Improving Disease Management in Primary Biliary Cholangitis

Interviewees:

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Support:	**The publication of this article was funded by Ipsen who were involved in its creation and development.**
Disclosure:	Culver has participated in advisory boards for Amgen, Zenus, Sanofi, GSK, Mirum, and Dr Falk; has received research support from NIHR BRC Oxford; consulting fees from Ipsen, Mirum, Intercept, GSK, Amgen, Zenus, Sanofi, Acepodia, Sail Biopharma, and Dr Falk; and payments or honoraria for lectures from Gilead, Ipsen, Mirum, GSK, Amgen, Zenus, and Dr Falk. Jones has received honoraria, consultation fees, and speaker fees from Advanz, CymaBay, Falk, GSK, Intercept, IPSEN, and Umecrine; and grant support from Intercept.
Disclaimer:	The opinions expressed in this article belong solely to the named interviewees.
Acknowledgements:	Medical writing assistance was provided by Caroline E. Cross, Reading, UK.
Keywords:	Alkaline phosphatase (ALP), fatigue, itch, primary biliary cholangitis (PBC), pruritus, total bilirubin (TB), second-line treatment.
Citation:	EMJ Hepatol. 2026;14[1]:100-105. https://doi.org/10.33590/emjhepatol/T0712786

Interview Summary

Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease that can progress from persistent inflammation to intrahepatic ductopenia, fibrosis, and ultimately end-stage biliary cirrhosis if inadequately treated. Although many patients are asymptomatic at diagnosis, fatigue and pruritus frequently develop and can severely impact quality of life, irrespective of disease stage. Diagnosis relies on cholestatic liver enzyme patterns, particularly raised alkaline phosphatase (ALP), alongside antimitochondrial antibodies (AMA). Failure to normalise ALP and bilirubin correlates with ongoing inflammation and future liver-related complications. While ursodeoxycholic acid (UDCA) remains the established first-line therapy, around 40% of patients show an inadequate biochemical response, leaving patients at continued risk of progression. EMJ spoke to PBC experts Emma Culver, Department of Hepatology, John Radcliffe Hospital, Oxford, UK; and David Jones, Department of Hepatology, Freeman Hospital, Newcastle, UK, who emphasise that optimal outcomes depend on timely access to second-line therapies, targeted symptom management, and a broader clinical appreciation of the disease's full impact. They highlight that normalising biochemical markers, addressing symptoms proactively, and intervening early are key to preventing disease progression and improving patients' quality of life.

INTRODUCTION

PBC is a chronic inflammatory autoimmune cholestatic liver disease, affecting approximately 0.33–5.80 in 100,000 people, predominantly females over 40 years old.[1] If left untreated, the disease can progress to intrahepatic ductopenia and end-stage biliary cirrhosis.[2] PBC is diagnosed through a combination of cholestatic liver enzyme patterns and the presence of AMAs, with either non-invasive fibroscan or a liver biopsy used to confirm diagnosis and stage the disease.[2] Raised serum ALP (>1.67×ULN) indicates the current activity of the disease, whilst raised TB (>1.0×ULN) and an elevated liver stiffness measurement (LSM) are markers of disease progression towards liver cirrhosis and end-stage liver disease.[2] Patients may be asymptomatic at diagnosis, but debilitating symptoms, including fatigue and pruritus, are common and can develop over time, independently of the extent of disease.[3] While first-line therapy with UDCA (13–15 mg/kg) is well established,[2] in approximately 40% of patients it is not sufficiently effective, and further intervention through second-line treatments and symptom management is needed to normalise biochemical markers, prevent disease progression, and improve patient quality of life.[4-6] Recent studies to explore the pathogenesis of PBC disease demonstrate that chronic inflammation and subsequent destruction of intrahepatic bile ducts can accompany liver cirrhosis in PBC.[7] In addition, inflammation can persist even when a biochemical response to first-line treatment is evident, indicating an ongoing risk of disease progression.[4] EMJ spoke to two PBC experts, Culver and Jones, who shared their expertise on how best to manage PBC. They highlighted the need for a wider understanding of the full impact of disease on individuals and how physicians might improve patient care with timely access to second-line treatments, with the aim of normalising biochemical markers and managing symptoms to help prevent disease progression and improve quality of life.

UNDERSTANDING THE FULL SPECTRUM OF PBC

According to Jones, there is no such thing as a 'typical' patient with PBC. In rare cases, patients present with advanced PBC-related cirrhosis, jaundice, and complications such as variceal bleeds. However, both Culver and Jones said that in their clinical experience, most PBC cases are identified at an earlier disease stage, when blood tests show abnormal liver function, such as raised ALP and TB, and/or autoantibodies that may indicate autoimmune liver disease.[2]

Another group of patients present with symptoms of severe fatigue or pruritus (itch). Culver elaborated that the impact of the disease on patients can be significant: "It can affect people physically, emotionally, and socially." In Culver's clinical experience, around 80% of patients with PBC seen in clinic describe fatigue, and this can be independent of disease severity. "Fatigue can manifest centrally as brain fog, difficulty concentrating, memory impairment, or more peripherally, with muscle weakness," Culver added. "Fatigue often occurs independently of pruritus." Clinically significant pruritus affects at least a third of patients with PBC, and the itch can be severe, negatively impacting sleep and mood, leading to anxiety and depression, Jones explained. Culver added that dry eyes and mouth (sicca complex) are also common, and in women, who may also be experiencing menopause, symptoms can include vaginal dryness and issues with sexual health.[8]

Although PBC is typically diagnosed in individuals between 40–60 years old, Jones said that as awareness grows, age at diagnosis is decreasing. "It is critical to look carefully at younger patients, because if they have PBC, they tend to have worse symptoms than older patients, and they may have more aggressive disease." Furthermore, Jones outlined, "the burden of disease and its impacts are greater in younger people because symptoms such as fatigue can have a greater impact on lifestyle than for older people who may not have the same caring responsibilities or work ambitions." Culver concurred and added that all patients with PBC are "living

with a rare, chronic autoimmune condition for which there is no cure, and although there are treatments to slow disease progression and help with symptoms, we often underestimate the concern and anxiety that a chronic condition can cause."

Jones went on to explain that "it's now clear there is a divergence between people who are at high risk of progression to more severe liver disease, and those where the disease processes are causing symptoms such as fatigue,"[9] adding that "if we can treat earlier with better treatment, we can stop that divergence and prevent people developing profound symptoms that impact quality of life."

TREATING PBC: BEYOND FIRST-LINE TREATMENT

Current treatment guidelines for PBC[2] take a step-up approach, with first-line therapy for all patients with PBC being UDCA at a weight-optimised dose of 13–15 mg/kg. "We explain to patients that this could be a lifelong medication and is effective in slowing disease progression and increasing transplant-free survival,"[2] Culver explained.

However, at least 40% of people prescribed UDCA do not respond adequately.[4] "When there is an inadequate response to UDCA," explained Jones, "we add in an additional second-line therapy, and we now have three or four therapies that we know are effective in the majority of people."[10] However, Jones continued, there are two problems with this treatment model. "Firstly, the model accepts that a degree of abnormality is okay, because to be a UDCA responder your blood tests can still be abnormal, and those individuals still have some risk of disease progression,"[4] Jones emphasised. "The guidelines say that an ALP of 1.67×ULN is okay, but it is not okay." Jones went on to explain that the second problem with the current model is that it builds in delay. "Currently, we have to wait a year to find out whether the patient responds to the first-line treatment, giving 12 months for the disease to get worse." The step-up model works best for people with the mildest disease, Jones continued. "I agree, we don't want to over treat, but I also don't want to under treat. If we could intervene early in disease, for those at high risk of progressing, we could change the whole natural history of the disease," Jones said.

Culver agreed, saying: "We know now that early prediction [of treatment response] is really important. We need to consider risk stratification at an early stage, at diagnosis, to identify patients who will have a higher risk of disease progression. We have evidence that decisions can be made much earlier, at 6 months, or even sooner, rather than waiting for the 12-month time point to assess biochemical response."[4,6]

SETTING APPROPRIATE TREATMENT GOALS WITH REGULAR MONITORING

"The conversation about treatment goals starts at diagnosis," Culver explained. "In my risk stratification process I am thinking about age, biochemistry, liver stiffness measurements, and symptoms. With those in mind, and in discussion with the patient, we agree on the treatment goals." Jones concurred and said "the combination of fibroscan to assess what injury has happened in the past, and biochemical markers that tell us what injury is happening now that will cause damage in the future, is effective for deciding whether second-line treatment should be introduced."

Personalising treatment goals is paramount for both Culver and Jones, and as part of this, both experts aim to normalise ALP and TB levels and halt progression of LSM in as many cases as possible. The evidence from the Global PBC study data are clear, said Jones. "The risk of disease increases as ALP increases."[5] In addition, Jones said: "We looked at how much inflammation there was ongoing in people in different groups; UDCA non-responders, UDCA responders with abnormal liver blood tests, and also responders with normal liver test results.[4] It's clear that disease is active and ongoing in people with any degree of abnormality in liver blood tests, even if they are UDCA responders.[4] If inflammation drives the disease and inflammation is still present, we need to control it."

In clinic, Jones uses a traffic light system to assess risk of PBC disease progression. "If you've got normal bloods and normal LSM you are on green, whereas if either of these is abnormal you are red or amber, depending on other factors such as age." Jones illustrated the point by saying that for a 30-year-old patient, the liver needs to function for another 50 years or so. "If there is existing liver scarring, we need to normalise blood markers," Jones continued. "People are reassured when we say we are going to set a target of normal blood tests."

To manage symptoms, both experts stressed the importance of setting targets that are patient centric. Jones used specific examples to illustrate this for fatigue, saying, "it could be something very specific like having the energy to go ballroom dancing, or improving memory sufficiently to remember the names of stations on a particular train line." Culver concurred and added that "there are additional targets we need to consider, such as bone mineral density and lipid levels." During early consultations, Culver discusses available second-line treatment options, the risks and benefits of these, and explains to patients that ongoing monitoring of biochemistry, liver stiffness, and symptoms is essential. Culver highlights the importance of monitoring for trajectory over time: "Even if ALP improves or normalises, it can rise again, and if the fibroscan is elevated, or on an increasing trajectory, I want to be able to take pre-emptive action as soon as possible." Culver emphasised: "It's also important to escalate treatment if symptoms are problematic, and I don't wait for the 6-month or 12-month time point to start therapy in those cases."

In Jones' clinic, patients are seen at least once a year, and more frequently depending on the patients' needs and circumstances. "If we are starting UDCA, or second-line treatment, we have a phone review at 2 months to check everything is okay, and then we see the patient in clinic at 6 months to assess response. At that point, we offer a prediction of where we are likely to go next," Jones explained. "Our service includes a specialist nurse-led clinic so patients can be seen every 3–6 months if treatment has changed, or symptoms are developing. We also include a drop-in session for anyone who is struggling with symptoms such as itch, keeping things as flexible as possible to meet the changing needs of patients," Jones added.

ASSESSING TREATMENT RESPONSES AND DELIVERING EFFECTIVE CARE

A combination of clinical and biochemical criteria is used to assess treatment responses, using the Global PBC scoring system, or similar.[11] Historically, an ALP level 1.67×ULN has been considered adequate for patients with PBC receiving first-line UDCA.[2] Age is also an important consideration as Culver and Jones explained, saying that younger patients are more likely to progress over time and experience the complications of their liver disease. Fibrosis is another important measure, explained Culver. "An LSM of >10 shows historic disease progression, and if the trajectory of fibrosis is upwards, even if the baseline LSM is <10, it can indicate disease progression is ongoing and thus a concern," Culver said.

Regular monitoring for patients is crucial. Ideally, Culver stated, "after starting a therapy, we want to assess patients within 1–2 months to see whether there is any response to therapy, or an intolerance, and also to check for symptoms. Biochemical responses to therapy may not be evident until 6 months, and follow-up appointments should be scheduled according to individual patient risk and needs," Culver added. "At each consultation, I consider the combination of biochemistry, fibrosis scoring, and symptoms collectively to decide whether escalation to second-line treatment is necessary."

The PBC service is supported by a clinical nurse specialist and gastrointestinal pharmacist. "It is important that we identify where patients may struggle with adherence to medication, need additional psychosocial support, and discuss the role of scheduled exercise programmes," Culver said. "Our pharmacist monitors medication

adherence and side effects and ensures we don't have patients stopping medication abruptly," Culver explained, adding that this multidisciplinary approach is vital to deliver effective patient care.

However, according to Jones, gaps in PBC care services are common, as highlighted in a recent audit of PBC care across the UK.[12] "What we found is that in a population-based evaluation of PBC care across the UK, overall, Centres of Excellence do well, but patients living more than 10 miles away from a specialist centre were more likely to receive poor quality care," Jones outlined. "In the UK, 95% of patients receive first-line UDCA, which is good, but for those requiring second-line therapies, that figure drops to 60% and less than 60% of patients were asked about PBC symptoms."[12] Jones explained that, in response to the findings, "we have developed a PBC care bundle that aims to minimise variation in clinical practice and improve adherence to key guideline standards."[13,14] In the UK there is also now a campaign led by The PBC Foundation, called Project 90:90, which aims for at least 90% of patients to receive at least 90% of the care standards set out in the current PBC guidelines.[2,15]

EFFECTIVE MANAGEMENT OF PBC SYMPTOMS

The main symptoms of PBC, fatigue and pruritus, are independent of each other, but each can affect 40–80% of patients.[7] Despite the high prevalence of symptoms, patients are reticent about discussing them at consultations. According to Culver and Jones, there are two reasons for this. "Firstly, patients often don't realise their fatigue or itch could be linked to PBC," explained Jones. "Secondly, doctors sometimes don't recognise fatigue as a problem, which is very disappointing."

Fatigue is very debilitating. "You have to take it seriously because it really has an impact on quality of life," Culver emphasised, continuing: "For younger patients it can dramatically impact their ability to function both as parents and socially and also as part of the working community." While Jones assesses fatigue in terms of what patients feel they can no longer do, Culver also uses numerical rating scores. "I think it helps to give fatigue a numerical rating score that you can objectively monitor over time, as well as assessing its impact on the patient's life. This allows you to document over time if things are changing. A similar approach to itch," Culver added.

In addition to central fatigue, which includes brain fog and lack of concentration, fatigue can be peripheral, affecting muscle strength and physical power. Imaging studies confirm that fatigue is associated with measurable changes in brain function.[16]

To encourage open discussion about symptoms during consultations, Jones said: "In clinic, we never use the word fatigue, we often talk about brain fog and 'batteries running down', and if this doesn't resonate with the individual, we move on. If it does resonate, then we drill down into it to find out what it is in their life that they cannot do anymore as a result."

"We talk about drug therapies, exercise, and coping strategies. Sometimes we need to rehabilitate people because the symptoms have been going on for a long time and they have adapted their lifestyles already," Jones continued. "However, in terms of drug therapies, we can struggle because UDCA does not treat fatigue. This means someone who responds to UDCA and has fatigue, under current guidelines and regulations in the UK, they are not eligible for a second-line treatment that could treat fatigue," Jones said.

Culver added: "It's important to engage people in the treatments that are available for associated conditions such as anaemia, low vitamin D, and thyroid disorders. In addition, we discuss non-pharmacological management strategies,[17] and available opportunities to go on a clinical trial of potential new treatments for fatigue."

"We should choose treatments according to their benefit," said Jones. "We are currently doing mechanistic studies to explore which drugs might help symptoms,

and there are ongoing clinical trials that use fatigue as an endpoint irrespective of other disease measures." Culver added: "For patients who experience persistent itch, we follow an escalation pathway from non-pharmacological measures, recommending they wear light clothing and take cool showers, to topical agents such as emollients, alongside pharmacological agents including peroxisome proliferator-activated receptor therapies."[18,19]

CONCLUSION

First- and second-line treatments for PBC are licensed and can be used effectively to slow disease progression and control symptoms. Experts recommend that patients are monitored more closely to identify a lack of response to first-line therapy and ensure timely escalation to second-line treatment, with liver biomarker normalisation as a key target for treatment. They recommend better symptom recognition and management, and improvements in standards of patient care to ensure all patients with PBC maintain their quality of life without fear of significant disease progression.

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ELA-ALL-002415 | Date of preparation: July 2026