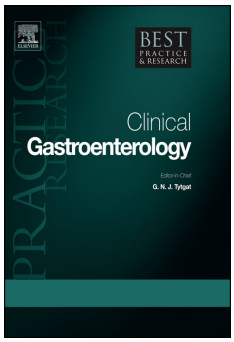
Patterns of Disease Progression and Incidence of Complications in Primary Biliary Cholangitis (PBC)

Janmohamed, Ashnila; Trivedi, Palak

DOI:
10.1016/j.bpg.2018.06.002

Accepted Manuscript



Patterns of disease progression and incidence of complications in primary biliary cholangitis (PBC)

Ashnila Janmohamed, Palak J. Trivedi

PII: S1521-6918(18)30038-6

DOI: 10.1016/j.bpg.2018.06.002

Reference: YBEGA 1575

To appear in: *Best Practice & Research Clinical Gastroenterology*

Received Date: 5 March 2018

Accepted Date: 8 June 2018

Please cite this article as: Janmohamed A, Trivedi PJ, Patterns of disease progression and incidence of complications in primary biliary cholangitis (PBC), *Best Practice & Research Clinical Gastroenterology* (2018), doi: 10.1016/j.bpg.2018.06.002.

Patterns of Disease Progression and Incidence of Complications in Primary Biliary Cholangitis (PBC)

Ashnila Janmohamed [1,2] and Palak. J. Trivedi* [1,2]

Ashnila Janmohamed BSc MBBS MRCP; Email address: janmohaA@adf.bham.ac.uk

Palak J Trivedi BSc MBBS MRCP PhD; Email address: p.j.trivedi@bham.ac.uk

1. National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre (BRC), Centre for Liver Research, Birmingham (UK)
2. Liver unit, University Hospitals Birmingham Queen Elizabeth, Birmingham (UK)

Address for Correspondence:

Palak J. Trivedi (p.j.trivedi@bham.ac.uk)

Room 06, Floor 02

Institute of Translational Medicine

University of Birmingham (UK)

B15 2TH

ABSTRACT

Clinical outcome for patients with primary biliary cholangitis (PBC) is dictated by development of cirrhosis, portal hypertension and its associated complications; including for some, a predisposition toward hepatocellular carcinoma. However rates of clinical progression vary, and accurately identifying disease course is of critical importance to patients, clinicians, as well as industry, who are committed to developing new effective and life-prolonging therapy as well as treating symptoms that appear disproportionate to underlying disease severity.

Patients seek reassurance and guidance as to their own prognosis, and clinicians wish to confidently recognise those at highest risk of poor outcomes as equally as they strive to reassure individuals with a more favourable disease trajectory. International registries have facilitated a much greater knowledge of disease incidence and heterogeneity of presenting phenotypes. In so doing they highlight the opportunity to provide a more individualized estimate of the clinical course that patients experience, and have led to a renewed approach to risk stratification; both in terms of 'hard outcomes' and also disease-associated complications in PBC specifically.

Keywords:

Primary biliary cholangitis; hepatic complications; decompensation; hepatocellular carcinoma; disease progression; APRI; stratification

Introduction

Whilst today we recognise more clearly the heterogeneous rates of disease progression that patients with primary biliary cholangitis (PBC) experience, this was less evident in older studies; in part a reflection of centre and referral bias, as well as the absence of very large cohort data to capture the broader spectrum of disease, both before and after intervention. This means some caution needs to be exercised when reviewing outcome data from earlier studies, as our understanding of PBC no longer considers the disease a single homogeneous process.

Within these constraints, historic population-based data from the UK illustrate that the average survival of untreated patients with 'classical PBC' is approximately 9-10 years from presentation, with ~25% developing chronic liver failure during this time (1). In the absence of effective therapy, the median time to develop extensive liver fibrosis was approximately 2 years, with a probability of remaining in early stage disease of 29% over 4 years (2-4). An early prospective study (n=236) identified that more than 50% of patients with stage 1-III PBC developed histologically proven cirrhosis within 4 years (5). Reciprocally, studies from the Mayo Clinic indicate that progression to cirrhosis after a follow-up period of 6 years was evident in 49% of all patients from the point of diagnosis (6).

However, fuller understanding of disease has evolved following the advent of anti-mitochondrial antibody (AMA) testing; reactivity of which in the presence of cholestasis facilitates detection at an earlier stage, often without need for liver biopsy (7-9). In a multicentre study conducted by the Global PBC Group (n=4805), not only was the mean age at PBC diagnosis seen to increase over time (from 47$\pm$10 years in

the 1970s to 57±12 years from 2010 onwards), but the proportion of patients having features of more aggressive presenting biochemical disease also changed significantly, with only 51% and 30% of patients diagnosed in the 1970s expressing a normal serum bilirubin or serum alkaline phosphatase (ALP) below twice the upper limit of normal (ULN), respectively, vs. 78% and 63% for patients diagnosed after 2010 (10). Notably, of the group with available liver histology (n=2217), 60% were identified as having early disease (stage I-II) when diagnosed pre-1990, rising to 77% for patients presenting after 2010.

The latter finding may explain the observed improvement in 10-year transplant free survival rates between aforementioned time points (48% vs. 80%) (10), at least in part. Application of the original histological classification systems proposed by Ludwig (11), Rubin (12) and Scheuer (13) have been shown to stratify the risk of disease progression in patients with PBC, which is perhaps best highlighted by the study published by Corpechot in 2008 (14). Across a prospectively evaluated cohort of 292 patients, the investigators showed that stage III-IV liver fibrosis, or moderate–severe interface hepatitis, purported a significantly increased risk of death or liver transplantation independently of liver biochemical values and UDCA treatment status (adjusted relative risk [RR] 1.5 and 1.9, respectively). However, the Toronto group report that significant ductopenia, defined as >50% bile duct loss at diagnosis, independently predicted histological fibrosis progression, and overrides the prognostic impact of interface hepatitis in the same biopsy specimens (15).

The degree of intrahepatic bile duct loss is usually not severe enough to cause jaundice unless established cirrhosis is present; however, a subgroup of patients with

PBC suffer with severe cholestatic jaundice and profound ductopenia in the absence of significant cirrhosis or fibrosis (16). In this 'premature ductopenic variant' patients are plagued by severe pruritus, may have cholestatic jaundice and be malnourished due to fat malabsorption in the absence of hepatocellular failure or significant portal hypertension. This form may affect 5-10% of PBC patients and although the extent of fibrosis may be limited initially, development of cirrhosis seems to be inevitable and rapid. Patients are unresponsive to UDCA therapy, and due to the markedly decreased quality of life and adverse effect of chronic severe cholestasis this progressive disease evolves over the course of <5 years to a stage where liver transplantation should be considered, even in the absence of significant fibrosis.

Many, more contemporary histological systems have been developed for studying PBC (17-19), with the aim of better characterising interface activity, ductopenia, chronic cholestasis and fibrotic indices (14-16, 20-22). However, as discussed, diagnosing PBC no longer requires liver biopsy; for disease identification is largely reliant on the biochemical context of presentation, in conjunction with positive serology (AMA; or anti-nuclear antibodies of the anti-sp100 or anti-gp210 class) (23). Whilst histology remains the 'gold-standard' for assessing the burden of inflammatory activity and fibrosis progression, the intrusiveness coupled with well-known sampling variability, disconcordant reporting in cholestatic disease, and non-routine applicability in clinical practice, has fostered the study of several non-invasive surrogates. The accuracy of vibration-controlled transient elastography (VCTE) in fibrosis staging has been demonstrated in several large PBC cohorts (24, 25), with prognostic capabilities independent of biochemical response evident in a single-centre retrospective experience of 150 patients (24). These studies are almost exclusively

conducted in UDCA-treated cohorts, and estimate that 50-55%, 20-21%, 14.5-17% and 8-14.5% of PBC patients have stage F0-F1, F2, F3 and F4 fibrosis respectively at diagnosis. The annual progression rate for F0-F3 fibrosis was 0.48 (±0.21) kPa, increasing to 4.06 (±0.72) kPa/year for those with stage F4 fibrosis. Perhaps most striking, a liver stiffness value >9.6 kPa (hazard ratio [HR]: 8.4), or an increase by >2.1 kPa/year (HR): 1.3) were identified as significant discriminatory thresholds for progression to hepatic decompensation events, liver transplantation or death (24).

The fact that most patients are now diagnosed at an earlier stage of disease in an era where liver biopsy does not constitute routine standard of care effectively precludes the study of 'hard' endpoints (histological progression, liver transplantation, death) when testing new therapy. Such challenges have driven a wealth of investigation into potential surrogate markers and risk prediction models, which highlight the impact of data that is sufficiently powered through duration of follow-up, and by the number of clinical events captured. Elevated serum bilirubin is well established as a marker of poor clinical outcome, and incorporated into historical prognostic models such as the Mayo PBC risk score to predict short-term survival (<2 years) in patients with advanced liver disease (26, 27). A study from New York in the 1970s showed that individuals with PBC initially experience a stable period of disease during which bilirubin remains constant, although once they develop a rapid rise in serum values, this signified a late-phase of disease and death would inevitably follow (calculated survival time for bilirubin values >34μmol/L, >102μmol/L and 170μmol/L of 4 years, 25 months and 17 months, respectively) (28).

A potentially more applicable surrogate early in the disease course is serum ALP. In the largest ever meta-analysis of individual patient data (*n*=4845), a near log-linear relationship was shown between ALP and subsequent risk of transplantation/death across several time points (29). This study demonstrated that ALP bestows prognostic information incremental to the predictive power of bilirubin and independent of follow-up time, presenting age, sex, disease stage, and treatment status (29). To this effect, several studies published between 2006-2014 illustrated strong associations between percentage reduction or absolute decreases/normalization in serum ALP over time (in isolation or combination with other biochemical covariates) and significantly improved clinical outcome (14, 15, 30, 31) (**Figure 1**). Although these 'biochemical response criteria' were originally derived from individual cohorts under UDCA therapy, they have subsequently been independently and externally validated at a multi-centre and international level inclusive of non-treated patients (20, 32, 33). These parameters form the benchmark for which treatment efficacy is gauged in PBC, as well as representing inclusion criteria for contemporary interventional studies of second-line therapy. It remains unclear, however, whether liver fibrosis stage (or its non-invasive assessment) confers additive predictive value.

Clinical course in the era of ursodeoxycholic acid (Figure 2)

Up until 2017, UDCA has been the only licensed medical therapy for PBC. The prospective, non-controlled pilot study reported by Poupon *et al.* in 1987 (*n*=15) was one of the first to demonstrate an improvement in serum liver biochemistry in PBC, with a mean reduction in serum ALP, alanine aminotransferase (ALT) and bilirubin values of 65%, 68% and 36% respectively of pre-treatment values following 2 years of UDCA treatment (dosage: 13-15 mg/kg/day) (34). Notably, for patients in whom

the drug had been stopped, a prompt rebound of serum biochemical values to pre-treatment levels was observed. A two-year double-blind multi-centre randomised controlled trial (RCT) led by the same group soon followed (n=146 patients), and showed that the mean serum bilirubin, ALP and ALT values decreased by 9%, 56% and 52% respectively from baseline, versus an increase of 68%, increase of 6% and an increase of 2% in the UDCA- and placebo-treated groups, respectively (p<0.001 for all comparisons) (35) .

The impact of UDCA treatment on serum liver biochemistry has been supported through a further wealth of clinical trial activity across North America and Europe. However, determining the impact of therapy on histological disease progression has proven more controversial given that liver biopsy is not performed routinely, particularly for patients in whom advanced disease is already evident. Nevertheless, paired liver biopsies from a proportion of the trial participants comprising the Canadian, French and Spanish studies (63%, 65%, and 44% of the original study cohorts, respectively) illustrate a variable improvement in scorings of bile duct paucity, ductular proliferation, leucocytic infiltrate, piecemeal necrosis, lobular inflammation, parenchymal necrosis and histological stage of disease in the UDCA treated-groups, and in a greater number of patients compared to placebo (35-37). The Mayo clinic data lent further support to this observation, wherein UDCA treatment significantly delayed histological progression to cirrhosis over 6.6±0.4 years (13% vs. 49% in UDCA-treated vs placebo-treated patients respectively, p<0.009) (6). Applying a Markov model to 103 patients from the French cohort further demonstrated a 5-fold lower progression rate from early stage disease to extensive liver fibrosis or cirrhosis (7% per year under UDCA vs. 34% under placebo,

p<0.002), with a 4-year probability of remaining in early stage disease of 76% vs. 29%, respectively (4). However, no significant changes in the degree of inflammatory activity or histological stage was observed in a prospective randomised trial of 61 patients from the Mayo clinic (38); and in a combined analysis of the 4 RCTs from Canada, France, Spain and the United States (*n*=367 overall; 200 of which were UDCA-treated), significant differences histologically were restricted to improvements in periportal necroinflammatory lesions and ductular proliferation, and only in the 177 patients having a baseline histological disease stage of I-II (39).

A protective effect of UDCA on the development of oesophageal varices has also been addressed prospectively, and in a study of 180 patients the 4-year probability was significantly lower in treated versus untreated individuals (16% vs. 58%; $p<0.001$) (40). Moreover, in an extension of the French clinical trial wherein both treatment arms subsequently received UDCA for a further two years, the incidence of hepatic decompensation, doubling of bilirubin, liver transplantation and death was significantly lower in patients treated with UDCA from the outset versus those originally randomised to placebo (9/72 vs. 20/73; RR: 0.28, $p<0.002$) (41). A meta-analysis of three RCTs (Mayo Clinic, USA; Canadian multi-centre; French multi-centre) provides further evidence of improved transplant-free survival in UDCA-treated patients (RR: 1.9, $p<0.001$) (42).

Conversely, the multi-centre trial by Combes *et al.* (*n*=150; UDCA dosage of 10-12 mg/kg/day) yielded more sobering results, with no significant difference in the incidence of hepatic decompensation, liver transplantation and mortality between UDCA- and placebo-treated groups over two years (56% vs. 69%, $p=0.098$) (43). The

RCTs from Spain (*n*=192; UDCA dosage of 14-16 mg/kg/day), Sweden (*n*=116; 500 mg/day), and Greece (*n*=86; 12-15 mg/kg/day) raised further questions over the impact on long-term clinical outcomes (37, 44, 45); wherein despite improvements in serum biochemistry (all 4 studies) and liver histology (Spanish study only), the transplant-free survival between UDCA- and placebo-treated patients was not significantly different. To this effect, several meta-analyses debate the prognostic merit of UDCA therapy in PBC (46). However, when interpreting such data, note must be taken of the number of patients enrolled, whether evaluation was of individual studies or of individual patient data, the baseline stage of disease in which UDCA was commenced, and the dosage of medication used. In an RCT of 155 patients, which gauged treatment effect by the magnitude of improvement in serum liver biochemistry values over two years, a dose of 13-15 mg/kg/day was shown to be superior to 5-7 mg/kg/day, and similar to 23-25 mg/kg/day (47).

Meta-analysis of the early clinical trials confined to those using an appropriate UDCA dose and with sufficient follow-up (at least 2 years; *n*=522 under UDCA treatment and *n*=516 who received placebo) has validated the improvement in liver biochemical values that were observed in the individual studies, although histologic evidence of disease progression was no different between groups (48). A total of 160 patients who were treated with UDCA and 186 control subjects died or underwent liver transplantation. This difference was significant in a fixed-effect model, although both suggested a clinically important treatment effect that was not significant because of an insufficient number of patients (48).

Nevertheless, definitive evidence of therapeutic efficacy was provided in 2014, via a multi-centre, individual patient data meta-analysis conducted by the Global PBC Study Group (n=4,845) (29). This landmark study confirmed significantly improved liver transplant free survival for treated versus untreated individuals (at 5 years, 10 years and 15 years: 90%, 78%, and 66% for UDCA-treated patients, respectively; vs. 79%, 59%, and 32% in the non-treated group, respectively; p<0.001 for all comparisons) (29). Pooled survival indices in the PBC population nevertheless remain lower than age- and sex-matched controls despite therapy, fuelling intense investigation into the factors defining UDCA treatment efficacy.

Linking biochemical surrogates to therapeutic efficacy

It has been suggested that any impact on transplant-free survival in UDCA vs. placebo-treated groups is attenuated following adjustment of baseline disease stage (49). However a combined analysis of trials from the Mayo clinic, Canada and France, suggested that the 4-year transplant-free survival rate is significantly improved even for patients classified as medium-risk (starting bilirubin 1.4-3.5 mg/dL), high risk (bilirubin >3.5 mg/dL) or with stage IV histological disease (42). The strong association between serum biochemistry and clinical response has been extensively studied given that the magnitude of biochemical change is not necessarily equal from patient to patient. Indeed, biochemical response criteria (**Figure 1**) provide good evidence to show that percentage reduction or absolute decreases/normalisation in serum bilirubin and ALP whilst on UDCA therapy, together with other biochemical covariates, are strongly predictive of prognosis (50).

The original UDCA response models continue to be refined across different patient populations (14, 15, 31, 51), and all currently proposed criteria highlight that an absence of biochemical improvement has clear prognostic implications. Approximately 60-70% of all patients with PBC successfully attain pre-defined biochemical thresholds within 6-24 months after UDCA-treatment, which are strongly associated with improved clinical outcomes, and a transplant-free survival akin to that of an age- and sex-matched population. By contrast, so-called 'biochemical non-responders' represent a high-risk group for disease progression and need for liver transplantation.

Although biochemical response criteria were originally derived from single-centre reports, all have been independently, externally and robustly validated at a global level (20, 32, 52), representing the highest level of evidence for risk prediction and stratification into PBC clinical trials (50). Whilst a small proportion with early-stage disease meet criteria free of therapy (53), this represents an understudied population and presently it is not yet possible to identify patients with a good prognosis regardless of intervention. Thus, UDCA is recommended as the first line treatment in all patients with PBC from the point of diagnosis (7).

Biochemical response criteria continue to be refined, and newer more sophisticated algorithms have been developed incorporating conventional parameters indicative of biochemical response and disease severity. By interrogating large, international multi-centre cohorts to predict transplant free survival, application of the AST/platelet ratio index (APRI), UK-PBC and GLOBE scores, are all shown to outperform prior biochemical response criteria for the prediction of death/liver transplantation (32, 52,

54). For instance, a GLOBE score of >0.30, which applied to 40% of UDCA-treated patients (*n*= 2488) was associated with a significant reduction in survival compared to age- sex- and calendar time matched population (32), improving the net classification of patients in to low- and high- risk groups by 10% (7).

Therapeutic options for UDCA non-responders

Non-response to UDCA is the current pre-requisite for consideration of second line treatment, although patients with an elevated APRI or fibrosis score according to VCTE represent additional high-risk groups (50). In 2016, obeticholic acid (OCA) gained approval as second-line therapy for PBC, following on from the successful results of respective clinical trials (55-57). The POISE phase III study recruited patients with PBC exhibiting a persistent elevation in serum ALP (prior biochemical non-response according to the modified Toronto criterion (15), and/or an elevated bilirubin; or reported intolerance to UDCA. The study involved three treatment arms: OCA at a dose of either 5 mg/day, 5 mg/day titrated up to 10 mg/day, and placebo. The primary endpoint during the 12-month double-blind period was attainment of both an ALP value <1.67 × ULN (with a ≥15% reduction from baseline) and a normal serum bilirubin. In an intention-to-treat analysis, the primary endpoint was met in 10% of the placebo group relative to 47% and 46% in the 10 mg and 5-10 mg dose-titrated OCA groups, respectively (p<0.0001 for both). Moreover, the mean decrease in serum ALP from baseline was 39% and 33% in the 10 mg and titrated OCA-groups, respectively, versus 5% for patients in receipt of placebo (p<0.0001 for both). Both OCA groups met pre-defined secondary endpoints including a reduction in serum AST and total serum bilirubin (both OCA groups p<0.001 vs. placebo).

OCA monotherapy (10 mg and 50 mg/day) has also shown statistically significant reductions in mean serum ALP values from baseline vs. placebo (-53.9% and -37.2% vs. 0.8%; $p<0.0001$) (57); and longer-term efficacy is currently being studied across prospective clinical outcome studies in PBC. This is of particular importance given the relative infrequency of PBC globally (9), and hence the limited number of patients studied thus far. Up till now, enrolment into clinical trials has been restricted to individuals demonstrating persistent elevations in serum ALP, with therapeutic efficacy gauged through percentage change or absolute decline. It is plausible therefore, that the beneficial effect of OCA will be restricted to patients failing to achieve biochemical response based on ALP criteria. However, there is no currently available data regarding therapeutic efficacy stratified according to the magnitude of serum ALP elevations at point of trial inclusion. Assessment of further surrogates of clinical outcome, including for instance APRI and liver stiffness measurements derived via transient elastography, would be of additional clinical benefit in this regard.

The ability of fibric acid derivates to exert anti-cholestatic effects (via activation of peroxisome proliferator-activated receptors [PPAR]) has received a wealth of attention as adjunctive therapy to UDCA, although currently represents an unlicensed intervention for PBC. A pooled complete biochemical response rate using fenofibrate +UDCA combination therapy is evident in 69% of patients, according to systematic review and meta-analysis by Grigorian *et al*. (58); and in a retrospective study conducted by the Toronto group (59) improvements in short-term liver decompensation-free and transplant-free survival, independently of liver biochemical

changes, were seen across a cohort of 120 prior UDCA non-responders (log rank p<0.001) (59).

Improvements in liver biochemistry are also evident using bezafibrate. In a non-blinded prospective randomised-controlled study (*n*=27; 100-120 months of treatment), serum ALP values were significantly lowered following UDCA+bezafibrate combination therapy (mean 290 IU/L+0.91) vs. UDCA alone (mean 461 IU/L+1.42; *p*<0.05), and associated with a trend toward improved overall survival (log rank *p*=0.057) (60). The Barcelona open-label study (*n*=28) also provides evidence of a significant improvement in itch severity, wherein all 12 patients who reported itch prior to starting bezafibrate treatment achieved complete or partial symptom resolution (61). Moreover, 20 and 24 UDCA non-responders attained a serum ALP reduction >40% within 6 and 12 months, respectively, with combination therapy (61). In an extension of these findings, *n*=26/48 UDCA-treated patients having an ALP persistently elevated >1.5xULN had normalised serum values over a median of 38 months, with partial or complete symptom resolution in all participants (62).

Despite improving surrogate markers of long-term prognosis, the depth of evidence supporting bezafibrate and fenofibrate in PBC has, up till now, remained limited to mostly groups of patients outside of clinical trial settings or with limited duration of follow-up. Moreover, the biochemical improvements associated with fibric acid derivatives have not been shown to sufficiently alter long-term probability of liver-related death or need for transplantation when stratified according to the UK-PBC risk score (54, 63), and may be counterbalanced by a negative impact on renal function

(60). In light of these limitations, a double-blind RCT evaluating bezafibrate in UDCA non-responders (Paris-II criteria; n=100) has recently completed. The primary endpoint was normalisation of all liver biochemical parameters and prothrombin time following 24 months of treatment, and met in 15 patients (30%) within the bezafibrate+UDCA combination arm vs. 0% with placebo+UDCA alone (64). Notably, ~70% of patients met biochemical response criteria in the bezafibrate treatment arm in addition to a 10% reduction of liver stiffness as measured by VCTE, compared to only 10% and +14% with placebo (p<0.001 and <0.01, respectively). Formal reporting of study findings is eagerly anticipated.

Very recently, the results of a clinical trial selectively targeting PPAR-δ have been published (65). In a multi-centre and international phase II double-blind placebo-controlled RCT, UDCA non-responders (Toronto criterion) received either Seladelapar in one of two doses, 50 mg/d or 200 mg/d, or placebo in a 1:1:1 study design (n=13, 10 and 12, respectively). Mean changes from baseline in serum ALP were; -2% in the placebo group, vs. -53% and -63% in the Seladelpar 50 mg and 200 mg groups, respectively (p<0.0001 for both groups vs. placebo). Unfortunately, 3 patients developed grade III elevations in serum aminotransferases (reversible on treatment cessation) and the study was prematurely terminated. Nevertheless, all five participants who received Seladelpar for the full 12 weeks normalised ALP values by the end of treatment.

Emerging insights into genetic risks and biological pathways have led to additional interest in therapies aimed at modulating bile acid physiology and targeting specific immune responses (**Figure 3)**. Whilst appropriate risk stratifiers and surrogate

endpoints of treatment efficacy now exist (50), early disappointing results with immunomodulation and molecular targeted therapies highlight critical difficulties in translating basic immunological insights into routine clinical practice (66). As our understanding of disease pathogenesis continues to evolve, it is hoped that a stepwise understanding of disease progression may permit more 'time course initiated' interventions, from the incipient stages of immune-intolerance, through to parenchymal remodelling and anti-fibrotic therapy in patients with established cirrhosis (67). A more detailed discussion of therapeutic alternatives in PBC is beyond the scope of this review, and will be covered elsewhere in this issue (68).

Complications (tentatively) linked to severity of liver disease

Portal hypertensive disease

Approximately 35% of patients have features of portal hypertension at presentation defined as a porto-hepatic gradient (PHG) >6 mmHg, **Table 1** (69). Notably, a significant difference in transplant-free survival is recognised when stratifying individuals according to low ($\leq$6 mmHg; n=86), intermediate (6–12 mmHg; n=20) and high ($\geq$12 mmHg; n=26) PHG values. There is further evidence that a reduction in hepatic veno-portal gradient (HVPG) whilst on UDCA-treatment associates with improved clinical outcome, stratifying through a 20% gradient-decline over 2 years (69). Of note, elevated AST values at baseline and 1 year after onset of UDCA were associated with an increased risk of death and liver transplantation in the same study (14, 52), and normalisation within 2 years of UDCA treatment was the only laboratory parameter significantly related to improved overall survival.

The rate at which portal hypertension develops throughout the clinical course of a PBC population is less well studied, given that regular and invasive pressure assessments do not form part of standard clinical practice. The prognostic capabilities of non-invasive surrogates such as APRI have thus been ascertained in PBC, given ability to infer portal hypertension non-invasively, and also the presence of liver fibrosis. Indeed, APRI has now been validated as an independent predictor of transplant-free survival across several international cohorts (52, 70, 71), and when applied at 1 year following UDCA therapy is able to identify the sub-group of PBC patients at risk of liver disease progression and earlier mortality, independently and additively to biochemical response criteria (**Figure 1**).

Whilst the majority of PBC patients who develop portal hypertension do so in relation to cirrhosis, approximately 5-10% of PBC-related gastro-oesophageal varices (GOV) manifest in early-stage liver disease secondary to pre-sinusoidal resistance (69, 72, 73). This is important to recognise, given that the presence of GOV is associated with poor 5- and 10-year survival rates in PBC patients; 63% and 26% respectively, in comparison to 91% and 83% in patients without GOV. These unacceptably poor outcomes led to development of the Newcastle Varices Prediction Score (NVPS), which incorporates serum albumin, ALP, platelet count and spleen size, to accurately predict the presence of GOV across all disease stages (area under the receiver operator characteristic curve [AUROC]: 0.9) (73). Notwithstanding the depth to which the NVPS is validated, there may be a pre-selection bias to the model as all patients in the original study were recruited only after an endoscopy referral was made. Moreover the study was not powered to discriminate effects of ‘clinically significant’ varices harbouring risk of haemorrhage, and the independent/additive

predictive value of the NVSP-score to conventional biochemical response criteria is uncertain.

Hepatic decompensation

Although UDCA has been shown to improve survival, contemporary studies report a cumulative 10-year incidence of developing cirrhosis of 40% (74). Transition from compensated to decompensated liver cirrhosis is infrequent (incidence rate [IR] 9.7-per-1,000 patient years] although imparts a significant mortality risk (time-dependent hazard ratio [HR]: 21.5 (75)). In a retrospective study of 3,224 PBC patients, the first observed decompensation event was most often ascites (63%); with variceal bleeding (23%), hepatic encephalopathy (8%) or a combination of (6%) being less prevalent. However the incidence of decompensation events has evolved significantly over time, with a 10-year cumulative complication rate of 13.5% for patients studied prior to 1990, 9.3% for between 1990 and 2000, and 5.8% for those included after the year 2000 (75).

Transplant-free survival differs significantly with respect to type of decompensation event (median survival after occurrence of variceal bleeding, encephalopathy, ascites or combination of the above: 4.0 years, 3.2 years, 1.6 years, and 0.6 years, respectively), likely reflecting progress in the modern management of variceal bleeding versus the lack of effective therapy in managing diuretic refractory ascites. Risk stratification via the GLOBE score, or an elevated APRI >0.54 after 12 months of UDCA therapy, is predictive for future hepatic decompensation events in PBC specifically (32, 52, 75), underscoring the prognostic importance of UDCA therapy from point of diagnosis.

Patients with both an APRI >0.54 and biochemical non-response had a higher 10-year complication risk of 37% compared to those patients with an APRI ≤0.54 who met biochemical response criteria (3%) (75). Similarly in a prospective study involving 262 PBC patients with a median follow up of 6.3 years, Shi et al also illustrated that incomplete or non-response was a significant risk factor for hepatic decompensation [HR 4.275 (95% CI 2.423-7.541)] (76).

Hepatocellular carcinoma

The overall incidence of hepatocellular carcinoma (HCC) is perceived to be lower for PBC patients compared to other chronic liver diseases (77), estimated at 3.4-cases per 1,000 patient years (*n*=4.565) (33). Although rare, the development of HCC is a critical event in the patient journey, being associated with significantly poorer transplant-free and overall survival (HR 22.61) (33).

The latest guidelines from EASL recommend that all cirrhotic patients with PBC should be subjected to cancer surveillance (7). This strategy has significant limitations given that the incidence of HCC in PBC appears greatest in men who fail to attain biochemical response irrespective of underlying liver disease stage (33, 78). This contrasts to women with evidence of advanced disease yet who respond to UDCA treatment and actually fall into a lower risk group wherein surveillance may not be cost effective (33). Indeed, biochemical response status is able to sub-stratify pre-existing at risk populations, independent and additive to disease stage, having clear connotations with regard to HCC surveillance paradigms (**Figure 4**). Of interest, a retrospective study by Cheung et al (n=144) identified that an APRI-r1 >0.54 is also

predictive, and together with UDCA response may be applied to refine HCC stratification a step further (79).

Complications secondary to chronic cholestasis

The reduced bile acid secretion as a consequence of prolonged cholestasis may result in a degree of lipid malabsorption, although profound vitamin deficiency is rare. Milder degrees of hypovitaminosis may however be detected in patients with prolonged jaundice, and early studies estimate a prevalence of approximately 30% in PBC patients (80). Elevated serum lipid levels are also evident in up to 80% of patients with PBC, yet rarely of clinical consequence. The pattern of hyperlipidaemia varies depending on stage of disease and paradoxically anti-atherogenic (7). Therefore patients are not treated routinely for PBC associated hyperlipidaemia, except for those with concomitant vascular risk factors.

By contrast, metabolic bone disease is observed in 20-40% of patients, and consequent fracture risk directly associated with low bone mass and indirectly to the duration (but not severity) of underlying liver disease (81, 82). The Barcelona group have identified that those with a bone mineral density (BMD) T-score lower than −1.5 carry greatest risk of fragility fractures; thus represent a group for which early bisphosphonate therapy is indicated (81). Notably, UDCA has been shown to attenuate hyperbilirubinaemia-induced osteoblast apoptosis *in vitro* although clinical correlates are yet to be substantiated (83).

Phenotypic heterogeneity and impact on disease progression

Symptomatic presentations

Approximately 60% of patients with PBC are asymptomatic at time of diagnosis, however as little as 5% remain symptom-free over time (1) (**Table 2**). It is apparent that presenting age and gender are also influential, with young women – a group who fail UDCA therapy more commonly – having the greatest symptom burden and elevated fatigue scores on quantitative testing (20). Pruritus and fatigue represent the archetypal symptoms in chronic cholestasis, and associated with significantly impaired quality of life for patients (84). Although non-specific and unrelated to liver disease severity, prognostic importance of fatigue is suggested by the Newcastle group, who in a prospectively evaluated PBC cohort (n=136) found that fatigued patients experienced significantly shorter transplant-free and overall survival (56% and 60%, respectively) relative to non-fatigued disease-matched controls (74% and 77%, respectively; p<0.0001) after 9 years of follow-up (85). The effect appears independent of UDCA treatment, although it remains unclear whether symptomatic presentations impart additional discriminatory value to biochemical response criteria. Consensus biological explanation for fatigue is also lacking, and current data points toward both peripheral and central mechanisms (85, 86). An in depth discussion regarding mechanisms, impact and management of symptoms in PBC is provided elsewhere in this issue (87)**.**

Presenting age and patient sex

Although PBC is widely considered a disease of middle age, approximately 25% of patients are aged 49 years or less at diagnosis. Moreover, an inverse correlation of patient age and likelihood of meeting biochemical response was identified in the

landmark study by the UK-PBC study group (20). Indeed, biochemical response rates (Paris-I) in women exceed 75% for those diagnosed above the age of 50, relative to ≤50% in those aged 40 and below. These results echo those of an earlier, single-centre study wherein younger age (<55 years) was associated with an elevated standardised mortality ratio (SMR; 7.4) even when adjusted for liver-related death (SMR: 218) (88). Younger women more often fail to meet response due to transaminase criteria, which may infer a more inflammatory phenotype of disease given that the grade of interface hepatitis adversely influences clinical outcome (14, 21, 54). The critical influence of presenting age in female patients may allow timely identification of at-risk patients, prior to assessment of 1-year biochemical response. Because of a relatively poor predicted survival it has been proposed that young women become eligible for clinical trial entry from the point of PBC diagnosis (89). However, the converse also holds true, in that half of all women presenting below the age of 50 will indeed attain biochemical response on UDCA therefore inappropriately selected for additional therapies should decisions be made from the outset.

Given that up to a quarter of the female PBC population may present at childbearing age, it is expected that some may wish to conceive. From a patient perspective, pruritus and its treatment are of practical concern, necessitating symptom specific therapy in over two-thirds of affected cases (90). An observational cohort study from Toronto found that >70% of women with PBC sustain normal liver biochemistry values throughout the gestational period, including those for whom disease is deemed ‘active’ prior to conception. Intra-partum biochemical flares occurred in a minority, and serious or adverse maternal consequences were rare. However, in support of an autoimmune aetiology, 72% of women develop flares in biochemical disease activity

post-partum, irrespective of pre-conception disease behaviour. Post-partum biochemical flares most often represented a transient anicteric cholestatic hepatitis with an isolated elevation in serum ALP that settled in the first post-partum year (on UDCA therapy), with disease progression being a rare occurrence.

A further key finding from the UK-PBC consortium relates to the influence of patient sex and response to UDCA; wherein men exhibited a lower propensity toward biochemical response than women (63% vs. 76% in women; $p<0.001$) (20). These differences may relate to a more advanced disease stage at diagnosis; and in another large well-characterised PBC cohort, event-rates were no longer different between men and women when stratified according to disease severity (91). Such observations are also likely to explain (in part) the elevated HCC-risk found in male PBC patients (74).

Immunoserological variants

Anti-mitochondrial antibodies are the hallmark of PBC, and whilst detectable in >80% of PBC patients AMA positivity holds no prognostic value (22, 23). Although diagnostic of PBC in the presence of biochemical cholestasis, AMA positivity may also be detectable in 0.5-1% of the general population (92-95).

The true frequency, characteristics and clinical outcomes of individuals with no clinical or biochemical evidence of PBC, yet who remain AMA positive, are largely unknown. Perhaps the most robust data series in this regard stems from a prospective French national study of 229 AMA-positive individuals (78% women; median age 58 years) wherein the subsequent 5-year incidence rate of PBC was only 16% (96).

However, 5-year mortality was 75%, compared to vs. 90% in an age- and sex-matched control population ($p<0.05$), despite the fact that no patient actually died secondary to PBC.

Up to 50% of patients with 'definite' PBC also test positive for disease-specific anti-nuclear antibodies (ANA), the commonest staining patterns being peri-nuclear/rim-like membranous (anti-gp210) and multi-nuclear dot (anti-Sp100). AMA reactivity holds no prognostic value, and clinical outcomes for AMA-negative patients are no different to serologically positive counterparts with PBC. By contrast, anti-gp210 positivity (present in ~30% of all PBC patients) predicts more aggressive disease, and in one study conferred a 6-fold increased risk of progression to liver failure/transplantation (97). Moreover, retrospective evaluation of a large PBC cohort from China found that the 5-year adverse outcome-free survival of anti-gp210-patients was 70%, vs. 85% for anti-gp210-positive patients, respectively ($p=0.005$). Although neither independent nor additive to the predictive power of biochemical response, anti-gp210 may assist in the earlier, prospective identification of high-risk patients (98).

Another notable ANA-staining pattern in PBC is anti-centromere (ACA), which although less-specific, poses a risk factor for developing portal hypertension (17.5 % vs. 3.8%; ACA-positive vs. ACA-negative; odds' ratio [OR] 4.2) (97). Anti-centromere antibodies are more frequently found in autoimmune connective tissue disease, particularly limited systemic scleroderma. Indeed, >60% of patients with PBC develop extra-hepatic autoimmune conditions however an impact on overall outcome is not readily perceptible (99).

Overlap syndromes and crossover presentations

Primary biliary cholangitis and autoimmune hepatitis (AIH) are both typified pathologically by a varying degree of immune-mediated liver injury, with broadly similar mechanistic themes (100). The imprecision of such processes, coupled with our incomplete understanding of disease aetiology, means that certain common features be they biochemical, serological or histological are often observed across the spectrum of autoimmune liver disease (101).

The term overlap 'syndrome' or crossover presentation is applied to describe ill-defined circumstances wherein, either concurrently or sequentially; there exists coexistence of AIH as well as clear features of PBC. However, the challenge remains that AIH does not have an absolute diagnostic test, rather diagnosed based on the presence and relative absence of various markers of clinical, biochemical, serological, and histological disease. In light of these clinical challenges the International Autoimmune Hepatitis Group (IAIHG) devised a series of weighted criteria with the principled intent of standardising parameters, and quantifying the strength of each, in order to ensure homogeneity of AIH patient populations in clinical trials. Unfortunately over time, the IAIHG scoring system is increasingly applied as a diagnostic test (a purpose for which it was never designed), implying that manifestations of AIH are somehow unique and can be confined to disease-specific borders. Manifestations that are also common to PBC, for instance interface hepatitis, presence of autoantibodies and elevated serum immunoglobulin levels, weaken the legitimacy of individual diagnoses, and have led to creation of a separate classification system for patients, the 'overlap syndromes.' In reality, however, so-

called overlap 'features' are frequently shared across the spectrum of autoimmune liver diseases, with some clearly being less categorical and objective than others. Overlap syndromes or crossover presentations are thus likely to represent, rather than a distinct process, the inherent distribution of clinical features across patient populations – the more extreme in distribution the more distinct overlap appears.

The incidence and prevalence of AIH overlap features in PBC are therefore hard to ascertain because of publication bias, arbitrary and imprecise definitions contained within the same overlap designation, and challenges in case definitions (serological overlap is arguably not of the same significance as histological overlap), and limitations to test interpretation (e.g. anti-nuclear antibodies must be interpreted in the context of their immunofluorescence staining pattern, rather than their presence and titre). With these caveats in mind, the most readily identified presentation of overlap is the simultaneous presence of both diseases, although less commonly the onset of AIH and PBC is temporally dissociated, usually with PBC presenting first, having a variable interval of 6 months to 13 years before the onset of AIH (102). Approximately 10% of patients with all the features of AIH may also be persistently AMA positive, which in itself is not synonymous with a distinct syndrome.

In a cohort study of AMA-positive patients with AIH (*n*=15) (103), those treated conventionally with steroids did not show any clinical or histological evidence of PBC despite continued detection of AMA over 27-years. Nevertheless, the same centre later published a case series of three AIH patients in whom a formal change to PBC diagnosis was made between 4 and 15 years following the original AIH presentation (104). By contrast, AMA-positive PBC with a degree of parenchymal

inflammation akin to that observed in AIH is well-recognised, usually in the form of interface or lobular hepatitis. In rare circumstances, this may be more pronounced than the cholestatic component with ALT or AST values as >5xULN. In this event disease progression is related in part to the severity of interface activity, and persistence of serum transaminase activity leading to UDCA non-response (14) (20). In a contemporary study by the Parisian group, approximately 55%, 9% and 12% of patients exhibited mild, moderate and severe interface hepatitis (19), although the precise number in whom (and severity with which) interface hepatitis manifests can be difficult to ascertain given the infrequency with which liver biopsy is performed in PBC. In any event the seminal trials of UDCA in PBC (n=292) identified moderate-severe interface hepatitis as conferring a two-fold greater risk of disease progression (liver transplantation/death) over a 16-year period (14).

In 2007 the Mayo clinic reported that over an average 5.75-year follow-up, 54% of patients with AIH/PBC overlap developed portal hypertensive disease vs. 28% with AIH alone; $p<0.01$), with features of hepatic decompensation and progression to liver transplantation/death also being more common (38% vs. 19%; $p<0.05$) (105). Conversely, when Joshi *et al*. evaluated 16 patients with PBC and overlapping features of AIH, the median change in serum biochemistry and immunoglobulin values was similar to a cohort with a more classical PBC phenotype after 2 years of UDCA alone, with very little change in hepatic lobular inflammatory activity (106). Thus it remains unclear whether the clinical outcome of AIH/PBC overlap is different to that of isolated AIH or PBC. A detailed discussion regarding therapeutic considerations for overlap presentations is beyond the scope of this review, and will be discussed elsewhere in the current issue (68).

CONCLUSION

The full appreciation of the breadth of PBC has evolved as awareness has risen, leading to a greater understanding of phenotypic presentations and variation therein. International cohort studies have facilitated a much greater understanding of the patient experience, with recognition that rates of clinical progression vary according to presenting age and sex, immunoserological and histological variants, symptomatology, and biochemical response to therapy. Whilst the latter defines 'at-risk' patients most readily, determining the rate of clinical progression prior to mandatory completion of 1 year on UDCA therapy is urgently commanded. The impact of patient age has been better captured in contemporary PBC risk scores, however the additive predictive value of histology and its non-invasive surrogates requires further investigation, particularly with regard to decompensation events. Moving forward, it is hoped that prospective biobanking with paired long-term clinical follow-up data will yield predictive markers from the point of diagnosis through interrogation of key pathways underlying non-response to conventional therapy, akin to that explored in other autoimmune diseases (107).

Table 1: The incidence of hepatic complications and prognostic implications

Complication	Incidence and prevalence (% patients with PBC)	Correlates and Potential Risk Factors	Prognostic Implications
Portal hypertension (defined as PHG>6.0 mm Hg)	Prevalence: 35% (n= 132 patients) (69)	• Elevated Mayo risk score (PHG correlates significantly with the Mayo risk score (r^2= 0.262 P<0.001 (69) • Advancing liver histological stage (r_s=0.414 P<0.001) (69) • 12.3% of non-cirrhotic patients may have an elevated PHG (69, 112-114)	• Severity of the PHG is associated with shorter transplant free survival. Percentage probability of transplant free survival at 15-years; 80% vs 60% vs 30% if PHG <= 6, 6-12, >12 mmHg respectively P<0.0003 (69) • Changes in PHG 24-months post-UDCA treatment may identify responders with survival akin to that of a control population. Decreased or stable PHG predictive of better survival (HR 4.64) (69)
Varices	Incidence at presentation: 9% (72) Incidence over time (UDCA untreated): 31% over 7 years (108) Overall prevalence (UDCA treated): 8%-19% (40, 109, 110)	• Male sex. One retrospective study (n= 325) found among patients with early histological disease, EVs were more likely to be present in males (111)	• Presence of GOV associated with reduced 5- (63% vs 91%) and 10- year (26% vs 83%) survival vs patients without GOV (73) • 50% of patients will have a bleed event

	Can manifest in 5-10% patients with early stage, pre-cirrhotic PBC (72, 73, 111)	• Low albumin < 4 g/dl (OR 6.02) (115) • Thrombocytopenia <140 x10^9 cells/L (OR 7.6) (110) • NVPS (incorporates serum albumin, ALP, platelet count and spleen size) accurately predicts presence of GOV across all disease stages (AUROC: 0.9) (73) • Elevated bilirubin ≥ 1.2 mg/dl (HR 5.4) (111, 115) • Mayo risk score ≥ 4.5 (OR 10.6) (110) • Advanced histological stage (stage III-IV) (69% of patients) (108)	

Hepatic decompensation	Overall incidence: 0.97% (75) Among patients who present with hepatic decompensation; ascites is the most frequent first event (63%) vs variceal bleeding (23%) vs hepatic encephalopathy (8%) vs combination of hepatic complications (6%) (75)	• Biochemical non-response 12-months post UDCA therapy (10- year cumulative incidence of first complication in biochemical non-responders (32.4%) vs responders (6.2%)) (75) • APRI > 0.54 (10-year complication rate if APRI > 0.54 (24.3%) vs APRI ≤ 0.54 (3.8%)) (52, 70, 75) • Advanced liver disease (biochemical and histological) - Biochemical: abnormal serum albumin and/or bilirubin (HR 4.34) (75) - Histological: advanced Scheuer classification (HR 1.77) (76, 116)	• Occurrence associated with reduced 10-year survival rates (10.4% vs 85.3%) vs patients without complications (75) • Median survival after: Variceal bleeding- 4.0 years Encephalopathy-3.2 years Ascites- 1.6 years Combination of the above- 0.6 years (75)

Hepatocellular carcinoma (HCC)	0.34% (33)	• Male sex (HR 2.91) (33) - Incidence in men vs women, 6.7 vs 2.6 cases per 1000 patient-years respectively (33) • Advancing age at PBC diagnosis (per 10-year increase) (HR 1.21) (33, 117, 118) • Advanced biochemical (HR 2.72) (33) and histological disease (OR 5.80) (117-121). • Inadequate biochemical response 12-months post UDCA therapy (HR 4.52) (33). An APRI - r1> 0.54 (HR 3.94) is predictive of HCC development (79)	• Significantly poorer transplant-free and overall survival in patients with HCC (HR 22.61) (33)

ALP- Alkaline phosphatase; AST- Aspartate transaminase; APRI- AST to platelet ratio index; APRI-r1- APRI at 1 year after treatment; EV- Esophageal varices; GOV- Gastrooesophageal varices; NVPS- Newcastle varices prediction score; PHG- Porto-hepatic gradient; UDCA- ursodeoxycholic acid

Table 2: Variant presentations in PBC and impact on disease progression

Phenotypic variants (% patient population)	**Impact on disease progression**
Symptomatic presentation	• 60% asymptomatic at presentation; less than 5% remain symptom free over time (1) • Fatigue and pruritus most common symptoms (non-specific); unrelated to disease severity In one prospective study (n=136 patients) fatigued patients experienced significantly shorter transplant free and overall survival (56% and 60% respectively) relative to non-fatigued disease-matched controls (74% and 77% respectively, P<0.0001) (85). In a second study, fatigue was associated with an increased risk of liver transplantation or liver related death (HR 9.6) (122)
Young presenting age (25%)	• Biochemical response rate is less than 50% in women aged ≤ 40 years (20)
Male sex (5-10%)	• Older age at presentation relative to women (median 60 vs. 55 years; P< 0.001) (20) • Higher frequency of biochemical non- response (63% vs 76%; P < 0.001) (91) . Possibly due to more advanced disease at diagnosis (20) • Increased HCC risk in biochemical non-responders and cirrhotics (33)

Immunoserological variants (% patient population)	**Impact on disease progression**
AMA negative (5-10% of all patients)	• Clinical course same as AMA-positive PBC
ANA positive (30-50% of all patients)	• PBC specific ANA (anti-gp210 and anti-Sp100) can be present concurrently with AMA • Testing for ANA may be useful in diagnosing PBC in AMA negative patients • Anti-gp210 positivity associated with aggressive disease; six-fold risk of progression to liver failure/transplant (97)
ACA positive	• Associated with significant portal hypertension (17.5% vs 3.8%; ACA-positive vs ACA-negative respectively) (97)
Histological variants (% patient population)	**Impact on disease progression**
Classical/typical PBC	• Slow and progressive decline in small bile ducts over time; parallel increase in fibrosis • Biliary cirrhosis over 10-20 years without UDCA treatment
Premature ductopenic variant (16) (5-10%)	• Characterised by rapid onset ductopenia in the absence of significant fibrosis or cirrhosis; Severe cholestatic jaundice • Unresponsive to UDCA therapy • Rapid progression towards cirrhosis in less than 5 years requiring liver transplantation
Interface hepatitis (moderate-severe)	• Positive correlation with serum AST/ALT • Moderate-severe activity independently predictive of biochemical non-response,

	histological stage progression, progression to transplantation and death (14, 21, 25) - Two fold risk of disease progression (liver transplantation/death) (14)
Biochemical non-responders	• GLOBE score > 0.30 associated with reduced survival compared with matched general population (HR 5.51 P< 0.0001) with 5-, 10- and 15- year transplant free survival rates of 79.7%, 57.4% and 42.5% respectively (32) • Increased risk of hepatic decompensation events and HCC (HR 4.52) (33, 75)

ACA- Anti-centromere antibodies; AMA- Anti-mitochondrial antibodies; ANA- Anti-nuclear antibodies; ALT- Alanine aminotransferase AST- Aspartate transaminase; HCC- Hepatocellular carcinoma; UDCA- Ursodeoxycholic acid

Figure 1: Evolution of biochemical response criteria in PBC

Several biochemical response criteria are proposed in PBC [A] successful attainment at 12 -24 months post UDCA therapy, or following diagnosis for non-treated patients, is associated with transplant-free survival akin to that of an age- and sex-matched control population. Approximately 2/3rds of the PBC population overall meet conventional biochemical response criteria, and [B] attempts have been made to validate earlier in the course of therapy in one study (3- and 6- vs 12-months) Application of the APRI score at 12 months (APRI-r1) to all pre-existing criteria has been shown to improve predictive performance, and [C] furthered the development of continuous scoring systems which incorporate both measures of treatment response and surrogate markers of disease severity.

Figure 2: Impact of UDCA on disease progression

Several studies have illustrated that UDCA is not only effective at improving liver biochemistry but delaying histological progression to cirrhosis, reducing hepatic decompensation rates and significantly improving 5-, 10-, and 15- year liver transplant free survival in patients with PBC. Absence of biochemical response to UDCA has significant prognostic implication including reduced liver transplant free survival and higher hepatocellular carcinoma risk. Biochemical response status can be used to stratify at-risk patients either independently or additively to disease stage. Continuous risk scores such as the UK-PBC score and GLOBE score, which incorporate surrogate markers of response to UDCA therapy, have been shown to outperform conventional risk models in accurately predicting risk of liver transplantation or liver- related death.

Figure 3: The PBC drug pipeline in 2018

Treatment of PBC has advanced over recent years and continues to evolve. Increased understanding into genetic risks and biological pathways have led to therapies aimed at modulating bile acid physiology and targeting immune responses. UDCA remains the standard of care in PBC. However a proportion of patients respond sub-optimally to UDCA therefore at risk of hepatic complications and liver transplantation. OCA, a farnesoid X receptor agonist, has been licensed as second line therapy in patients with inadequate/non-response to UDCA. Other non-licensed drugs showing ongoing promise in phase 2/3 clinical trials in PBC include PPAR agnoists (benzafibrate and seladelapar) and inhibitors of ileal bile acid transport (GSK 2330672 aimed at treating pruritus).

Figure 4: Incidence of hepatocellular carcinoma and thresholds for surveillance in at risk groups

The overall annualised incidence of HCC cases is estimated at 3.4 for every 1000 patient-years according to the Global PBC Study Group, although varies greatly depending upon patient sex, disease stage and biochemical response status. Male patients who are non-responders have the highest incidence of HCC irrespective of disease stage, whereas by contrast, women who respond to UDCA despite advanced disease have a much lower incidence that falls below the threshold in which surveillance is recommended by EASL and AASLD (vertical dotted line). Indeed, biochemical response status may sub-stratify pre-existing at risk populations, independent and additive to disease stage, having significant implications with regard to HCC surveillance paradigms.

PRACTICE POINTS

- Rates of disease progression are variable across the PBC population, being impacted by heterogeneous phenotypic, histological and immunoserological presentations.
- Transplant-free survival is improved for patients under ursodeoxycholic acid treatment, with outcome benefit most evident in patients meeting biochemical response criteria.
- The GLOBE and UK-PBC scores provide objective quantification measures that accurately predict transplant-free survival at specific time-points.
- Hepatic decompensation events are rare (<1% per year) but confer a heightened transplant/mortality risk >20-fold.
- HCC risk is heightened risk for men, in addition to patients failing to meet biochemical response criteria; whereas the incidence in biochemical responders is low, even in the presence of advanced liver disease.

RESEARCH AGENDA

- The additive predictive value of histology and its non-invasive surrogates to contemporary PBC risk scores requires further investigation.

- Prospective bio-banking with paired long-term clinical follow-up data may be useful in yielding predictive markers from the point of diagnosis.

References

1. Prince M, Chetwynd A, Newman W, Metcalf JV, James OF. Survival and symptom progression in a geographically based cohort of patients with primary biliary cirrhosis: follow-up for up to 28 years. Gastroenterology. 2002;123(4):1044-51.
2. Christensen E, Crowe J, Doniach D, Popper H, Ranek L, Rodes J, et al. Clinical pattern and course of disease in primary biliary cirrhosis based on an analysis of 236 patients. Gastroenterology. 1980;78(2):236-46.
3. Locke GR, 3rd, Therneau TM, Ludwig J, Dickson ER, Lindor KD. Time course of histological progression in primary biliary cirrhosis. Hepatology. 1996;23(1):52-6.
4. Corpechot C, Carrat F, Bonnand AM, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. Hepatology. 2000;32(6):1196-9.
5. Christensen E, Neuberger J, Crowe J, Altman DG, Popper H, Portmann B, et al. Beneficial effect of azathioprine and prediction of prognosis in primary biliary cirrhosis. Final results of an international trial. Gastroenterology. 1985;89(5):1084-91.
6. Angulo P, Batts KP, Therneau TM, Jorgensen RA, Dickson ER, Lindor KD. Long-term ursodeoxycholic acid delays histological progression in primary biliary cirrhosis. Hepatology. 1999;29(3):644-7.
7. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67(1):145-72.
8. Boonstra K, Kunst AE, Stadhouders PH, Tuynman HA, Poen AC, van Nieuwkerk KM, et al. Rising incidence and prevalence of primary biliary cirrhosis: a large population-based study. Liver Int. 2014;34(6):e31-8.
9. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. J Hepatol. 2012;56(5):1181-8.
10. Murillo Perez F, Goet JC, Lammers WJ, Gulamhusein A, van Buuren HR, Ponsioen CY, et al. Milder disease stage in patients with primary biliary cholangitis over a 44-year period: A changing natural history. Hepatology. 2017.
11. Ludwig J, Dickson ER, McDonald GS. Staging of chronic nonsuppurative destructive cholangitis (syndrome of primary biliary cirrhosis). Virchows Arch A Pathol Anat Histol. 1978;379(2):103-12.
12. Rubin E, Schaffner F, Popper H. Primary Biliary Cirrhosis. Chronic Non-Suppurative Destructive Cholangitis. Am J Pathol. 1965;46:387-407.
13. Scheuer P. Primary biliary cirrhosis. Proc R Soc Med. 1967;60(12):1257-60.
14. Corpechot C, Abenavoli L, Rabahi N, Chretien Y, Andreani T, Johanet C, et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology. 2008;48(3):871-7.
15. Kumagi T, Guindi M, Fischer SE, Arenovich T, Abdalian R, Coltescu C, et al. Baseline ductopenia and treatment response predict long-term histological

progression in primary biliary cirrhosis. Am J Gastroenterol. 2010;105(10):2186-94.
16. Vleggaar FP, van Buuren HR, Zondervan PE, ten Kate FJ, Hop WC, Dutch Multicentre PBCsg. Jaundice in non-cirrhotic primary biliary cirrhosis: the premature ductopenic variant. Gut. 2001;49(2):276-81.
17. Kakuda Y, Harada K, Sawada-Kitamura S, Ikeda H, Sato Y, Sasaki M, et al. Evaluation of a new histologic staging and grading system for primary biliary cirrhosis in comparison with classical systems. Hum Pathol. 2013;44(6):1107-17.
18. Nakanuma Y, Zen Y, Harada K, Sasaki M, Nonomura A, Uehara T, et al. Application of a new histological staging and grading system for primary biliary cirrhosis to liver biopsy specimens: Interobserver agreement. Pathol Int. 2010;60(3):167-74.
19. Wendum D, Boelle PY, Bedossa P, Zafrani ES, Charlotte F, Saint-Paul MC, et al. Primary biliary cirrhosis: proposal for a new simple histological scoring system. Liver Int. 2015;35(2):652-9.
20. Carbone M, Mells GF, Pells G, Dawwas MF, Newton JL, Heneghan MA, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. Gastroenterology. 2013;144(3):560-9 e7; quiz e13-4.
21. Corpechot C, Carrat F, Poupon R, Poupon RE. Primary biliary cirrhosis: incidence and predictive factors of cirrhosis development in ursodiol-treated patients. Gastroenterology. 2002;122(3):652-8.
22. Ozaslan E, Efe C, Heurgue-Berlot A, Kav T, Masi C, Purnak T, et al. Factors associated with response to therapy and outcome of patients with primary biliary cirrhosis with features of autoimmune hepatitis. Clin Gastroenterol Hepatol. 2014;12(5):863-9.
23. Zeman MV, Hirschfield GM. Autoantibodies and liver disease: uses and abuses. Can J Gastroenterol. 2010;24(4):225-31.
24. Corpechot C, Carrat F, Poujol-Robert A, Gaouar F, Wendum D, Chazouilleres O, et al. Noninvasive elastography-based assessment of liver fibrosis progression and prognosis in primary biliary cirrhosis. Hepatology. 2012;56(1):198-208.
25. Floreani A, Cazzagon N, Martines D, Cavalletto L, Baldo V, Chemello L. Performance and utility of transient elastography and noninvasive markers of liver fibrosis in primary biliary cirrhosis. Dig Liver Dis. 2011;43(11):887-92.
26. Murtaugh PA, Dickson ER, Van Dam GM, Malinchoc M, Grambsch PM, Langworthy AL, et al. Primary biliary cirrhosis: prediction of short-term survival based on repeated patient visits. Hepatology. 1994;20(1 Pt 1):126-34.
27. ter Borg PC, Schalm SW, Hansen BE, van Buuren HR, Dutch PBCSG. Prognosis of ursodeoxycholic Acid-treated patients with primary biliary cirrhosis. Results of a 10-yr cohort study involving 297 patients. Am J Gastroenterol. 2006;101(9):2044-50.
28. Shapiro JM, Smith H, Schaffner F. Serum bilirubin: a prognostic factor in primary biliary cirrhosis. Gut. 1979;20(2):137-40.
29. Lammers WJ, van Buuren HR, Hirschfield GM, Janssen HL, Invernizzi P, Mason AL, 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(6):1338-49 e5; quiz e15.

30. Corpechot C, Chazouilleres O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. J Hepatol. 2011;55(6):1361-7.
31. Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. Gastroenterology. 2006;130(3):715-20.
32. Lammers WJ, Hirschfield GM, Corpechot C, Nevens F, Lindor KD, Janssen HL, 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(7):1804-12 e4.
33. Trivedi PJ, Lammers WJ, van Buuren HR, Pares A, Floreani A, Janssen HL, et al. Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study. Gut. 2016;65(2):321-9.
34. Poupon R, Chretien Y, Poupon RE, Ballet F, Calmus Y, Darnis F. Is ursodeoxycholic acid an effective treatment for primary biliary cirrhosis? Lancet. 1987;1(8537):834-6.
35. Poupon RE, Balkau B, Eschwege E, Poupon R. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. N Engl J Med. 1991;324(22):1548-54.
36. Heathcote EJ, Cauch-Dudek K, Walker V, Bailey RJ, Blendis LM, Ghent CN, et al. The Canadian Multicenter Double-blind Randomized Controlled Trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology. 1994;19(5):1149-56.
37. Eriksson LS, Olsson R, Glauman H, Prytz H, Befrits R, Ryden BO, et al. Ursodeoxycholic acid treatment in patients with primary biliary cirrhosis. A Swedish multicentre, double-blind, randomized controlled study. Scand J Gastroenterol. 1997;32(2):179-86.
38. Batts KP, Jorgensen RA, Dickson ER, Lindor KD. Effects of ursodeoxycholic acid on hepatic inflammation and histological stage in patients with primary biliary cirrhosis. Am J Gastroenterol. 1996;91(11):2314-7.
39. Poupon RE, Lindor KD, Pares A, Chazouilleres O, Poupon R, Heathcote EJ. Combined analysis of the effect of treatment with ursodeoxycholic acid on histologic progression in primary biliary cirrhosis. J Hepatol. 2003;39(1):12-6.
40. Lindor KD, Jorgensen RA, Therneau TM, Malinchoc M, Dickson ER. Ursodeoxycholic acid delays the onset of esophageal varices in primary biliary cirrhosis. Mayo Clin Proc. 1997;72(12):1137-40.
41. Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. The UDCA-PBC Study Group. N Engl J Med. 1994;330(19):1342-7.
42. Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology. 1997;113(3):884-90.
43. Combes B, Carithers RL, Jr., Maddrey WC, Lin D, McDonald MF, Wheeler DE, et al. A randomized, double-blind, placebo-controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology. 1995;22(3):759-66.
44. Vuoristo M, Farkkila M, Karvonen AL, Leino R, Lehtola J, Makinen J, et al. A placebo-controlled trial of primary biliary cirrhosis treatment with colchicine and ursodeoxycholic acid. Gastroenterology. 1995;108(5):1470-8.

45. Papatheodoridis GV, Hadziyannis ES, Deutsch M, Hadziyannis SJ. Ursodeoxycholic acid for primary biliary cirrhosis: final results of a 12-year, prospective, randomized, controlled trial. Am J Gastroenterol. 2002;97(8):2063-70.
46. Rudic JS, Poropat G, Krstic MN, Bjelakovic G, Gluud C. Ursodeoxycholic acid for primary biliary cirrhosis. Cochrane Database Syst Rev. 2012;12:CD000551.
47. Angulo P, Dickson ER, Therneau TM, Jorgensen RA, Smith C, DeSotel CK, et al. Comparison of three doses of ursodeoxycholic acid in the treatment of primary biliary cirrhosis: a randomized trial. J Hepatol. 1999;30(5):830-5.
48. Shi J, Wu C, Lin Y, Chen YX, Zhu L, Xie WF. Long-term effects of mid-dose ursodeoxycholic acid in primary biliary cirrhosis: a meta-analysis of randomized controlled trials. Am J Gastroenterol. 2006;101(7):1529-38.
49. Chan CW, Gunsar F, Feudjo M, Rigamonti C, Vlachogiannakos J, Carpenter JR, et al. Long-term ursodeoxycholic acid therapy for primary biliary cirrhosis: a follow-up to 12 years. Aliment Pharmacol Ther. 2005;21(3):217-26.
50. Trivedi PJ, Corpechot C, Pares A, Hirschfield GM. Risk stratification in autoimmune cholestatic liver diseases: Opportunities for clinicians and trialists. Hepatology. 2016;63(2):644-59.
51. Kuiper EM, Hansen BE, de Vries RA, den Ouden-Muller JW, van Ditzhuijsen TJ, Haagsma EB, et al. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. Gastroenterology. 2009;136(4):1281-7.
52. Trivedi PJ, Bruns T, Cheung A, Li KK, Kittler C, Kumagi T, et al. Optimising risk stratification in primary biliary cirrhosis: AST/platelet ratio index predicts outcome independent of ursodeoxycholic acid response. J Hepatol. 2014;60(6):1249-58.
53. Papastergiou V, Tsochatzis EA, Rodriguez-Peralvarez M, Thalassinos E, Pieri G, Manousou P, et al. Biochemical criteria at 1 year are not robust indicators of response to ursodeoxycholic acid in early primary biliary cirrhosis: results from a 29-year cohort study. Aliment Pharmacol Ther. 2013;38(11-12):1354-64.
54. Carbone M, Sharp SJ, Flack S, Paximadas D, Spiess K, Adgey C, 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(3):930-50.
55. Hirschfield GM, Mason A, Luketic V, Lindor K, Gordon SC, Mayo M, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. Gastroenterology. 2015;148(4):751-61 e8.
56. Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med. 2016;375(7):631-43.
57. Kowdley KV, Luketic V, Chapman R, Hirschfield GM, Poupon R, Schramm C, et al. A randomized trial of obeticholic acid monotherapy in patients with primary biliary cholangitis. Hepatology. 2017.
58. Grigorian AY, Mardini HE, Corpechot C, Poupon R, Levy C. Fenofibrate is effective adjunctive therapy in the treatment of primary biliary cirrhosis: A meta-analysis. Clin Res Hepatol Gastroenterol. 2015;39(3):296-306.

59. Cheung AC, Lapointe-Shaw L, Kowgier M, Meza-Cardona J, Hirschfield GM, Janssen HL, et al. Combined ursodeoxycholic acid (UDCA) and fenofibrate in primary biliary cholangitis patients with incomplete UDCA response may improve outcomes. Aliment Pharmacol Ther. 2016;43(2):283-93.
60. Hosonuma K, Sato K, Yamazaki Y, Yanagisawa M, Hashizume H, Horiguchi N, 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. Am J Gastroenterol. 2015;110(3):423-31.
61. Lens S, Leoz M, Nazal L, Bruguera M, Pares A. Bezafibrate normalizes alkaline phosphatase in primary biliary cirrhosis patients with incomplete response to ursodeoxycholic acid. Liver Int. 2014;34(2):197-203.
62. Reig A, Sese P, Pares A. Effects of Bezafibrate on Outcome and Pruritus in Primary Biliary Cholangitis With Suboptimal Ursodeoxycholic Acid Response. Am J Gastroenterol. 2018;113(1):49-55.
63. Hegade VS, Khanna A, Walker LJ, Wong LL, Dyson JK, Jones DEJ. Long-Term Fenofibrate Treatment in Primary Biliary Cholangitis Improves Biochemistry but Not the UK-PBC Risk Score. Dig Dis Sci. 2016;61(10):3037-44.
64. Corpechot C CO, Rousseau A,Guyader D, Habersetzer F, Mathurin P et al. A 2-year multicenter, double-blind, randomized, placebo-controlled study of bezafibrate for the treatment of primary biliary cholangitis in patients with inadequate biochemical response to ursodeoxycholic acid therapy (Bezurso). Journal of Hepatology 2017;66(1):S89.
65. Jones D, Boudes PF, Swain MG, Bowlus CL, Galambos MR, Bacon BR, et al. Seladelpar (MBX-8025), a selective PPAR-delta agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study. Lancet Gastroenterol Hepatol. 2017;2(10):716-26.
66. Hirschfield GM, Gershwin ME, Strauss R, Mayo MJ, Levy C, Zou B, et al. Ustekinumab for patients with primary biliary cholangitis who have an inadequate response to ursodeoxycholic acid: A proof-of-concept study. Hepatology. 2016;64(1):189-99.
67. Mousa HS, Carbone M, Malinverno F, Ronca V, Gershwin ME, Invernizzi P. Novel therapeutics for primary biliary cholangitis: Toward a disease-stage-based approach. Autoimmun Rev. 2016;15(9):870-6.
68. Harms eaM. Pharmacological therapies for Primary biliary cholangitis Best Practice and Research: Clinical gastroenterology. 2018;32(1).
69. Huet PM, Vincent C, Deslaurier J, Cote J, Matsutami S, Boileau R, et al. Portal hypertension and primary biliary cirrhosis: effect of long-term ursodeoxycholic acid treatment. Gastroenterology. 2008;135(5):1552-60.
70. Joshita S, Umemura T, Ota M, Tanaka E. AST/platelet ratio index associates with progression to hepatic failure and correlates with histological fibrosis stage in Japanese patients with primary biliary cirrhosis. J Hepatol. 2014;61(6):1443-5.
71. Cheung KS, Seto WK, Fung J, Lai CL, Yuen MF. Prognostic Factors for Transplant-Free Survival and Validation of Prognostic Models in Chinese Patients with Primary Biliary Cholangitis Receiving Ursodeoxycholic Acid. Clin Transl Gastroenterol. 2017;8(6):e100.

72. Ikeda F, Okamoto R, Baba N, Fujioka S, Shoji B, Yabushita K, et al. Prevalence and associated factors with esophageal varices in early primary biliary cirrhosis. J Gastroenterol Hepatol. 2012;27(8):1320-8.
73. Patanwala I, McMeekin P, Walters R, Mells G, Alexander G, Newton J, et al. A validated clinical tool for the prediction of varices in PBC: the Newcastle Varices in PBC Score. J Hepatol. 2013;59(2):327-35.
74. Trivedi PJ, Hirschfield GM. Primary biliary cirrhosis: Renaming primary biliary cirrhosis-clarity or confusion? Nat Rev Gastroenterol Hepatol. 2015;12(12):678-9.
75. Harms MH, Lammers WJ, Thorburn D, Corpechot C, Invernizzi P, Janssen HLA, et al. Major Hepatic Complications in Ursodeoxycholic Acid-Treated Patients With Primary Biliary Cholangitis: Risk Factors and Time Trends in Incidence and Outcome. Am J Gastroenterol. 2017.
76. Shi TY, Zhang LN, Chen H, Wang L, Shen M, Zhang X, et al. Risk factors for hepatic decompensation in patients with primary biliary cirrhosis. World J Gastroenterol. 2013;19(7):1111-8.
77. Sharma SA, Kowgier M, Hansen BE, Brouwer WP, Maan R, Wong D, et al. Toronto HCC risk index: A validated scoring system to predict 10-year risk of HCC in patients with cirrhosis. J Hepatol. 2017.
78. Rong G, Wang H, Bowlus CL, Wang C, Lu Y, Zeng Z, et al. Incidence and risk factors for hepatocellular carcinoma in primary biliary cirrhosis. Clin Rev Allergy Immunol. 2015;48(2-3):132-41.
79. Cheung KS, Seto WK, Fung J, Mak LY, Lai CL, Yuen MF. Prediction of hepatocellular carcinoma development by aminotransferase to platelet ratio index in primary biliary cholangitis. World J Gastroenterol. 2017;23(44):7863-74.
80. Phillips JR, Angulo P, Petterson T, Lindor KD. Fat-soluble vitamin levels in patients with primary biliary cirrhosis. Am J Gastroenterol. 2001;96(9):2745-50.
81. Guanabens N, Pares A, Marinoso L, Brancos MA, Piera C, Serrano S, et al. Factors influencing the development of metabolic bone disease in primary biliary cirrhosis. Am J Gastroenterol. 1990;85(10):1356-62.
82. Menon KV, Angulo P, Weston S, Dickson ER, Lindor KD. Bone disease in primary biliary cirrhosis: independent indicators and rate of progression. J Hepatol. 2001;35(3):316-23.
83. Ruiz-Gaspa S, Dubreuil M, Guanabens N, Combalia A, Peris P, Monegal A, et al. Ursodeoxycholic acid decreases bilirubin-induced osteoblast apoptosis. Eur J Clin Invest. 2014;44(12):1206-14.
84. Mells GF, Pells G, Newton JL, Bathgate AJ, Burroughs AK, Heneghan MA, et al. Impact of primary biliary cirrhosis on perceived quality of life: the UK-PBC national study. Hepatology. 2013;58(1):273-83.
85. Jones DE, Al-Rifai A, Frith J, Patanwala I, Newton JL. The independent effects of fatigue and UDCA therapy on mortality in primary biliary cirrhosis: results of a 9 year follow-up. J Hepatol. 2010;53(5):911-7.
86. Griffiths L, Jones DE. Pathogenesis of primary biliary cirrhosis and its fatigue. Dig Dis. 2014;32(5):615-25.
87. Jones D. Symptoms in PBC – Pathophysiology and Management. Best Practice and Research: Clinical gastroenterology. 2018;32(1).
88. Kubota J, Ikeda F, Terada R, Kobashi H, Fujioka S, Okamoto R, et al. Mortality rate of patients with asymptomatic primary biliary cirrhosis diagnosed

at age 55 years or older is similar to that of the general population. J Gastroenterol. 2009;44(9):1000-6.
89. Dyson JK, Hirschfield GM, Adams DH, Beuers U, Mann DA, Lindor KD, et al. Novel therapeutic targets in primary biliary cirrhosis. Nat Rev Gastroenterol Hepatol. 2015;12(3):147-58.
90. Trivedi PJ, Kumagi T, Al-Harthy N, Coltescu C, Ward S, Cheung A, et al. Good maternal and fetal outcomes for pregnant women with primary biliary cirrhosis. Clin Gastroenterol Hepatol. 2014;12(7):1179-85 e1.
91. Cheung AC LW, Hirschfield GM, Invernizzi P Mason AL, Ponsioen CL et al. Age, bilirubin and albumin, regardless of sex, are the strongest independent predictors of biochemical response and transplantation-free survival in patients with primary biliary cirrhosis. Journal of Hepatology. 2015;62:S798.
92. Turchany JM, Uibo R, Kivik T, Van de Water J, Prindiville T, Coppel RL, et al. A study of antimitochondrial antibodies in a random population in Estonia. Am J Gastroenterol. 1997;92(1):124-6.
93. Shibata M, Onozuka Y, Morizane T, Koizumi H, Kawaguchi N, Miyakawa H, et al. Prevalence of antimitochondrial antibody in Japanese corporate workers in Kanagawa prefecture. J Gastroenterol. 2004;39(3):255-9.
94. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ, et al. Primary biliary cirrhosis. Hepatology. 2009;50(1):291-308.
95. Mattalia A, Quaranta S, Leung PS, Bauducci M, Van de Water J, Calvo PL, et al. Characterization of antimitochondrial antibodies in health adults. Hepatology. 1998;27(3):656-61.
96. Dahlqvist G, Gaouar F, Carrat F, Meurisse S, Chazouilleres O, Poupon R, et al. Large-scale characterization study of patients with antimitochondrial antibodies but nonestablished primary biliary cholangitis. Hepatology. 2017;65(1):152-63.
97. Nakamura M, Kondo H, Mori T, Komori A, Matsuyama M, Ito M, et al. Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis. Hepatology. 2007;45(1):118-27.
98. Yang F, Yang Y, Wang Q, Wang Z, Miao Q, Xiao X, et al. The risk predictive values of UK-PBC and GLOBE scoring system in Chinese patients with primary biliary cholangitis: the additional effect of anti-gp210. Aliment Pharmacol Ther. 2017;45(5):733-43.
99. Floreani A, Franceschet I, Cazzagon N, Spinazze A, Buja A, Furlan P, et al. Extrahepatic autoimmune conditions associated with primary biliary cirrhosis. Clin Rev Allergy Immunol. 2015;48(2-3):192-7.
100. Liaskou E, Hirschfield GM, Gershwin ME. Mechanisms of tissue injury in autoimmune liver diseases. Semin Immunopathol. 2014;36(5):553-68.
101. Trivedi PJ, Hirschfield GM. Review article: overlap syndromes and autoimmune liver disease. Aliment Pharmacol Ther. 2012;36(6):517-33.
102. Poupon R, Chazouilleres O, Corpechot C, Chretien Y. Development of autoimmune hepatitis in patients with typical primary biliary cirrhosis. Hepatology. 2006;44(1):85-90.
103. O'Brien C, Joshi S, Feld JJ, Guindi M, Dienes HP, Heathcote EJ. Long-term follow-up of antimitochondrial antibody-positive autoimmune hepatitis. Hepatology. 2008;48(2):550-6.
104. Dinani AM, Fischer SE, Mosko J, Guindi M, Hirschfield GM. Patients with autoimmune hepatitis who have antimitochondrial antibodies need long-term

follow-up to detect late development of primary biliary cirrhosis. Clin Gastroenterol Hepatol. 2012;10(6):682-4.
105. Silveira MG, Talwalkar JA, Angulo P, Lindor KD. Overlap of autoimmune hepatitis and primary biliary cirrhosis: long-term outcomes. Am J Gastroenterol. 2007;102(6):1244-50.
106. Joshi S, Cauch-Dudek K, Wanless IR, Lindor KD, Jorgensen R, Batts K, et al. Primary biliary cirrhosis with additional features of autoimmune hepatitis: response to therapy with ursodeoxycholic acid. Hepatology. 2002;35(2):409-13.
107. Lee JC, Lyons PA, McKinney EF, Sowerby JM, Carr EJ, Bredin F, et al. Gene expression profiling of CD8+ T cells predicts prognosis in patients with Crohn disease and ulcerative colitis. J Clin Invest. 2011;121(10):4170-9.
108. Gores GJ WR, Dickson ER, Zinsmeister AR, Jorgensen RA, Langworthy A. Prospective evaluation of esophageal varices in primary biliary cirrhosis: development, natural history and influence of survival. Gastroenterology. 1989;96:1552-9.
109. Angulo P, Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Kamath PS, et al. Utilization of the Mayo risk score in patients with primary biliary cirrhosis receiving ursodeoxycholic acid. Liver. 1999;19(2):115-21.
110. Levy C, Zein CO, Gomez J, Soldevila-Pico C, Firpi R, Morelli G, et al. Prevalence and predictors of esophageal varices in patients with primary biliary cirrhosis. Clin Gastroenterol Hepatol. 2007;5(7):803-8.
111. Ali AH, Sinakos E, Silveira MG, Jorgensen RA, Angulo P, Lindor KD. Varices in early histological stage primary biliary cirrhosis. J Clin Gastroenterol. 2011;45(7):e66-71.
112. Abraham SC, Kamath PS, Eghtesad B, Demetris AJ, Krasinskas AM. Liver transplantation in precirrhotic biliary tract disease: Portal hypertension is frequently associated with nodular regenerative hyperplasia and obliterative portal venopathy. Am J Surg Pathol. 2006;30(11):1454-61.
113. Navasa M, Pares A, Bruguera M, Caballeria J, Bosch J, Rodes J. Portal hypertension in primary biliary cirrhosis. Relationship with histological features. J Hepatol. 1987;5(3):292-8.
114. Colina F, Pinedo F, Solis JA, Moreno D, Nevado M. Nodular regenerative hyperplasia of the liver in early histological stages of primary biliary cirrhosis. Gastroenterology. 1992;102(4 Pt 1):1319-24.
115. Bressler B, Pinto R, El-Ashry D, Heathcote EJ. Which patients with primary biliary cirrhosis or primary sclerosing cholangitis should undergo endoscopic screening for oesophageal varices detection? Gut. 2005;54(3):407-10.
116. Tanaka A HJ, Takikawa H and Japan-PBC consortium. Incidence and predictive factors of decompensating events in primary biliary cholangitis-experiences of 3194 cases in Japan Journal of Hepatology. 2016;64:S425-S630.
117. Silveira MG, Suzuki A, Lindor KD. Surveillance for hepatocellular carcinoma in patients with primary biliary cirrhosis. Hepatology. 2008;48(4):1149-56.
118. Suzuki A, Lymp J, Donlinger J, Mendes F, Angulo P, Lindor K. Clinical predictors for hepatocellular carcinoma in patients with primary biliary cirrhosis. Clin Gastroenterol Hepatol. 2007;5(2):259-64.
119. Jones DE, Metcalf JV, Collier JD, Bassendine MF, James OF. Hepatocellular carcinoma in primary biliary cirrhosis and its impact on outcomes. Hepatology. 1997;26(5):1138-42.

120. Cavazza A, Caballeria L, Floreani A, Farinati F, Bruguera M, Caroli D, et al. Incidence, risk factors, and survival of hepatocellular carcinoma in primary biliary cirrhosis: comparative analysis from two centers. Hepatology. 2009;50(4):1162-8.
121. Harada K, Hirohara J, Ueno Y, Nakano T, Kakuda Y, Tsubouchi H, et al. Incidence of and risk factors for hepatocellular carcinoma in primary biliary cirrhosis: national data from Japan. Hepatology. 2013;57(5):1942-9.
122. Bjornsson E, Kalaitzakis E, Neuhauser M, Enders F, Maetzel H, Chapman RW, et al. Fatigue measurements in patients with primary biliary cirrhosis and the risk of mortality during follow-up. Liver Int. 2010;30(2):251-8.

ACKNOWLEDGEMENT

Declaration of personal and funding interests: AJ and PJT received institutional funding from the National Institute for Health Research Birmingham Liver Biomedical Research Unit.

Conflict of interest: None

The views expressed are those of the authors and not necessarily those of the national health system, the National Institute for Health Research or the Department of Health.

Figure 1

A

Barcelona	ALP ≤1 x ULN or decreased by ≥ 40%	At 1 year
Paris-I	ALP ≤3 x ULN and AST ≤2 x ULN and bilirubin <1 mg/dL	At 1 year
Rotterdam	Normalisation of abnormal bilirubin and/or albumin	At 1 year
Toronto	ALP <1.67 x ULN	At 2 years
Paris II	ALP ≤1.5 x ULN and AST ≤1.5 x ULN and bilirubin <1 mg/dL	At 1 year

B

Beijing	Paris-I, Barcelona or Toronto criteria, evaluated at earlier timepoints	3 - 6 months
APRI-r1	Biochemical response (Barcelona, Paris I/II, or Toronto) and APRI ≤0.54	1 year

C

GLOBE	Prognostic index comprising age, and bilirubin, ALP, albumin, and platelet count	1 year
UK-PBC	Prognostic index comprising albumin platelet count, bilirubin, ALT or AST, and ALP	1 year

Figure 2

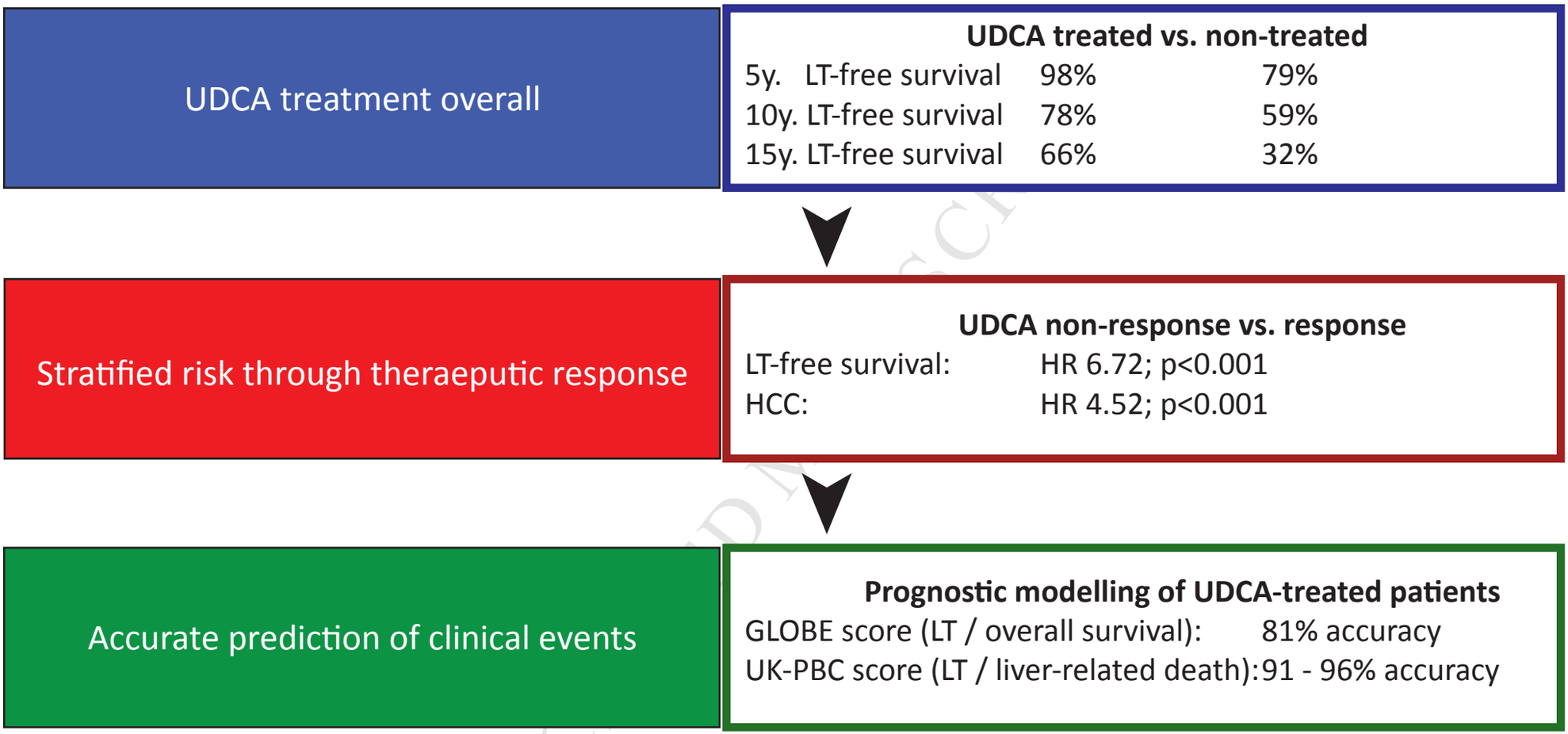


Figure 3

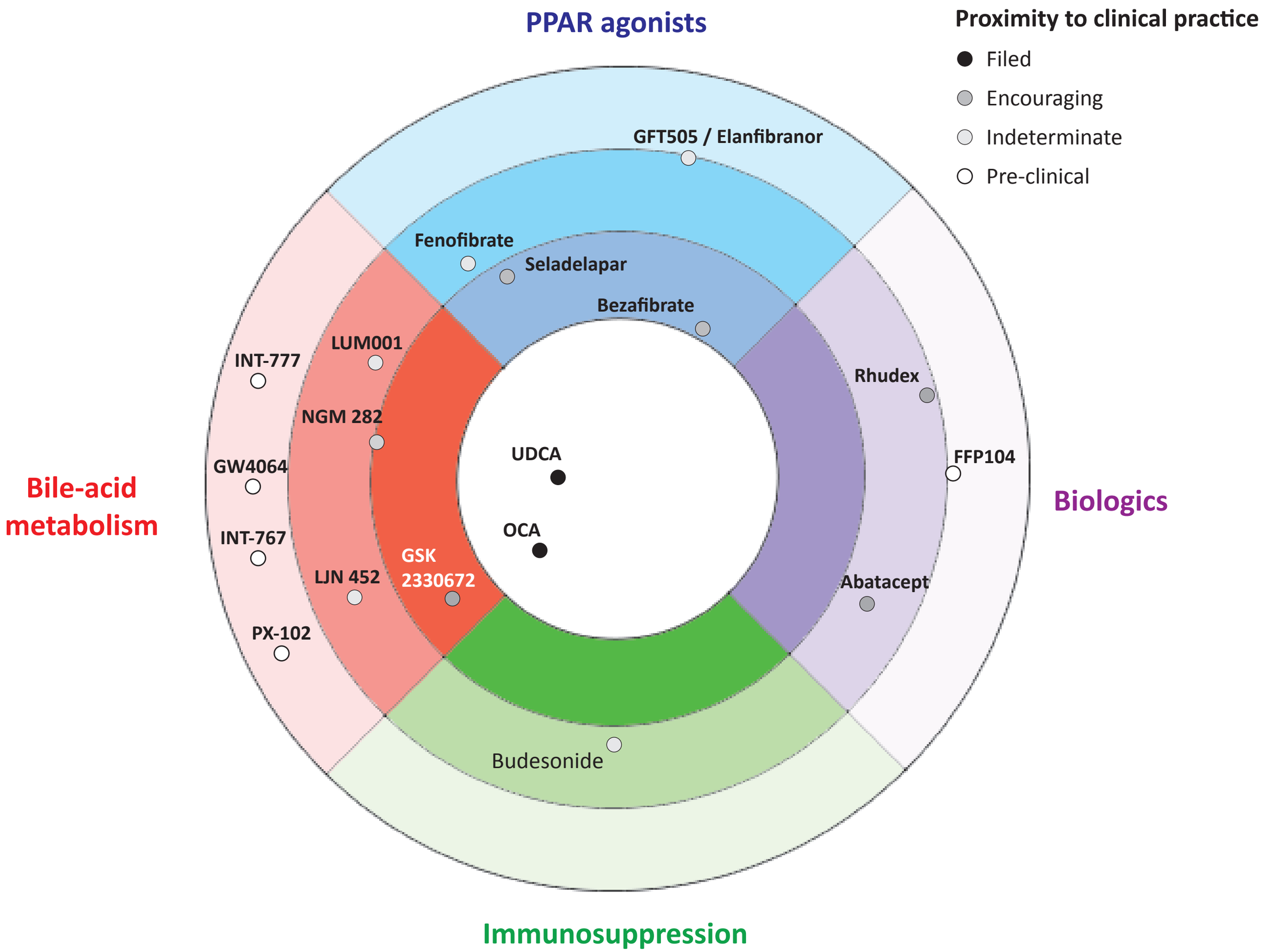


Figure 4