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REVIEW

Disease-modifying therapies and symptomatic management for primary biliary cholangitis

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Abstract

Primary biliary cholangitis is a chronic condition characterised by autoimmune destruction of intralobular bile ducts. Publications have shown widespread gaps in the care of patients with primary biliary cholangitis. This article reviews the literature regarding currently licensed first- and second-line therapies and evaluates therapeutic options for symptomatic management of primary biliary cholangitis.

Ursodeoxycholic acid is recommended for all patients with primary biliary cholangitis, with obeticholic acid available as second-line therapy, both having demonstrated safety and efficacy. Potential disease-modifying therapies, such as fibrates and budesonide, require further investigation before licensing. Cholestyramine is first-line therapy for pruritus, albeit with limited evidence and common side-effects. There is no licensed therapy for primary biliary cholangitis-related fatigue; treating underlying causes where applicable is recommended.

Disease-modifying and symptomatic therapies must be considered in tandem when managing patients with primary biliary cholangitis. Emerging therapies show initial promise but further randomised trials with long-term follow up are required to evaluate their efficacy as single or combination therapies.

Key words: Cirrhosis; Obeticholic acid; Primary biliary cholangitis; Primary biliary cirrhosis; Ursodeoxycholic acid

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Introduction

Primary biliary cholangitis (formerly primary biliary cirrhosis) is the most common chronic autoimmune disease of the liver. Publications have shown widespread gaps in the care of patients with primary biliary cholangitis (Sivakumar et al, 2021). This review evaluates the literature regarding licensed first- and second-line therapies for 'classical' primary biliary cholangitis, discusses therapeutic options for symptomatic management of primary biliary cholangitis and provides scope for future work.

Up to 60% of patients are asymptomatic at diagnosis, with fatigue and pruritus commonly reported in those with symptoms. Other possible presentations include cholestatic jaundice and characteristic features of advanced cirrhotic liver disease (Hirschfield et al, 2018).

Classical primary biliary cholangitis is typically diagnosed between the age of 45 and 69 years using criteria outlined in Table 1 (Hirschfield et al, 2018).

Liver biochemistry and primary biliary cholangitis-specific serological markers are preferred as they provide high diagnostic accuracy. Liver biopsy is only recommended in the absence of diagnostic autoantibodies or clinical suspicion of co-existing liver disease (Hirschfield et al, 2018).

Management of primary biliary cholangitis involves disease-modifying pharmacotherapy using ursodeoxycholic acid and obeticholic acid as first- and second-line therapies respectively. Treatment response and prognosis are commonly assessed by biomarkers of cholestasis, namely alkaline phosphatase and bilirubin. In select patients with end-stage liver disease or intractable pruritus, liver transplantation is indicated. Additional symptomatic management is needed to improve patients' health-related quality of life (Hirschfield et al, 2018). Figure 1 summarises the management options discussed in this review. All pharmacological therapies are administered orally.

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Table 1. Diagnostic criteria for primary biliary cholangitis

After exclusion of extrahepatic biliary obstruction or other comorbidity affecting the liver, a diagnosis of primary biliary cholangitis can be established by fulfilling at least two of the following criteria:	
Diagnostic modality	**Criteria**
Liver biochemistry	Presence of cholestatic liver biochemistry with significant elevation of alkaline phosphatase and/or gamma-glutamyl transferase
Autoantibodies	Presence of anti-mitochondrial antibodies at a titre of 1:40 or higher (or presence of other primary biliary cholangitis-specific autoantibodies (sp100 or gp210), if negative for anti-mitochondrial antibodies)
Liver biopsy	Histopathological evidence of primary biliary cholangitis (ie non-suppurative destructive granulomatous lymphocytic cholangitis and destruction of intralobular bile ducts)

From Hirschfield et al (2018)

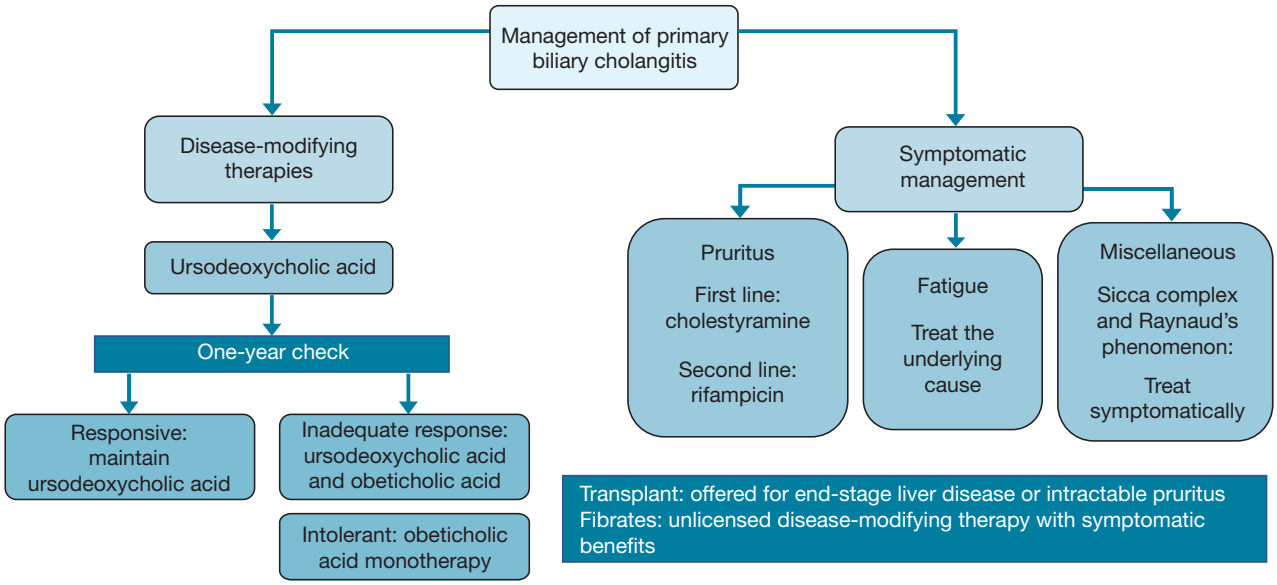

Figure 1. Disease-modifying therapies and symptomatic management in patients with primary biliary cholangitis. Management of disease complications is not included. Patients intolerant of ursodeoxycholic acid may be identified before the 1-year check.

Management

Disease-modifying therapies

Ursodeoxycholic acid

Ursodeoxycholic acid, a hydrophilic bile acid, is first-line therapy at a dose of 13–15 mg/kg/day recommended for all patients with primary biliary cholangitis (Hirschfield et al, 2018). Ursodeoxycholic acid has several proposed mechanisms of action, one being domination of the bile acid pool to reduce the proportion of harmful endogenous bile acids (Poupon et al, 1994). In primary biliary cholangitis, chronic cholestasis causes hepatotoxicity by retaining hydrophobic bile acids in the liver (Lindor et al, 1994). Giving ursodeoxycholic acid means that the predominantly hydrophilic pool causes less hepatocellular damage, slowing disease progression (Heathcote et al, 1994).

The first large, randomised controlled trial (n=129) investigated the efficacy of ursodeoxycholic acid vs placebo (Poupon et al, 1994). At the 2-year interim analysis, evidence of benefit led to the placebo group being switched to intervention. The subsequent 2 years compared two groups of patients receiving ursodeoxycholic acid, inevitably underestimating its efficacy. Response to treatment, defined by absence of hyperbilirubinaemia, complications or adverse events, was significantly higher in the original intervention group (P<0.002), and clinical outcomes of transplantation or mortality were lower in this group at 4 years (P=0.005). This suggests that starting ursodeoxycholic acid earlier may delay disease progression. However, this trial remained underpowered to reliably measure outcomes such as transplantation and mortality in a slowly progressing disease such as primary biliary cholangitis.

A randomised, placebo-controlled trial (n=180) found significant improvements in bilirubin levels in patients taking ursodeoxycholic acid at 1 (P<0.0001) and 2 years (P=0.004) (Lindor et al, 1994). No significant difference in transplantation or mortality was observed, with no toxicity or adverse events reported. Again, the study remained underpowered to evaluate differences in transplantation and survival. Unlike the previous study, this trial examined early disease (portal hepatitis and/or periportal hepatitis) and advanced disease (septal fibrosis and/or bridging necrosis and/or cirrhosis), finding treatment with ursodeoxycholic acid to be effective in reducing bilirubin levels in both disease severities (Lindor et al, 1994).

Another randomised controlled trial (n=220) found significant reductions in bilirubin levels from 3 months onwards in patients receiving ursodeoxycholic acid (P<0.001) (Heathcote et al, 1994). Alkaline phosphatase and alanine transaminase levels also improved (P<0.001), demonstrating efficacy against placebo. Akin to Lindor et al (1994), no significant difference in transplantation or mortality was observed between the two groups (Heathcote et al, 1994). However, all patients had histologically confirmed primary biliary cholangitis, whereas diagnosis in current practice rarely requires histology, thus limiting applicability of these findings (Hirschfield et al, 2018). Similar to previous studies, ursodeoxycholic acid did not improve symptoms or lead to drug toxicity.

Data from these trials were combined to evaluate the effect of treatment with ursodeoxycholic acid on transplantation and survival in a sufficiently-powered pooled analysis (Poupon et al, 1997). Transplant-free survival was higher in patients taking ursodeoxycholic acid compared with those taking placebo (P<0.001). A subsequent randomised controlled trial (n=155) investigated three safe, well-tolerated doses (5–7, 13–15 and 23–25 mg/kg/day) (Angulo et al, 1999). Improvements in alkaline phosphatase (P=0.0001) and aspartate transaminase levels (P=0.0001), Mayo risk score (P=0.002) and ursodeoxycholic acid enrichment in the duodenal bile acid pool (P=0.0001) were found only in those taking the two higher doses but not in those taking 5–7 mg/kg/day. To achieve maximum efficacy at minimum cost, 13–15 mg/kg/day was recommended as the dose of choice, supporting conclusions drawn by Poupon et al (1997).

A randomised controlled trial comparing ursodeoxycholic acid with placebo (n=103) found the drug to be associated with a five-fold lower annual progression rate from early disease to extensive fibrosis or cirrhosis (P<0.002) (Corpechot et al, 2000). Another key histological finding demonstrated the inability of ursodeoxycholic acid to reverse disease progression. Unlike others, this trial was adequately powered allowing for definitive disease staging. However, short-term biochemical improvements from ursodeoxycholic acid therapy may not be reflected in histology (Lindor et al, 1994), limiting the utility of liver biopsy in assessing the effects of treatment in patients with mild disease.

Ursodeoxycholic acid is an efficacious disease-modifying therapy but does not improve symptoms. It is generally well-tolerated with few adverse events. Higher-powered studies with longer follow up are needed to evaluate the role of long-term ursodeoxycholic acid in management of primary biliary cholangitis. An ongoing multicentre cohort study investigating the efficacy, safety and tolerability of treatment (https://clinicaltrials.gov/ct2/show/NCT04076527) and a phase IV randomised controlled trial measuring the efficacy of ursodeoxycholic acid at standard and reduced doses (https://clinicaltrials.gov/ct2/show/NCT04650243) may provide further insights.

Obeticholic acid

The second-line therapy aimed at preventing progression of primary biliary cholangitis is obeticholic acid (initially 5 mg/day, titrated up to 10 mg/day as tolerated at 6 months). The key indications for use of obeticholic acid are as monotherapy in patients who cannot tolerate ursodeoxycholic acid or add-on therapy in patients responding inadequately to ursodeoxycholic acid (Hirschfield et al, 2018). The latter is required in up to 40% of patients (Hirschfield et al, 2015), with insufficient response at 1 year defined biochemically by the modified Toronto criteria (alkaline phosphatase >1.67× upper limit of normal and/or increased bilirubin levels) (Hirschfield et al, 2018). As non-responsiveness to ursodeoxycholic acid potentiates poorer transplant-free survival (Hirschfield et al, 2015), safe and effective alternative therapies are needed.

Obeticholic acid potently and selectively binds the farnesoid X receptor to suppress bile acid synthesis and upregulate bile acid transporters (Kowdley et al, 2018). The net effect facilitates choleresis, which protects hepatocytes from bile acid toxicity (Nevens et al, 2016). This mechanism of action differs from that of ursodeoxycholic acid, explaining the additional efficacy seen in combination therapy (Hirschfield et al, 2015).

Hirschfield et al (2015) investigated obeticholic acid in patients with primary biliary cholangitis (n=165) and found all doses to be superior to placebo in reducing alkaline phosphatase levels at 3 months (10 mg, 25 mg and 50 mg/day; P<0.0001). These improvements were maintained over a subsequent 12-month open-label extension. Despite promising findings, 10% of users discontinued the drug owing to severe pruritus. As pruritus is a prevalent symptom of primary biliary cholangitis (Hegade et al, 2015), this is a fundamental flaw of obeticholic acid therapy. Aside from mild to moderate nausea, no other substantial adverse events were documented.

A major strength of this trial was the highly representative study population; patients who displayed characteristics typical of primary biliary cholangitis were enrolled internationally (Hirschfield et al, 2015). All patients took concomitant ursodeoxycholic acid throughout the study, allowing generalisability to patients receiving combination therapy but rendering the findings inapplicable to those on obeticholic acid monotherapy. Additionally, the broad range of doses, which were adjusted as clinicians deemed necessary, introduced an unexplored confounding factor. Most notably, this study only investigated use of obeticholic acid over 1 year, which is the greatest limitation of a trial examining a lifelong disease.

To substantiate these findings, the POISE trial was conducted (n=216); a 12-month phase III randomised controlled trial comparing obeticholic acid with placebo (Nevens et al, 2016). This study also benefitted from an international cohort and multiple doses (5–10 mg and 10 mg/day). To further the phase II trial, several additional endpoints were analysed. Liver enzymes, alkaline phosphatase and total bilirubin levels decreased in those taking obeticholic acid compared with those taking placebo (P<0.001), but no difference was seen in fibrosis scores. Pruritus increased in a dose-dependent manner with obeticholic acid, reproducing earlier results (Hirschfield et al, 2015). Despite no significant reduction in symptoms, over 87% of patients taking obeticholic acid still deemed participation worthwhile (Nevens et al, 2016). Future studies should elucidate patient perceptions of long-term obeticholic acid use to better understand the impact of adverse events on adherence. Unfortunately, this study was underpowered to evaluate clinical outcomes, so larger sample sizes are needed in future trials. The trial was also limited by a short-term double-blind study period and 93% of participants taking combined therapy, questioning the reliability of their conclusions regarding efficacy of obeticholic acid monotherapy.

An international study investigated obeticholic acid monotherapy in patients with primary biliary cholangitis (Kowdley et al, 2018). In concordance with previous findings, alkaline phosphatase levels were reduced in patients taking obeticholic acid compared with placebo (P<0.0001), with reductions maintained over a 6-year open-label extension. However, the extensive use of ursodeoxycholic acid, combined with many patients initiating first-line therapy during the study, resulted in small sample sizes. Future studies would benefit from enrolling ursodeoxycholic acid-intolerant patients. As obeticholic acid monotherapy has proven biochemical efficacy, trials directly comparing ursodeoxycholic acid with obeticholic acid are warranted.

Overall, obeticholic acid effectively achieves primary biochemical endpoints, most notably reducing alkaline phosphatase levels. However, pruritus is commonly exacerbated in a dose-dependent manner. To provide clarity on long-term obeticholic acid use in patients with primary biliary cholangitis, the results of a 10-year phase IV trial are awaited (https://clinicaltrials.gov/ct2/show/NCT02308111).

Liver transplantation

Eligibility for liver transplantation in patients with primary biliary cholangitis typically requires a United Kingdom Model for End-Stage Liver Disease (UKELD) score ≥49 or a variant indication (such as intractable pruritus). Post-transplantation, patients have good survival (80–85% at 5 years) and improved health-related quality of life. Despite an increase in overall liver transplants, primary biliary cholangitis-specific transplantation

has declined over recent decades since the introduction of ursodeoxycholic acid. This may reflect improvements in pharmacological management of disease progression and detection of primary biliary cholangitis at an earlier stage (Carbone and Neuberger, 2014).

Recurrent primary biliary cholangitis post-transplant has been reported in 21–37% of recipients at 10 years and up to 43% at 15 years, with median time to recurrence between 3.5 and 5 years. Owing to various potential causes of elevated liver biochemical markers post-transplant and protocol liver biopsy no longer being commonly performed, the prevalence of recurrent primary biliary cholangitis is likely underestimated (Carbone and Neuberger, 2014).

Multicentre case series have demonstrated a decreased risk of recurrent primary biliary cholangitis with ursodeoxycholic acid and ciclosporin use post-transplant (Bosch et al, 2015; Montano-Loza et al, 2019). Contrary to previous findings (Carbone and Neuberger, 2014), a multicentre case series (n=785) found recurrent primary biliary cholangitis was significantly associated with graft loss and mortality (Montano-Loza et al, 2019). These findings warrant further study of prevention of recurrent primary biliary cholangitis with long-term follow up.

In summary, liver transplantation in indicated patients has proven efficacy, but recurrent primary biliary cholangitis occurs frequently post-transplant and may impact graft loss and mortality.

Emerging potential therapies

Fibric acid derivatives (fibrates)

Trials have found that fibrates, potent agonists of peroxisome proliferator-activated receptors, improve biochemistry and symptoms in patients with primary biliary cholangitis (Corpechot et al, 2018). Of note, ethical considerations require baseline ursodeoxycholic acid therapy to be given with both fibrates and placebo. A small pilot study (n=20) analysing fenofibrate (160 mg/day) showed a significant decrease in alkaline phosphatase (P<0.0001) and aspartate transaminase levels (P=0.0032). However, non-significant reductions in bilirubin and albumin levels, or pruritus, provided insufficient evidence to perform further randomised controlled trials (Levy et al, 2011).

Bezafibrate has been studied more extensively than fenofibrate. Elevated creatinine levels seen in multiple bezafibrate studies have raised concerns regarding nephrotoxicity, suggesting it may be inappropriate in patients with poor renal function (Hosonuma et al, 2015; Corpechot et al, 2018). One prospective randomised controlled trial found a significant increase in serum creatinine levels with bezafibrate (400 mg/day). However, alkaline phosphatase levels and Mayo risk score were significantly reduced, showing improved survival (log-rank P=0.057). This study benefitted from a long-term safety assessment, but its small sample size (n=27), unblinded nature and inclusion of primary biliary cholangitis patients with dyslipidaemia introduced bias, affecting the applicability (Hosonuma et al, 2015).

A larger randomised controlled trial (n=100) showed improved liver biochemistry (P<0.001) and reduced pruritus with 2 years of bezafibrate therapy (Corpechot et al, 2018). No difference in adverse events vs placebo was found. This multicentre trial was strengthened by including patients at all stages of primary biliary cholangitis. Overall, a meta-analysis showed that bezafibrate improved liver biochemistry, but was associated with increased adverse events (Yin et al, 2015). The small sample sizes, high heterogeneity and high risk of bias in studies stress the need to investigate long-term prognosis and adverse events in bezafibrate therapy.

Overall, there is more evidence for the use of bezafibrate than fenofibrate as an effective add-on therapy to ursodeoxycholic acid. As it causes less pruritus than obeticholic acid, this strengthens its use as a possible second-line therapy. Fibrates are unlicensed so future work would benefit from evaluating bezafibrate monotherapy. Results for studies directly comparing obeticholic acid to bezafibrate as a preferred second-line therapy are anticipated (https://clinicaltrials.gov/ct2/show/NCT04594694).

Budesonide

A randomised controlled trial by Leuschner et al (1999) showed combined budesonide and ursodeoxycholic acid therapy to be superior to ursodeoxycholic acid monotherapy

in reducing alkaline phosphatase levels and improving liver histology. Concerns over long-term use were raised in a later trial as bone mineral density was significantly reduced in patients taking dual therapy (Angulo et al, 2000). However, this trial included patients with stage IV liver disease and lacked statistical testing between stages, casting doubts over the generalisability of results. Thus, budesonide is believed to be safer in earlier stages of liver disease (Angulo et al, 2000; Hempfling et al, 2003).

A randomised controlled trial (n=62) has shown improved biochemistry (P=0.0029) but no improvement in liver histology with budesonide (Hirschfield et al, 2021), contrasting pre-existing literature. This could be because a subset of patients (n=33) were only followed for 1 year, not allowing sufficient time to display potential histological benefits. This randomised controlled trial was larger than previous studies, but was still underpowered.

Budesonide has been deemed safe in patients in the earlier stages of primary biliary cholangitis. However, larger prospective studies with longer follow up are required to determine long-term safety and efficacy.

Symptomatic management

Pruritus

As ursodeoxycholic acid and obeticholic acid do not significantly improve pruritus, symptomatic management is needed to improve patient health-related quality of life. Cholestyramine, a bile acid sequestrant, is first-line therapy, albeit with limited evidence and common adverse events including bloating and constipation. As a non-absorbable resin with anionic binding properties, cholestyramine (4–16 g/day as tolerated) must be taken 2–4 hours before and after other medications (including ursodeoxycholic acid) to avoid interference with intestinal absorption (Rust et al, 2000).

Rifampicin is the second-line treatment for pruritus in patients with primary biliary cholangitis, having demonstrated efficacy in multiple randomised controlled trials and meta-analyses (Khurana and Singh, 2006). However, it requires regular monitoring, as its considerable side-effect profile includes haemolysis, hepatotoxicity and effects on vitamin K absorption (Prince et al, 2002).

Fatigue

Fatigue occurs in most patients with primary biliary cholangitis, having the greatest impact on health-related quality of life. It does not respond to treatment with ursodeoxycholic acid or obeticholic acid, and there are no licensed therapies for fatigue in these patients (Khanna et al, 2019). Investigating and treating other causes such as anaemia, hypothyroidism or heart failure is recommended (Hirschfield et al, 2018).

A small pilot study (n=15) found mitochondrial dysfunction in patients with primary biliary cholangitis to potentially cause excessive muscle acidosis, prolonged recovery time and therefore increased fatigue (Hollingsworth et al, 2008). A randomised controlled trial (n=57) explored the possible role of rituximab in improving anaerobic threshold and therefore reducing fatigue (Khanna et al, 2019). Although the anaerobic threshold was increased, this did not correlate with symptomatic improvements, highlighting the need for further study into the pathophysiology of primary biliary cholangitis.

Effective symptomatic treatment for fatigue in patients with primary biliary cholangitis remains unclear so alternative approaches, such as exercise therapy (Khanna et al, 2019), should be explored while accounting for the subjective nature of fatigue and the limitations this involves.

Miscellaneous

Sicca complex is common in patients with primary biliary cholangitis and should be managed symptomatically (Hirschfield et al, 2018). Patients with dry eyes may benefit from artificial tears or muscarinic receptor agonists such as pilocarpine. Those with xerostomia should be given oral hygiene advice. Patients experiencing minor symptoms of Raynaud's phenomenon should follow practical advice. For more marked symptoms, calcium-channel blockers may be prescribed with referral where appropriate. For both, guidelines should be followed and patients referred for specialist care where necessary (Hirschfield et al, 2018).

Key points

- Disease-modifying and symptomatic therapies must be considered in tandem when managing patients with primary biliary cholangitis.
- Ursodeoxycholic acid and obeticholic acid are both safe and efficacious as first- and second-line disease-modifying therapies, but pruritus is commonly experienced with obeticholic acid.
- Liver transplantation in indicated patients has proven efficacy, but disease may recur post-transplant.
- Bezafibrate, an unlicensed add-on therapy, has not been associated with increased pruritus, strengthening its use as a potential second-line therapy.
- Symptomatic management of pruritus involves cholestyramine and/or rifampicin, the investigation of associated causes for fatigue and routine management of other symptoms.
- Emerging therapies show initial promise but further randomised trials with long-term follow up are required to evaluate their efficacy as single or combination therapies.

Special considerations

Pregnancy

Ursodeoxycholic acid is prescribed for pregnant patients with primary biliary cholangitis by the majority of obstetricians (Hirschfield et al, 2018). Stringent studies in pregnancy have found the drug to be safe with no teratogenic effects (Kondrackiene et al, 2005). Ursodeoxycholic acid was deemed safer than cholestyramine with respect to pruritus in pregnant patients, and resulted in lower rates of preterm birth ($P<0.05$) and improved biochemistry (aspartate transaminase and alanine transaminase levels $P<0.01$). However, the applicability of these findings is unclear because of the small sample size ($n=42$) and lower than recommended doses of ursodeoxycholic acid (8–10 mg/kg/day) (Hirschfield et al, 2018).

The PITCHES trial ($n=605$) investigated the safety of ursodeoxycholic acid in pregnancy (Chappell et al, 2019). It found ursodeoxycholic acid to be safe with no difference in perinatal outcomes, including in-utero fetal death and preterm delivery. Furthermore, ursodeoxycholic acid effectively lowered alanine transaminase levels ($P<0.0001$) compared with placebo. However, the authors controversially argued that routine ursodeoxycholic acid use in pregnancy should be discontinued because of the lack of in-vivo benefits.

Conclusions

Disease-modifying and symptomatic therapies must be considered in tandem when managing patients with primary biliary cholangitis. Ursodeoxycholic acid is the mainstay management to alter disease progression, with second-line obeticholic acid available. Liver transplantation is indicated for select patients but carries a risk of disease recurrence. Potential disease-modifying therapies require further investigation into safety and efficacy before licensing. Symptomatic management involves cholestyramine and rifampicin for pruritus, investigation of associated causes for fatigue and routine management for other symptoms. Emerging therapies should undergo further testing with long-term follow up to evaluate their efficacy as single or combination therapies.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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