A systematic approach to the management of cholestatic pruritus in primary biliary cirrhosis

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ABSTRACT

Pruritus (itch) is an important symptom of primary biliary cirrhosis (PBC), an archetypal cholestatic liver disease. Cholestatic pruritus can be a debilitating symptom causing significant deterioration in patients' quality of life. Effective management of pruritus in PBC involves awareness among clinicians to adequately assess its severity, and treatment with specific drug therapies in line with current practice guidelines. In PBC, antipruritic drugs are not universally effective and/or have significant side effects, and despite best efforts with various combinations of drugs, some patients remain significantly symptomatic, eventually opting for invasive or experimental treatments. Therefore, there is a clear unmet need for better alternative treatments for patients with refractory or intractable cholestatic pruritus. Recent advances in the understanding of pathogenesis of cholestatic pruritus and bile acid physiology have raised hopes for novel therapies, some of which are currently under trial. In this review, we aim to provide a practical guide to the management of this important and complex problem, discussing current knowledge and recent advances in the pathogenesis, summarise the evidence base for available therapeutic approaches and update potential novel future therapies for the management of pruritus in PBC.

INTRODUCTION

Primary biliary cirrhosis (PBC) is an archetypal autoimmune chronic cholestatic liver disease characterised biochemically by elevation in serum alkaline phosphatase (ALP) and gamma-glutamyl transferase (cholestatic liver function tests (LFTs)), serologically by presence of anti-mitochondrial antibodies and pathologically by apoptotic damage to the biliary epithelial cells lining the small intrahepatic ducts. In untreated patients, chronic immune-mediated injury results

in cholestasis and parenchymal injury, which culminate in fibrosis and ultimately end-stage liver disease with associated complications such as portal hypertension, gastro-oesophageal varices, ascites and hepatocellular cancer. Like other autoimmune diseases, PBC predominantly affects women (female-to-male ratio 10:1)¹ and typically patients are women presenting at the age of ≥ 40 . Patients are increasingly, however, diagnosed at a younger age and frequently in the asymptomatic stage of the disease. This is partly due to the increased awareness of the condition among clinicians and widespread availability of the non-invasive diagnostic serological tests.

Pruritus and fatigue are the extrahepatic symptoms accounting for the greatest burden for patients with PBC. In the majority of patients with PBC, pruritus remains mild and tolerable, but in a significant proportion of patients, it may be persistent, leading to severe sleep deprivation, depression, and ultimately, even suicidal ideations. For clinicians, pruritus in PBC and other cholestatic liver diseases is a relevant topic. Knowledge of the condition and specific drugs used for the management of cholestatic pruritus are curriculum requirements for UK trainees in gastroenterology (box 1). Also, a recent study of patients with PBC in the UK reported suboptimal use of antipruritic drugs in patients with itch and suggested a need for improvement in the awareness among clinicians for better management of cholestatic pruritus in PBC.²

NATURAL HISTORY OF PRURITUS IN PBC

There is scarcity of published literature on the epidemiology of pruritus in PBC.

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Box 1 Physician gastroenterology 2010 curriculum requirement for UK gastroenterology trainees applicable to the current review:

- ▶ Shows recognition of the potential complications of cholestasis, including pruritus.
- ▶ Aware of the investigations and treatment of cholestatic pruritus.
- ▶ Knows the therapeutic options and potential complications of colestyramine, rifampicin and naltrexone.

It is reported that pruritus occurs in 20–70% of patients with PBC at some point in their illness.^{3 4} In the national UK-PBC cohort (n=2705) of patients recruited between 2007 and 2011, up to 70% reported some experience of itch and 46% reported persistent itch (frequent or all the time) since the diagnosis of PBC.² Pruritus can develop at any stage of the disease, and it may be the presenting symptom that leads to the eventual diagnosis of PBC. In one study, 75% of patients with PBC reported that pruritus preceded their PBC diagnosis.⁵ Indeed, a significant number of initially asymptomatic patients subsequently develop pruritus in the course of their illness. For example, in a large cohort study of 770 patients with PBC from northeast England, the proportion of initially asymptomatic patients developing pruritus was 15%, 31% and 47% at 1, 5 and 10 years of follow-up, respectively.⁶ Once pruritus develops, its severity often fluctuates from day to day and it may diminish over time, especially when the disease becomes more advanced and liver synthetic function deteriorates.³ However, in the majority of patients, it is unlikely to completely resolve unless effective treatment is started.⁷ In a recent study of >2300 patients with PBC, pruritus severity was significantly higher in patients who were unresponsive to ursodeoxycholic acid (UDCA) therapy and showed no association with LFTs or with disease duration.⁸ The same study also suggested that intensity of pruritus may be associated with the age at disease presentation. The pruritus score (measured on a visual analogue scale (VAS)) was 64% higher in patients with PBC who presented at younger than age 30 (n=24) in comparison to those presented at older than age 70 (n=178), suggesting that younger patients with PBC are more likely to have severe pruritus.⁸

PATHOGENESIS OF PRURITUS IN PBC

PBC is characterised by chronic immune-mediated destruction of small-sized intrahepatic bile ducts resulting in secondary hepatocyte secretory failure and cholestasis. Pruritus resulting from cholestasis is a complex field, and its pathophysiology remains incompletely understood. It is suggested that in

cholestasis compounds (normally excreted in bile) are released into the systemic circulation. Among these compounds, one or more pruritogen(s) may diffuse from the plasma to the skin where they stimulate neural itch fibres. Subsequent transmission to the spinal cord and the brain then elicits a motor response of scratching. Although significant progress has been made in recent years to understand the pathogenesis of this symptom, to date no single substance has been conclusively shown to be the causative pruritogen in cholestasis. The role of bile salts (bile acids) has been controversially discussed, whereas that of endogenous opioids has been supported by several experimental and clinical studies. However, their role in the pathogenesis of cholestatic pruritus is not unequivocal as there are studies and observations to dispute the evidence. Recently, lysophosphatidic acid (LPA), a potent itch neuron activator,^{9 10} was suggested as a potential pruritogen in cholestasis.^{11 12} The bulk of circulating LPA is formed by autotaxin (ATX), a lysophospholipase D enzyme, and serum ATX activity correlates with itch intensity in cholestatic patients and the response to antipruritic treatments.^{11 12} More importantly, rapid relief in itch and strong decline in the serum ATX activity were seen in patients with treatment-resistant cholestatic pruritus when they underwent endoscopic nasobiliary drainage (NBD).¹² It is proposed that in cholestasis an as-yet unidentified (probably biliary) factor increases circulating ATX activity, in turn increasing the levels of LPA, which mediates itch.¹³ Very recently, it has been postulated that cholestatic itch may be caused by activation of the plasma membrane receptor TGR5 that, among various cell types, is also expressed on sensory neurons. It has been demonstrated that TGR5 is activated by bile salts and that intradermal injection of bile salts causes itch in wild-type mice but not in mice lacking the TGR5 receptor.^{14 15}

A detailed description of pathogenesis of cholestatic itch and evidence for and against various candidate pruritogens in cholestasis is outside the scope of this review and has been comprehensively covered elsewhere.^{16–18} Box 2 provides summary evidence supporting three common theories of potential pruritogens in cholestatic pruritus. There is experimental and clinical evidence to support that cholestatic pruritus results from a complex interplay of increased levels of LPA caused by increased ATX activity, increased opioidergic neurotransmission and direct or indirect actions of bile salts (bile acids) and their metabolites, resulting in triggering of pruritoceptive nerve fibres.

CLINICAL PRESENTATION

Clinicians treating patients with PBC should note that pruritus is independent of biochemical severity, duration of the disease and histological stage of PBC.³³ Therefore, it is not unusual to see a patient with

Box 2 Summary of current evidence of potential pruritogens in cholestatic pruritus

1. Bile acids:

Pros:

- ▶ Serum levels of bile salts elevated in cholestasis.¹⁹
- ▶ Feeding cholylsarcosine (synthetic bile acid) to cholestatic patients aggravates their pruritus.²⁰
- ▶ Intradermal application of bile salts induces pruritus in healthy volunteers.^{21 22}
- ▶ Dramatic reductions in pruritus seen in patients undergoing nasobiliary drainage (which removes bile salts from enterohepatic circulation) or extracorporeal albumin dialysis (which removes bile salts from systemic circulation).^{23–25}
- ▶ Some antipruritic effects of colestyramine/colesevelam (bind to bile salts in the intestine and reduce serum levels of bile acids).^{26–28}

Cons:

- ▶ No correlation has been found between plasma bile salt levels and itch intensity in cholestatic patients.
- ▶ Patients with bile salt synthesis defects, while cholestatic, generally do not suffer from itch.

2. Endogenous opioids:

Pros:

- ▶ Administration of opiate antagonists to patients with cholestasis is associated with an opiate withdrawal-like reaction and relief of pruritus.²⁹
- ▶ Increased concentration of endogenous opioids in cholestasis.^{30 31}
- ▶ Intraspinal administration of opioid agonists induces pruritus (eg, itching after epidural or spinal morphine).³²

Con:

- ▶ No correlation has been found between plasma endogenous opioid levels and itch intensity in cholestatic patients.

3. Autotaxin (ATX) and lysophosphatidic acid (LPA):

Pros:

- ▶ Serum LPA concentrations markedly increased in cholestatic patients.¹¹
- ▶ LPA injected intradermally into mice induced dose-dependent scratch response.¹¹
- ▶ Irrespective of the cause of cholestasis, serum ATX activity markedly elevated in patients with cholestatic pruritus (compared with cholestatic patients without pruritus and healthy controls).¹²
- ▶ Significant correlation between serum ATX activity and intensity of itch perception in cholestatic patients.¹²
- ▶ Serum ATX activity responds to and is closely correlated with effectiveness of therapeutic interventions.¹²

Cons:

- ▶ Causal relationship between ATX and itch remains to be proven.
- ▶ Serum ATX is also increased in other pathological conditions not all of which are associated with itch.

early-stage PBC and normal LFTs to present with severe itch, whereas patients with advanced PBC and liver synthetic dysfunction might have no pruritus. It is also important to be mindful of other differential diagnoses when a patient with PBC presents with pruritus. As pruritus is clearly not unique to cholestasis, other cutaneous (eg, psoriasis, atopic dermatitis) and systemic causes (eg, uraemia, lymphoma, myeloproliferative conditions) should be excluded.³⁴ However, patients with cholestatic pruritus usually describe some characteristic features that can aid in diagnosis. Majority describe their itch as a sensation of irritation deep under the skin—‘creepy crawlies’, ‘bugs crawling’ or ‘deep itch’. Those with severe itch report that the itch is ‘relentless’ or so severe that it leads to wanting to ‘tear their skin off’ or ‘scratching until bleeds’.⁵ Unlike patients with dermatological conditions, PBC patients with pruritus do not develop primary pruritic skin lesions and scratching barely alleviates their itch.¹⁶ However, intense scratching may produce excoriations, folliculitis, lichenification and rarely prurigo nodularis. For reasons that are not

entirely clear, pruritus intensity in PBC shows seasonal (worse in the heat) and diurnal variations (worse at late evening and night time). It typically affects limbs, palms and soles of the feet (palmoplantar) but generalised itch may also occur. It is often exacerbated by psychological stress and contact with certain fabrics (eg, wool). Hormone replacement therapy, premenstrual period, menstruation and late-stage pregnancy may also worsen cholestatic pruritus, suggesting a role of female sex hormones.¹⁶

Assessment of pruritus

A patient with PBC presenting with pruritus needs systematic evaluation. Presence of skin lesions (other than scratch marks) should prompt referral to dermatology to rule out skin conditions contributing to pruritus.³⁵ Assessment of itch severity is useful not only to allow objective assessment of impact on patients’ health and quality of life (QoL) but also to evaluate the effect of therapy. As itch is a sensation, its quantification is inherently difficult and subject to considerable inter-individual and intra-individual variation. Scratching,

Table 1 Tools used for the assessment of pruritus in PBC**1. Grading scale**

For example, on a scale of 0 to 10, where 0 is no itch and 10 is unbearable itch, how would you rate the worst itching you have experienced in the last seven days?

Worst itch: _____/10

2. Visual analogue scale (VAS)

For example, please mark on the scale below, indicating the worst itch you have experienced in the last seven days

No itch

Unbearable itch

3. PBC-40 itch score

	Never	Rarely	Occasionally	Frequently	Always
(i) Itching disturbed my sleep	1	2	3	4	5
(ii) I scratched so much, I made my skin raw	1	2	3	4	5
(iii) I have felt embarrassed because of the itching	1	2	3	4	5

Total score obtained by adding the individual scores. Maximum score 15, minimum score 3. Itch intensity: <3, none; 4–8, mild; 9–11, moderate; >12, severe.

PBC, primary biliary cirrhosis

the behavioural response to itch, can be quantified using piezo-film technology.³⁶ However, such complex techniques are used exclusively in clinical trials and are not routinely available in clinical practice. Instead, simple questionnaires that are not time consuming and do not burden healthcare providers and patients are preferred. These include the grading scale (GS), VAS, PBC-40 questionnaire (table 1) and 5D itch scale.

In the GS, patient is asked to rank the severity of itch on a scale of 0 (no itch) to 10 (worst itch). Similarly, in the VAS, itch severity is decoded into a point on a line from 0 to 10. GS and VAS are useful for detecting or monitoring change in an individual over time or with treatment. Both GS and VAS are simple tools but they are not specific to PBC. They require the patient to use thought processes to convert their itch severity to a mark on a continuum, and in the VAS the scoring requires manual measuring of the mark with a ruler.³⁷

PBC-40 is a disease-specific QoL assessment tool developed and validated for self-completion by patients with PBC.³⁸ It consists of 40 items grouped into six domains of typical PBC symptoms (fatigue, itch, cognition, emotional, social and other symptoms). The itch domain consists of three questions framed as statements (table 1).

More recently, the 5D itch scale has been designed to characterise the extent of itch and its impact by defining five dimensions of itch. This single-page questionnaire grades the itch according to the

duration, degree (severity), direction (getting better or worse), disability (impact on QoL) and distribution (skin sites affected). It is not validated for cholestatic itch specifically as only 63 of 234 patients included in this study had pruritus due to liver disease,³⁷ but it is easy to use and informative for clinical as well as research purposes.

Investigations

Blood tests usually show cholestatic LFT but serum bilirubin and alanine transaminase may be normal (particularly in early-stage PBC). Elevated serum bilirubin and jaundice usually suggest biliary obstruction (extrahepatic cholestasis) or advanced PBC. All patients with cholestasis and pruritus should have a trans-abdominal ultrasonography in which a finding of intrahepatic duct dilatation suggests an alternative process of biliary obstruction that may warrant further evaluation using CT and/or MRI/magnetic resonance cholangiopancreatography.³ Generally, treatment of biliary obstruction (which involves endoscopic, surgical or transcutaneous biliary diversion depending on the aetiology) promptly relieves pruritus. Other systemic causes of pruritus (such as uraemia, lymphoma and myeloproliferative diseases) may coexist. These conditions should be considered, appropriately investigated and referred to relevant specialties for further management.

Currently, there is no diagnostic role of measuring serum ATX activity in PBC patients with pruritus.

Table 2 Currently available drugs for the treatment of pruritus in PBC

Approach	Drug	Dose (/day)	Proposed mechanism of action	Comments
First line	Colestyramine Colesevelam	4–16 g 3.75 g in 2–3 divided doses	Bile acid resins. Bind to the bile acids, reduce their reabsorption in the intestine and increase faecal excretion	<ul style="list-style-type: none"> ▶ Morning and afternoon dose preferred ▶ Separate at least 4 h from other drugs ▶ Unpleasant taste (colestyramine) ▶ Bloating, constipation and diarrhoea (less with colesevelam)
Second line	Rifampicin (rifampin)	150–600 mg	<ul style="list-style-type: none"> ▶ Pregnane X receptor (PXR) agonist ▶ PXR-mediated down regulation of ATX transcription ▶ Inducer of microsomal enzymes leading to increased metabolism of endogenous pruritogenic compounds (including opiates) ▶ Inhibition of bile salt uptake by hepatocytes ▶ Altered intestinal metabolism of pruritogens by antibiotic effect on the intestinal microbiota 	<ul style="list-style-type: none"> ▶ Fortnightly monitoring of blood count and liver biochemistry ▶ Hepatitis (~10% risk), liver failure and haemolysis
Third line	Naltrexone	50 mg	Mu opioid antagonist	<ul style="list-style-type: none"> ▶ Start at 12.5 mg/day, increase every 2–3 days; monitor liver biochemistry ▶ Opioid withdrawal like reaction (abdominal pain, high blood pressure, tachycardia, goose bumps and nightmares)
Fourth line	Sertraline	100 mg	Serotonin reuptake inhibitor, antipruritic mechanism unclear	<ul style="list-style-type: none"> ▶ Start at 25 mg/day, increase gradually

ATX, autotaxin; PBC, primary biliary cirrhosis.

However, serum ATX activity may be a useful diagnostic marker in intrahepatic cholestasis of pregnancy (ICP), a condition defined by pruritus but often with only mild cholestasis. As ICP is associated with serious adverse maternal and fetal outcomes,³⁹ accurate diagnosis of ICP in pregnant women presenting with pruritus is crucial. Serum ATX activity (cut-off value 27 nmol/mL/min) has been shown to accurately distinguish ICP from other pruritic disorders of pregnancy and pregnancy-related liver diseases.⁴⁰ In women with sustained pruritus after delivery, other underlying liver diseases, including PBC, should be investigated.

TREATMENT OF CHOLESTATIC PRURITUS

Physicians treating patients with itchy PBC should aim for effective symptom control as any improvement in the itch symptom is likely to have a positive effect on the patient's mood, quality of sleep and help his/her social function. Drugs endorsed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) guidelines (both in 2009) for the treatment of cholestatic pruritus include bile acid resins (colestyramine), rifampicin, opiate antagonists (naltrexone, naltrexone) and sertraline.^{3–4} Although the evidence base for some of these drugs is not high, the guidelines recommend their use in a step-wise manner. Table 2 summarises the current drug therapies, and figure 1 shows our approach to cholestatic pruritus ('treatment ladder').

UDCA, the current standard of care and so far the only disease-modifying therapy licensed for PBC, is not effective in treating pruritus.⁴ In fact, it may exacerbate itch in some patients ('paradoxical itch'), which necessitates stopping or reducing UDCA. It is also noteworthy that antihistamines have no role as

antipruritic agents in PBC and their routine use should be discouraged.⁴ They can make sicca symptoms (eg, dry mouth) worse.³ Use of sedative antihistamines should be reserved in those with significant nocturnal itch. General skin care should be encouraged and patients with mild, localised itch should be offered topical emollients with a coolant (eg, preparations containing aqueous cream and menthol).

Colestyramine (cholestyramine) is the guideline-recommended first-line therapy for pruritus in PBC.^{3–4} Controlled trials and a meta-analysis have confirmed that it is a safe and effective therapy for cholestatic pruritus.^{26–28 41 42} Its unpleasant taste limits its regular use. Colesevelam is a novel anion binding resin with a sevenfold higher bile acid-binding capacity and fewer side effects. Evidence to support colesevelam is scarce. The only published randomised placebo controlled trial of colesevelam (35 patients) in cholestatic pruritus was unable to demonstrate that it was more effective than a placebo in alleviating the severity of pruritus of cholestasis.⁴³ However, a trial of colesevelam should be offered to patients who respond to colestyramine but are unable to tolerate its side effects. Patients should be advised to take colestyramine and colesevelam at least 4 h apart from other medications as they might interfere with their intestinal uptake.

Patients intolerant to or not responding to bile acid resins should be switched to rifampicin (second-line therapy).^{3–4} Rifampicin has the strongest evidence base for the treatment of cholestatic itch and is effective in about 70% of patients. Two meta-analyses reviewing five studies (n=62) on short-term (7–14 days) use of rifampicin have confirmed its safety and efficacy in treating cholestatic pruritus.^{41 44} However, the majority of patients with PBC who

Figure 1 Cholestatic pruritus treatment ladder. If there is no response with one category of drugs, ‘move up’ the ladder. Patient may need combination of treatments to achieve and/or maintain symptom remission. Particular treatments may not be suitable for all patients. ENBD, endoscopic nasobiliary drainage; MARS, molecular adsorbent recirculating system; LT, liver transplantation.

develop rifampicin-induced liver injury (‘rifampicin hepatitis’)⁴⁵ have been shown to do so in the first two months of therapy. In the Bachs *et al*⁴⁶ study, 2/16 (12.5%) of patients with PBC treated with rifampicin (10 mg/kg/day) for mean 11.7 months developed hepatitis within two months of starting therapy. Similarly in the case report by Prince *et al*,⁴⁷ 3/41 (7.3%) of patients with PBC developed significant hepatitis and two of these were within first two months of rifampicin therapy. In clinical practice, it is now accepted that significant hepatotoxicity develops in only a limited number of patients with PBC receiving rifampicin. However, as the factors predicting ‘at risk’ patients are unknown, regular monitoring of LFTs in the first two months is recommended in all patients.⁴ Also, as there is no clear evidence on the effect of rifampicin dose on hepatotoxicity, it should be started at 150 mg once daily and increased cautiously to maximum 600 mg daily based on clinical need.⁴ In those who develop rifampicin hepatitis, prompt cessation of therapy usually improves LFTs.

Naloxone (intravenous) and naltrexone (oral) are the third-line drugs recommended for cholestatic pruritus.^{3 4} They are generally well tolerated but can induce ‘opioid withdrawal reaction’. This can be avoided (or reduced) by giving naloxone as a continuous intravenous infusion for 72 h followed by oral naltrexone started at 12.5 mg daily and discontinuation of the infusion. The dose of naltrexone can be gradually titrated to maximum 50 mg daily with regular monitoring of LFTs (hepatotoxicity is rare but has been reported).⁴⁸

Sertraline is the fourth-line drug recommended by both EASL and AASLD guidelines. There is evidence to support its use,^{49 50} but its mechanism of antipruritic action is not fully understood. However, experience with sertraline for pruritus treatment has been disappointing for many clinicians.⁴

Other drugs that are not guideline recommended but can be used in resistant pruritus are cimetidine and gabapentin. Patients with medically refractory or intractable pruritus despite maximal therapy with combination of the above-mentioned drugs should be referred to tertiary centres that have experience with experimental and/or more invasive interventions. Treatments that can provide immediate albeit short-term relief from cholestatic pruritus include ultraviolet B phototherapy,⁵¹ NBD,^{23 24} plasmapheresis^{52 53} and extracorporeal albumin dialysis or molecular adsorbent recirculating system.^{25 54–59} However, these invasive treatments can be associated with complications (eg, risk of pancreatitis with NBD). Finally, refractory cholestatic pruritus in PBC is a variant indication for liver transplantation and such patients should be offered referral to a transplant centre even in the absence of cirrhosis or liver synthetic dysfunction.^{3 4}

NOVEL THERAPIES

Recent advances in the understanding of the bile acid physiology and pathophysiology of cholestatic pruritus have raised hopes for novel therapies to treat pruritus in PBC.

ASBT inhibitor

Currently, the main class of drugs being investigated in clinical trials as antipruritic agent is apical sodium-dependent bile acid transporter (ASBT) inhibitor (also called ileal bile acid transporter (IBAT) inhibitor). The scientific rationale for ASBT (IBAT) inhibition is based on its physiological role in the enterohepatic circulation of bile acids.⁶⁰ ASBT is predominantly located in the terminal part of the small intestine.⁶¹ It mediates the uptake of conjugated bile acids across the brush border membrane of the ileal enterocyte. Subsequently, the bile acids are carried through the intestinal wall into the blood stream, where they are circulated to the liver via the portal vein. Pharmacological inhibition of IBAT is expected to block the uptake of bile acids in the terminal ileum, increase their excretion in the faeces and decrease the amount of bile acids returning to the liver via the enterohepatic circulation. An experimental study showed that inhibition of intestinal bile acid absorption by ASBT inhibitor A4250 attenuates bile acid-mediated cholestatic liver injury by reducing biliary bile acid output.⁶² Therefore, pharmacological diversion of bile acids has a potential therapeutic role in cholestatic pruritus. By reducing the hepatic and systemic concentration of bile acids, ASBT inhibitor is

expected to improve pruritus. Currently, two phase II multicentre placebo-controlled randomised double-blind clinical trials are investigating the safety and efficacy of the ASBT inhibitors in PBC patients with pruritus (ClinicalTrials.gov identifier: NCT01899703 and NCT01904058).

Fibrates

Recently, there has been an increase in enthusiasm about fibrates (fenofibrate and bezafibrate) as novel anticholestatic therapy for PBC. Growing body of literature confirms that fibrates produce significant improvement in liver biochemistry (mainly ALP) when used in combination with UDCA in patients with PBC with suboptimal biochemical response to UDCA.⁶³ Of these studies, interestingly, two studies with bezafibrate and one study with fenofibrate reported improvement or disappearance of pruritus in patients with PBC treated with fibrates.^{64–66} Also, anecdotal observations suggest that fibrates improve itch in some patients with PBC. The beneficial effect of fibrates as anticholestatic agents is primarily due to their peroxisome proliferator-activated receptor agonist action.⁶³ But the precise molecular mechanism(s) of action of fibrates in improving cholestatic itch, if any, is currently unknown. To elucidate the potential effect of fibrates on cholestatic itch, a European multicentre randomised placebo-controlled trial of bezafibrate is currently in preparation (Prof Beuers, personal communication).

ATX and LPA inhibitors

Recent experimental evidence for the role of ATX and LPA in the pathogenesis of cholestatic pruritus suggests that inhibiting ATX or blocking the LPA receptors could potentially improve pruritus in PBC. Therefore, both ATX and LPA are attractive medicinal targets in cholestatic pruritus. Although they have not reached clinical trials for this goal, ATX inhibitors are being developed and studied as anticancer drugs.⁶⁷ Whether or not they could be used in treating patients with cholestatic pruritus requires further experimental studies and clinical trials.

CONCLUSION

Pruritus is an unpleasant symptom that is prevalent and often significant complaint in patients with PBC. It should be assessed and treated as carefully as other aspects of the disease. Specific antipruritic therapy should complement disease-modifying drugs such as UDCA and comprise a step-up approach with guideline-recommended therapies. Ultimately, the possible risks and potential benefits of more invasive strategies might be considered to provide patients with an acceptable QoL. Currently ongoing research on the so far enigmatic pathophysiology of cholestatic itch may provide us with new therapeutic targets in the near future. Ileal bile acid transport inhibitors and

fibrates are under investigation as potential future antipruritic agents in treating cholestatic pruritus.

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