GUIDELINE REVIEW

Guideline review: British Society of Gastroenterology/UK-PBC Primary Biliary Cholangitis treatment and management guidelines

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ABSTRACT

New guidelines have been produced for the management of primary biliary cholangitis, an infrequent but nonetheless important autoimmune liver disease. We provide a succinct commentary and overview of the key features of disease management that arise from these recent guideline recommendations, with a focus on therapy with licensed agents (ursodeoxycholic acid and obeticholic acid) as well as personalised management of disease complications and associated symptoms.

COMMENTARY

Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease affecting >15 000 individuals in the UK.¹ Although the clinical course is slowly progressive in the majority, subgroups of patients may progress to an end-stage liver disease requiring liver transplantation. For decades, ursodeoxycholic acid

(UDCA) was the only therapy available for PBC. However, the approval of obeticholic acid (OCA) as second-line therapy for patients with inadequate response to UDCA has substantially changed the treatment landscape.² The new British Society of Gastroenterology/UK-PBC Primary Biliary Cholangitis guidelines have been produced with the aim of assisting clinicians in the diagnosis and management of patients with PBC.³

Diagnosis of PBC is usually made, in the correct context, in patients with repeated elevation of alkaline phosphatase (ALP) (>6 months) in combination with the presence of antimitochondrial antibody (>1 in 40 titres by immunofluorescence) or highly PBC-specific antinuclear antibodies. A liver biopsy to confirm the diagnosis is indicated in the absence of diagnostic autoantibodies or to clarify diagnosis when clinical suspicion

Figure 1 Proposed British Society of Gastroenterology/UK-PBC pillars of care key to the optimal clinical management of PBC and its associated complications. Dose adjustment is necessary for Obeticholic acid when prescribed to patients with Child-Pugh B and C liver disease. ELF, enhanced liver fibrosis; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

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Table 1 Treatment of symptoms and complications

Concern	Importance	Recommendation
Pruritus	<ul style="list-style-type: none"> ▶ Significantly impairs QOL ▶ 80% experience pruritus during the course of disease 	<ul style="list-style-type: none"> ▶ Exclude bile duct obstruction if indicated ▶ Use bile acid sequestrants first-line, rifampicin second-line and naltrexone third line ▶ Consider gabapentin, sertraline or referral to a specialist centre (to include trials) as needed
Reduced energy	<ul style="list-style-type: none"> ▶ Affects up to 50% of patients and is associated with poor QOL 	<ul style="list-style-type: none"> ▶ No single effective therapy ▶ Use a structured approach with effective treatment of comorbid conditions such as pruritus (in particular nocturnal itch), depression, sleep apnoea, autonomic dysfunction; review medications ▶ Consider associated thyroid disease, immune/autoimmune mediated anaemia (pernicious, haemolytic, celiac disease) as alternative causes of fatigue ▶ Patients with severe fatigue should be considered for referral to specialist centres
Autoimmune conditions	<ul style="list-style-type: none"> ▶ Conditions include: celiac, thyroid disease and primary Sjögren's syndrome 	<ul style="list-style-type: none"> ▶ Screen at baseline and monitor clinically ▶ Testing for development of conditions based on clinical need ▶ Consider artificial tears and saliva for sicca complex. Pilocarpine or cevimeline can be used if symptoms are refractory
Lipids	<ul style="list-style-type: none"> ▶ Elevation is typically HDL and lipoprotein X 	<ul style="list-style-type: none"> ▶ No evidence to suggest an increased risk of cardiovascular events ▶ Need for lipid-lowering therapy should be evaluated using standard cardiovascular risk assessment
Osteoporosis	<ul style="list-style-type: none"> ▶ Variable impact; most notable with advanced liver disease 	<ul style="list-style-type: none"> ▶ All patients should have a risk assessment for osteoporosis; treat and monitor according to national guidelines, including vitamin D supplementation, eg, 1000 IU/day.

HDL, high-density lipoprotein.

of coexisting liver disease (eg, features of autoimmune hepatitis; non-alcoholic fatty liver disease) may impact on patient management. Imaging should be used to exclude alternative diagnoses, such as biliary and infiltrative disease. In most cases, abdominal ultrasound is sufficient. In seronegative patients, magnetic resonance cholangiopancreatography is warranted to exclude primary sclerosing cholangitis (PSC); MRI is typically normal in patients with PBC, and not otherwise needed routinely.

Key to the management of patients with PBC is a structured life-long follow-up, recognising the variability in disease course and required intensity of follow-up between patients. In so doing, the guidelines recognise three important pillars: *treat* and *risk stratify* (1), *stage* and *survey* (2), and *actively manage* (3) (figure 1). Following a PBC diagnosis, life-long UDCA *treatment* at 13–15 mg/kg/day should be offered to all patients. At baseline, *risk factors* for the progressive disease should be evaluated and include: advanced disease stage, younger age at presentation and male sex. *Disease stage* should be evaluated using non-invasive tools at baseline and should be monitored during follow-up to detect progressive disease. An important aspect of treating patients with PBC is the *active management* of symptoms, in particular, pruritus, sicca complex, arthralgias and fatigue (table 1). These symptoms, although not linearly associated with disease progression, may significantly impact on quality of life and clinicians should inquire specifically about their impact on the patient.

On-treatment risk assessment should be performed in all patients by 1 year of UDCA, using a recognised biochemical risk stratification tool the clinician is

familiar with. The easiest approach focuses on values of alkaline phosphatase (ALP) and bilirubin, since these are robustly validated markers of disease progression in PBC.^{4,5} It is clear that multiple extensively validated dichotomous criteria and continuous models for the evaluation of inadequate response exist, but there is insufficient evidence to recommend one over another on the grounds of head-to-head data.^{6,7} The UK guidelines proposed the use of the so-called 'Toronto' criteria for biochemical response (ALP value $>1.67 \times$ ULN and/or abnormal total bilirubin), since these were criteria used in randomised controlled trials of second-line therapy.⁸

Those patients with an inadequate response to UDCA should then be considered for second-line therapy. OCA is the only presently licenced agent for patients intolerant of, or with insufficient response to UDCA, starting at an initial dose of 5 mg/day, titrating to 10 mg/day at 6 months if tolerated. The effects of OCA were evaluated in a 12 month, double-blind, placebo-controlled, phase III trial in which 217 patients with PBC who had an inadequate response to UDCA were randomly assigned to UDCA+OCA at a dose of 10 mg, OCA at a dosage of 5 mg with titration to 10 mg if tolerated or placebo. In this study, a significant proportion of patients had positive effects of OCA on important surrogates of disease progression, with ~46% of patients reaching the primary endpoint of ALP level <1.67 times the upper limit of normal, with a reduction of at least 15% from baseline and normal bilirubin. Clinicians should be aware that dose adjustment of OCA is indicated in patients with advanced liver disease as per the drug label. Pruritus is a side effect of OCA that needs proactive

recognition for the minority of patients whose pruritus worsens with OCA. Off-label therapy has been evaluated recently in a randomised controlled trial of bezafibrate. This study showed a substantial proportion of UDCA non-responsive patients have improvement in biochemical parameters after 2 years of bezafibrate add-on therapy but with a risk of hepatotoxicity (aminotransferase level $>5 \times$ ULN in 6%).⁹ Use of this drug as a second-line therapeutic option in UDCA non-responsive patients, akin to the use of OCA, awaits formal licensing.

The question remains how often one should reassess risk in patients with PBC. There is no evidence-based interval as to when to repeat risk evaluation. The guidelines recommend annual serum liver tests and documented repeat risk assessment every 3 years. PBC is a lifelong disease, with a slow natural history and a need for long-term surveillance. It is important to consider that the baseline disease stage is strongly associated with the rate of progression towards cirrhosis. Historically, 17% of patients with baseline fibrosis stage (F) 1% and 76% of patients with F3 will go on to develop cirrhosis within 10 years of follow-up.¹⁰ As a biopsy is not routine practice, assessment of disease stage at baseline and the monitoring of development of advanced disease stage are important and should be considered by using non-invasive measures in addition to routine blood, such as ultrasound, transient elastography (TE) and serum markers of fibrosis (eg, enhanced liver fibrosis test). Patients with mild disease and normal serum liver tests on treatment, likely do not need intensified surveillance beyond routine evaluation annually. Those with advanced disease at presentation, or who are stratified to high-risk as a result of an inadequate response to UDCA biochemically, should, however, be prioritised and monitored for progressive liver fibrosis according to locally available resources.

The identification of cirrhosis clinically is important to ensure patients receive appropriate surveillance for hepatocellular carcinoma (HCC), varices and timely transplant referral. Local and national guidelines are appropriate for screening, and for example, BAVENO VI-based guidelines for variceal surveillance have been validated for PBC recently.¹¹ Patients with hepatic decompensation or elevation of bilirubin values $>50 \mu\text{mol/L}$ should be referred for transplant assessment.

The care of low-risk patients, that is, patients without cirrhosis, ALP <1.67 and normal bilirubin after 1 year of UDCA, could logically be led from primary care if appropriate shared-care pathways were implemented for patients. UDCA non-responsive patients, those with advanced liver fibrosis/cirrhosis, features of portal hypertension or complex symptoms have a disease for which hospital-led care remains indicated. Equally, early referral to specialist centres is sensible for the management of high-risk, younger, UDCA non-responsive patients. Likewise, patients who may require

Key points

- ▶ After diagnosis and initial evaluation, patients with primary biliary cholangitis (PBC) should be offered structured life-long follow-up.
- ▶ Clinical management entails the *initiation of treatment, risk stratification, staging and monitoring*, as well as *active management* of symptoms.
- ▶ Following a diagnosis of PBC, all patients should be offered treatment with life-long ursodeoxycholic acid (UDCA) at 13–15 mg/kg/day.
- ▶ *Risk stratification* incorporates baseline factors (advanced disease at presentation, young age at diagnosis and male sex), as well as on-treatment factors, with the most readily available and robustly validated stratification being the application of a biochemical response criterion usually after 6–12 months of UDCA.
- ▶ Patients intolerant to UDCA treatment, and/or those with an inadequate response as evidenced by for example an elevated alkaline phosphatase (ALP) $>1.67 \times$ ULN, 1 year after initiation of UDCA treatment, should be considered for second-line therapy. Obeticholic acid is the only licenced second-line therapy; other agents (eg, bezafibrate) are not presently licenced.
- ▶ At diagnosis and during follow-up, non-invasive assessment of disease *stage* should be performed to survey for progressive liver disease.
- ▶ All patients should have an ongoing evaluation for the presence of symptoms, particularly fatigue and itch. These symptoms should be *actively managed*.

a liver transplant, develop HCC, those with concern for features of autoimmune hepatitis, or intractable symptoms, or in the context of complex therapeutic questions, benefit from consultation with a specialist centre. All patients can benefit from patient lead support groups; in the UK, these include specific PBC patient support (PBC Foundation), as well as general liver charities (British Liver Trust, LIVERNORTH Liver4Life).

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