani C MP, Berrino F, Bastiaannet E, Gavin A, Galceran J, Ameijide A, Siesling S, Mangone L, Ardanaz E, Hédelin G, Mateos A, Micheli A, Sant M, EUROCARE Working Group. Predictions of survival up to 10 years after diagnosis for European women with breast cancer in 2000-2002. Int J Cancer 2013 May 15; 132(10):2404-12. .

[40]. Poupon RE, Poupon R, Balkau B Ursodiol for the long-term treatment of primary biliary cirrhosis. The UDCA-PBC Study Group. The New England journal of medicine 1994; 330: 1342-1347.

[41]. Corpechot C Primary Biliary Cirrhosis Beyond Ursodeoxycholic Acid. Seminars in liver disease 2016; 36: 15-26.

[42]. Carbone M, Sharp SJ, Flack S, et al. The UK-PBC risk scores: Derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cholangitis. Hepatology 2016; 63: 930-950.

[43]. Lammers WJ, Hirschfield GM, Corpechot C, et al. Development and Validation of a Scoring System to Predict Outcomes of Patients With Primary Biliary Cirrhosis Receiving Ursodeoxycholic Acid Therapy. Gastroenterology 2015; 149: 1804-1812 e1804.

[44]. Floreani A, Franceschet I, Perini L, et al. New therapies for primary biliary cirrhosis. Clinical reviews in allergy & immunology 2015; 48: 263-272.

[45]. Hosonuma K, Sato K, Yamazaki Y, et al. A prospective randomized controlled study of long-term combination therapy using ursodeoxycholic acid and bezafibrate in patients with primary biliary cirrhosis and dyslipidemia. The American journal of gastroenterology 2015; 110: 423-431.

[46]. Nevens F, Andreone P, Mazzella G, et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. The New England journal of medicine 2016; 375: 631-643.

[47]. Goodwin B, Jones SA, Price RR, et al. A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. Molecular cell 2000; 6: 517-526.

[48]. Ananthanarayanan M, Balasubramanian N, Makishima M, et al. Human bile salt export pump promoter is transactivated by the farnesoid X receptor/bile acid receptor. The Journal of biological chemistry 2001; 276: 28857-28865.

[49]. Li H, Chen F, Shang Q, et al. FXR-activating ligands inhibit rabbit ASBT expression via FXR-SHP-FTF cascade. American journal of physiology. Gastrointestinal and liver physiology 2005; 288: G60-66.

[50]. Denson LA, Sturm E, Echevarria W, et al. The orphan nuclear receptor, shp, mediates bile acid-induced inhibition of the rat bile acid transporter, ntcp. Gastroenterology 2001; 121: 140-147.

[51]. Pellicciari R, Costantino G, Camaioni E, et al. Bile acid derivatives as ligands of the farnesoid X receptor. Synthesis, evaluation, and structure-activity relationship of a series of body and side chain modified analogues of chenodeoxycholic acid. Journal of medicinal chemistry 2004; 47: 4559-4569.

[52]. EMA/CHMP/666310/2016 http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2016/10/WC500214166.pdf.

[53]. Hirschfield GM, Mason A, Luketic V, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. Gastroenterology 2015; 148: 751-761 e758.

Table 1. Qualitative or quantitative indices assessing the prognosis of PBC on the basis of biochemical response to ursodeoxycholic acid

Indices	UDCA-response criteria	Time of evaluation after starting UDCA	Predictive Performance*	
			Global PBC Study Group	UK PBC Consortium
Qualitative				
Toronto	ALP ≤ 1.67 x ULN	2 y	0.61	0.70
Barcelona	ALP normal or ALP reduction > 40%	1 y	0.58	0.61
Paris-I	ALP < 3 x ULN, AST< 2 x ULN, normal bilirubin	1 y	0.70	0.81
Rotterdam	Normal bilirubin, normal albumin	1 y	0.69	-
Paris-II	ALP < 1.5 x ULN, AST < 1.5 x ULN, normal	1y	0.63	0.75

	bilirubin			
Global-PBC	ALP < 2 x ULN, normal bilirubin	1 y	-	-
Rochester	ALP < 2 x ULN, Mayo Score <4.5	6 m	-	-
Ehime	Normal GGT or GGT reduction > 70%	6 m	-	-
Quantitative UK score	ALP, AST/ALT and bilirubin at y + albumin and platelet count at baseline	1y	-	0.95
Globe Score	ALP, bilirubin, albumin and platelet count at y + age at baseline	1y	0.81	-

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gammaglutamyl transpeptidase; IgG, immunoglobulin G; LSM, liver stiffness measurement; UDC, ursodeoxycholic acid; ULN, times the upper limit of normal.

*= predictive performance based on C-statistic for all-cause death or LT, derived from the derivation and validation of cohorts of the Global PBC study group [43] or the UK PBC Consortium [42]. Adapted from Corpechot C. et al. 2016 [41]