Evaluation and Management of Pruritus in Primary Biliary Cholangitis

Miriam M. Düll, MD\textsuperscript{a}, Andreas E. Kremer, MD, PhD, MHBA\textsuperscript{b,*}

KEYWORDS

- Bezafibrate • Gabapentinoids • IBAT • Opioid receptors • Therapy • UVB

KEY POINTS

- Pruritus affects 2 out of 3 patients with PBC during their course of disease. Moderate to severe itch intensity may dramatically reduce their quality of life.
- Greater awareness of pruritus among physicians is needed to achieve the best possible treatment and symptom control.
- Other pruritic factors besides the underlying hepatobiliary disease should always be excluded.
- Treatment consists of optimal topical and—if necessary—systemic therapies such as cholestyramine, rifampicin, bezafibrate, naltrexone, sertraline, and gabapentin.
- Therapy refractory patients should be included in ongoing clinical trials or treated with ultraviolet B or invasive approaches such as albumin dialysis or biliary drainage.

INTRODUCTION

Primary biliary cholangitis (PBC) is an immune-mediated disease of the hepatobiliary system that leads to the destruction of small bile ducts, resulting in chronic intrahepatic cholestasis.\textsuperscript{1} Laboratory chemistry is dominated by a cholestatic profile with elevated alkaline phosphatase, serum bile acids, and potentially bilirubin as a late progression marker of the disease. In PBC, intrahepatic cholestasis, which might be caused on both the hepatocellular and cholangiocellular level, is frequently associated with chronic pruritus, fatigue, sicca syndrome, arthralgia, and abdominal discomfort.\textsuperscript{2}
Itch sensations lasting over 6 weeks are classified as chronic pruritus, which is often present in patients with cholestatic disorders such as PBC. Chronic pruritus may seriously reduce quality of life in these patients. In particular, moderate to severe nighttime itch causes sleep deprivation, exhaustion, and significantly worsens fatigue. These factors ultimately favor the development of depression and even suicidal ideas.

In addition to its unpleasant character, itching can represent a challenging symptom of PBC and is typically unresponsive to commonly applied antipruritic medication such as antihistamines. Fortunately, novel therapeutic approaches for the treatment of pruritus as a symptom of PBC have been established in recent years. Nevertheless, most of these options are applied in an off-label manner or administered as part of clinical trials, of which the latter is hoped to result in more effective and approved drug treatments.

This review summarizes the clinical picture, diagnostic approach, and current treatment options of pruritus in the context of PBC and provides an outlook on potential future therapeutic approaches.

CLINICAL PICTURE OF PRURITUS IN PRIMARY BILIARY CHOLANGITIS

Itching due to PBC typically affects the extremities, often involving the palms and soles. However, pruritus may also be present on other body parts or is generalized in a significant number of patients. Pruritus can arise at any stage of PBC, independent of severity of cholestasis or medical interventions. Itching may present as the first symptom of PBC and sometimes precede the diagnosis for months to even years, as so-called premonitory pruritus. One study suggested that 75% of patients report pruritus preceding the diagnosis of PBC.

Other data reported that a substantial number of PBC patients develop pruritus after an initial asymptomatic period, with approximately 30% reporting about pruritus onset after 5 years and almost 50% after 10 years of follow-up. On the other hand, in advanced stages of PBC including progression to liver cirrhosis, itching may reduce in intensity or even vanish completely despite ongoing severe cholestasis. Recently, the authors' group underlined the lack of correlation between intensity of laboratory cholestasis markers, opioid metabolites, and itch intensity in patients with cholestatic liver diseases such as PBC and primary sclerosing cholangitis (PSC). Although the severity of symptoms does not correlate with stage of disease in PBC, severe pruritus can point to an aggressive, ductopenic variant, which is associated with poorer prognosis.

Itching can become intractable, especially if resistant to currently available treatment options; therefore, it can be considered as an indication for liver transplantation, even without the presence of advanced reduction of liver function. Similar to other conditions associated with chronic pruritus, itching in PBC often follows a circadian rhythm, with the highest intensity reported in the evening or late at night. A study objectively surveyed scratching activity in patients with PBC with a vibration transducer, consisting of a square piezoelectric film taped to one fingernails. Patients scratched most intensely in the late afternoon and early evening hours; this is at least partly in accordance with other forms of chronic pruritus, which often aggravate at night, possibly due to limited sensory input and warmth in bed. Female patients particularly report about more severe intensity of pruritus during times of hormonal changes such as in the luteal phase of the menstrual cycle, in the third trimester of pregnancy, or during hormonal replacement therapy. This observation points to female sex hormones as potential contributing factors in the pathophysiology of cholestatic pruritus.
Data on the epidemiology of chronic pruritus in systemic diseases is still scarce. In recent years, however, more information on pruritus in patients with PBC has become available, especially through national cohort data. Earlier research estimated a lifetime prevalence of pruritus in 70% to 80% in patients with cholestatic liver disorders, particularly in PBC. The UK-PBC study group recently presented supporting data by evaluating 2194 PBC patients, of whom 73.5% experienced pruritus during their course of disease; 34.5% of patients with PBC stated persistent pruritus, with 11.7% reporting severe intensity of pruritus. In an online survey of 577 patients with PBC in Germany, the authors’ own group reported a point prevalence of 56% of pruritus lasting for more than 6 weeks. Around 70% of affected patients even indicated that they suffered from pruritus for many years. Another study suggested that pruritus intensity might be associated with younger age at the time of the PBC diagnosis. So far, no specific environmental influences including geographic or dietary factors could be associated with the presence or onset of pruritus in patients with PBC.

During the last decades, the molecular mechanisms of itch signaling have been subject to intensive research with a focus on in vitro and in vivo experiments in cellular and animal models. This research discovered novel pruritogens, their receptors, and potential signaling pathways in acute and chronic itch. The underlying causes of chronic pruritus in human, especially in patients with systemic diseases such as PBC, however, remain only partially understood. For hepatic pruritus, previous basic research, observations in clinical studies, and positive response of patients to certain treatments have identified several possible contributing factors (for detailed overview of potential signaling pathways see Fig. 1):

- Presence of cholephilic pruritogens in the enterohepatic circulation
  - Removal of bile contents improves pruritus in chronic cholestatic disorders such as PBC
    - by oral medication (anion exchange resins or inhibitors of the ileal bile acid transporter [IBAT]) or mechanically by (naso)biliary drainage.
  - Certain bile acid subspecies and potentially bilirubin activate the Mas-related G protein–coupled receptor family X4 (MRGPRX4), which is expressed in a subset of small-diameter sensory neurons, particularly mediating itch-related signals with a major role in nonhistaminergic itch.
  - The semisynthetic bile acid and selective farnesoid X receptor agonist obeticholic acid (OCA), licensed as second-line treatment in PBC, can induce and/or intensify pruritus.
  - Formation, biotransformation, and/or secretion of potential pruritogens in the liver and/or the gut
    - Effective treatment of hepatic pruritus with rifampicin, an inducer of hepatic biotransformation and pregnane X receptor (PXR) agonist, and bezafibrate, a peroxisome-proliferator activated receptor (PPAR) agonist.
  - Influence of potential pruritogens on endogenous opioidergic and serotoninergic systems
    - Mild antipruritic effect in cholestatic pruritus of μ-opioid antagonists (eg, naltrexone), k-opioid agonists (eg, nalfurafine), and selective serotonin reuptake inhibitors (SSRIs) (eg, sertraline).
A rodent-based model with surgically induced cholestasis and a small number of patients with cholestatic PBC displayed systemically elevated opioid levels and upregulation of opioid markers in liver tissue. Presence of potential pruritogens in the systemic circulation. Hepatic pruritus can be ameliorated by treatment with plasmapheresis, plasma separation, albumin dialysis, and anion absorption. Increased concentrations of autotaxin (ATX), the enzyme hydrolyzing lysophosphatidic acid (LPA) from its precursor molecule lysophosphatidylcholine, were reported in sera of patients suffering from hepatic pruritus compared with nonpruritic patients with PBC and various other liver diseases. Systemic ATX activity correlated with the itch intensity in patients with PBC and other hepatobiliary diseases and decreased with successful therapeutic interventions.

EVALUATION OF PRURITUS IN PRIMARY BILIARY CHOLANGITIS

The initial workup of a patient with PBC with pruritus should exclude other dermatologic and systemic causes such as chronic kidney disease–associated pruritus (CKDaP) and endocrine causes such as hypothyroidism, diabetes, or anemia (Fig. 2). Although dermatologic diseases often present with pruritic and lesional skin areas, the itchy skin of patients with PBC typically exhibits no primary efflorescences; this may change in time, as intense scratching can induce secondary skin lesions such as excoriations, lichenification, prurigo nodules, and, in case of continued skin damage, even scarring. During the course of chronic pruritus, these secondary lesions...
might resemble those of primary dermatologic disorders, which can create difficulty in the differential diagnosis and treatment of pruritus (see Fig. 2).25

Because itching presents as a common and in many cases burdening symptom, the presence of pruritus should be assessed in all patients with PBC alongside other symptoms such as fatigue and arthralgia, when taking the patient’s history at the time of diagnosis and throughout all follow-up visits (see Fig. 2). Patients may not associate their itching with the underlying liver disease and will therefore not report about it without explicit enquiry by health care professionals. Consequently, patients may not receive adequate antipruritic treatment. Patients treated with OCA as a second-line drug option for PBC might also develop de-novo or intensified pruritus, which should regularly be assessed during medical follow-up visits.

If patients with PBC indicate itch sensations, it is key to collect a thorough anamnesis and clinical examination focused on properties of pruritus. The basic assessment should include intensity, time of start and time course, quality, localization, triggering, and relieving factors as well as the patient’s opinion on origin and burden of pruritus.46 Questionnaires can be helpful and timesaving tools for patients and practitioners to receive detailed self-reported information. It is also important to document other preexisting medical conditions besides PBC, as well as allergies and atopic diathesis, and to obtain a detailed list of recent drug intake including phytotherapeutics and dietary supplements. Patients with PBC, for example, often additionally suffer from hypothyroidism due to Hashimoto thyroiditis, which can add to induction of pruritus. To further evaluate the course and intensity of pruritus, patients may keep record of pruritic activity in form of a diary on paper or in a digital format, which can be assessed together with a health care professional during follow-up visits for therapeutic choices and changes.

Visual analogue scales (VAS) and numeric rating scales (NRS) are commonly used objective evaluation tools of pruritic intensity in clinical practice and studies.47 Yet, itch sensations are intra- and interindividually very subjective, fluctuating, and remain difficult to objectify.9 In clinical drug trials, various itch assessing tools and primary

Fig. 2. Evaluation and diagnostic path of pruritus in patients with PBC.
endpoints are currently applied. These different outcome variables challenge the comparability of study results, and standardized measures are warranted to increase reliability and quality of data.

The clinical examination includes inspection of the entire skin to screen for primary and secondary skin lesions including scalp and hair, nails, mucous membranes, and if indicated as itchy, the anogenital region. Inspection of the patients’ back is helpful to distinguish primary from secondary skin lesions. Some patients might exhibit scratch lesions with sparing of the mid-back. This so-called butterfly sign results from the inability to reach and scratch this area by hand. It is recommended to photo-document skin pathologies, to allow for comparisons throughout follow-up visits. Finally, a complete physical examination should be performed to rule out other pathologies that may be responsible for chronic pruritus.

MANAGEMENT OF PRURITUS IN PRIMARY BILIARY CHOLANGITIS

General Principles in the Management of Pruritus in Primary Biliary Cholangitis

It is important to educate patients on pruritus as a symptom of PBC and available treatment strategies depending on intensity and clinical burden. All patients should be advised on general pruritus-relieving measures for self-application:

- Avoidance of circumstances increasing dryness and/or irritation of the skin
  - Heat (eg, sauna)
  - Very frequent washing and bathing with hot water
  - Ice packs
  - Contact of skin with possible irritants (eg, chamomile, tea-tree oil)
  - Consumption of large amounts of hot and/or spicy food, hot drinks, or alcohol
  - Tight clothing or clothes derived from animal wool
  - Use of overly scented detergents
  - Extensive rubbing of the skin after showering/bathing
  - Psychological factors, for example, stress

- Positive factors to protect the skin and decrease pruritic activity
  - Mild, nonalkaline soaps and oils for showering/bathing
  - Luke-warm water for showering or bathing, not exceeding 20 minutes
  - Mild and moisturizing topicals on the whole skin on a daily basis (eg, containing urea)
  - Topical agents with cooling and/or anesthetic effects (eg, emollients containing 1%–2% menthol or polidocanol) for pruritic skin areas
  - Soft, permeable clothes, especially cotton-based textiles
  - Shortening of fingernails to avoid severe skin damage

Psychological aspects might play a significant role, especially concerning scratching activity. Some patients could therefore benefit from relaxation techniques such as autogenic training or psychological interventions for coping with the itch-scratch circle.

Medical Treatment Options in the Management of Pruritus in Primary Biliary Cholangitis

In most cases of clinically relevant pruritus in patients with PBC, nonmedical treatment and interventions will not provide sufficient efficacy in itch reduction. Over the last decade, new treatment options for pruritus in cholestatic liver diseases have become available. Still, most currently applied therapeutic options are based on few randomized, placebo-controlled trials and cohort studies. If pruritus cannot be sufficiently
managed by available treatment attempts, experimental medical and interventional approaches should be taken into consideration after referral to expert centers.\textsuperscript{48} Of note, the bile acid sequestrant cholestyramine remains the only approved drug for treating pruritus associated with cholestatic liver diseases (Table 1). All other drugs are applied in an “off-label” approach, on which patients have to be informed. The current EASL and AASLD guidelines include recommendations to apply a step-by-step treatment approach for pruritus in patients with PBC.\textsuperscript{20,45,49} These recommendations can be supplemented by further therapeutic options that are presented within this review (see Table 1; Table 2). Table 3 summarizes current clinical drug trials for pruritus in PBC.

Ursodeoxycholic acid (UDCA) remains the first-line anticholestatic treatment of PBC,\textsuperscript{12,45} positively affecting overall and liver transplant–free survival rates. Still, UDCA does not improve pruritus, and additional medication is required.

Cholestyramine
The bile acid sequestrant and anion exchange resin cholestyramine represents the only approved and therefore guideline–recommended first-line treatment option for pruritus in hepatobiliary diseases including PBC.\textsuperscript{45,49} In addition to bile acids, it can bind various other amphiphilic substances in the intestine, which might act as potential pruritogens.\textsuperscript{5} Cholestyramine was effective in reducing pruritic intensity within 2 weeks in older nonplacebo-controlled trials with small patient numbers.\textsuperscript{48} The sequestrant is most commonly applied in granular compounding with a single sachet equaling to 4 g, which is the recommended starting dosage. The intake can be increased to up to $4 \times 4$ g qd. It is important to educate patients about a 2- to 4-hour pause between the intake of cholestyramine and other medication, in particular of disease-modifying medication for PBC such as UDCA, OCA, and fibrates, to minimize risk of insufficient uptake of these drugs.\textsuperscript{50} From clinical experience, the effect of cholestyramine on pruritic intensity is usually not sufficient to treat moderately and severely affected patients, even at higher dosages. Because of gastrointestinal adverse effects and unpalatable taste, patients are often reluctant to take cholestyramine for a longer time. In case of insufficient improvement of pruritus after 14 days of intake, we recommend to discontinue cholestyramine and to start alternative options. Interestingly, colesevelam, an anion exchange resin with a much higher adsorbing affinity to bile acids, was not superior to placebo in reducing itch intensity in a randomized, placebo–controlled study, albeit systemic bile acid concentrations dropped by almost 50%.\textsuperscript{51} In a clinical setting, cholestyramine is often still prescribed as first-line therapy to patients with PBC and pruritus, mainly to justify a necessary change to more effective off-label treatments.

Rifampicin
Rifampicin is an agonist of the PXR as well as able to induce important liver enzymes and transporters such as cytochrome P450 3A4 or multidrug resistance–associated protein 2 involved in biotransformation and excretion of various endogenous and exogenous substances. It, therefore, holds the potential to change the hepatic metabolism and elimination of possible pruritogens. From its original antibiotic use, rifampicin might also influence the gut and skin microbiome, possibly contributing to its antipruritic activity.\textsuperscript{52} However, a recent study did not observe differences in stool microbiota of patients with pruritic PBC, patients with asymptomatic PBC, and a healthy control group, questioning at least the gut microbiome in the pathophysiology of pruritus in PBC.\textsuperscript{53} Rifampicin is also able to induce downregulation of ATX expression in a PXR-dependent mechanism, which
<table>
<thead>
<tr>
<th>label</th>
<th>Cholestyramine</th>
<th>Rifampicin</th>
<th>Bezafibrate</th>
<th>Naltrexone</th>
<th>Sertraline</th>
<th>Gabapentin</th>
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<tbody>
<tr>
<td>starting dose</td>
<td>4 g/d</td>
<td>150 mg/d</td>
<td>(200–)400 mg/d</td>
<td>12.5 mg/d (or low-dose naloxone)</td>
<td>50 mg/d</td>
<td>100–300 mg/d</td>
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<td>max. recommended dose</td>
<td>16 g/d</td>
<td>450–600 mg/d</td>
<td>400 mg/d</td>
<td>150 mg/d</td>
<td>100 mg/d</td>
<td>3600 mg/d</td>
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<tr>
<td>AE/interactions</td>
<td>Interference with intestinal absorption of other medication, in particular UDCA and fat-soluble vitamins (such as vitamin A, D, E, and K)</td>
<td>• Induction of hepatic enzymes—altered metabolism of other drugs (eg, oral anticoagulants, oral contraceptives, antiepileptic drugs)</td>
<td>• Hepatotoxicity in up to 5% of patients</td>
<td>• Dose reduction in case of impaired renal function, contraindicated in dialysis patients</td>
<td>AE: opioid-like withdrawal reactions (low starting dose, eg, 12.5 mg/d or naloxone), increased pain sensations, confusion</td>
<td>AE: hyponatremia, QT prolongation, nausea, vomiting, sleep disturbance, restlessness, change in appetite</td>
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<td></td>
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<td>• Risk of myopathy as well as increased risk of rhabdomyolysis with concomitant statin use</td>
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<td>• In long-term treatment: hepatotoxicity in up to 5% of patients</td>
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<td>Advice</td>
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<td>• 2- to 4-h interval to oral intake of other medication</td>
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<td>• Change to other drugs if not effectively treating pruritus after 2 wk</td>
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<td>• Doses of 150–300 mg/d often sufficient</td>
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<tr>
<td>• Monitoring of transaminases after 2, 6, and 12 wk, afterward in 12-wk intervals and in case of dose changes</td>
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<tr>
<td>• Fenofibrate as less effective alternate</td>
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<td>• For in-patients or in case of severe pruritus: intravenous application of naloxone (0.002–0.2 μg/kg/min; bolus of 0.4 mg if necessary), subsequent switch to naltrexone</td>
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<tr>
<td>• Regular monitoring of retention parameters</td>
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<td>• Pregabalin as alternate drug (use doses of 75–600 mg/d)</td>
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**Abbreviations:** AE, adverse events; ECG, electrocardiography.
may decrease the amount of LPA, a suspected pruritogen in cholestatic pruritus.\textsuperscript{42} The clinical relevance of these mechanisms in itch-reducing efficacy of rifampicin is still unclear. Rifampicin is regarded an effective and safe second-line treatment option in pruritus due to PBC with daily dosages of 150 to 600 mg.\textsuperscript{34,54} Many patients clinically benefit from intake of 150 mg rifampicin within 2 weeks of initial application. Hepatotoxicity is a potential, but not common, serious adverse effect during treatment with rifampicin\textsuperscript{45}; therefore, transaminases should be tested at 2, 6, and 12 weeks after begin of rifampicin and in case of dose change.\textsuperscript{4} Other adverse effects include particularly gastrointestinal symptoms such as nausea and abdominal discomfort. Patients taking rifampicin should be advised about the possible but harmless induction of orange-red–colored body fluids such as urine, stool, or tears.

The barbiturate phenobarbital induces the enzyme CYP3A4 to a similar extent as rifampicin but reduced pruritic intensity in patients with PBC to a lower extent in an older randomized, controlled trial.\textsuperscript{55} Phenobarbital may only be considered as an experimental off-label approach with 1 to 5 mg/kg qd in case of insufficient control of pruritus with other treatment options.

\textbf{Fibrates}

In recent years, bezafibrate, an unselective PPAR agonist, has been investigated for its anticholestatic and antiinflammatory as well as antipruritic activity in patients with PBC.\textsuperscript{56} PPARs act as intracellular transcription factors and broadly affect the regulation of gene expression involved in energy metabolism, cellular differentiation, and organ growth.\textsuperscript{57} Fibrates bind on the PPAR subtypes \(\alpha\), \(\gamma\), and \(\delta\) and have already been applied to treat dyslipidemia since the 1960s, as they lower triglyceride and low-density lipoprotein levels. Cohort studies initially in Japan and later in western countries investigated bezafibrate for its positive effects as a disease-modifying treatment option

\textbf{Table 2}

\textbf{Nonpharmacological interventions for pruritus in patients with primary biliary cholangitis}

<table>
<thead>
<tr>
<th>UVB Phototherapy</th>
<th>Extracorporeal Albumin Dialysis (MARS, Prometheus, DIALIVE)</th>
<th>Biliary Drainage (Nasobiliary Drainage, Transcutaneous Biliary Drainage, External Biliary Diversion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Application 2–3 times/wk</td>
<td>● 2–3 dialysis sessions on subsequent days</td>
<td>● Invasive/surgical procedures</td>
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<tr>
<td>● Broad band might be more effective than narrow band UVB light</td>
<td>● Antipruritic effect may last for weeks to months</td>
<td>● Pruritus often strongly improved during biliary drainage, with relapse after removal/ discontinuation within days to weeks</td>
</tr>
<tr>
<td>● Precautions: o Increased risk of skin cancer in immunosuppressed patients</td>
<td>● Invasive method: o Insertion of dialysis catheter needed</td>
<td>● Risk of complications from invasive procedure including infections (eg, cholangitis, pancreatitis, peritonitis), bleeding, perforation, hospitalization and mortality</td>
</tr>
<tr>
<td>o Avoidance of concomitant application of photo-sensitizing drugs</td>
<td>● Necessary hospitalization of patients</td>
<td>● Application recommended only in specialized centers with experience in the intervention</td>
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<tr>
<td>● Limited availability</td>
<td>● Additional positive effect on liver function in patients with liver transplant and graft rejection</td>
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<tr>
<td>● Application recommended in consultation with experienced dermatologists</td>
<td>● Application recommended only in specialized centers with experience in the intervention</td>
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</table>

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### Table 3
Recent clinical drug trials for treatment of pruritus in patients with primary biliary cholangitis

<table>
<thead>
<tr>
<th>Substance Class</th>
<th>Drug</th>
<th>Dosage</th>
<th>Phase</th>
<th>Comment</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>KOR agonists</td>
<td>Nalfurafine (TRK-820)</td>
<td>2.5–5 μg po qd</td>
<td>Licensed in Japan for uremic and hepatic pruritus</td>
<td>Not available in Europe and United States</td>
<td>Kumada, Hepatol Res 2017, PMID: 27753159</td>
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<tr>
<td></td>
<td></td>
<td>2.5 μg po qd (12 wk)</td>
<td>Phase IV (PBC patients)</td>
<td></td>
<td>Yagi, J Gastroenterol 2018, PMID: 29663077; NCT02659696</td>
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<td></td>
<td>Difelikefalin (CR-845)</td>
<td>0.5 mg/kg iv after hemodialysis treatment</td>
<td>Intravenous application FDA approved for CKDaP</td>
<td>Currently reviewed for approval by EMA</td>
<td>Fishbane, NEJM 2021, PMID: 31702883; NCT03422653; NCT03995212</td>
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<tr>
<td></td>
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<td>1 mg po bid</td>
<td>Phase II (patients with PBC)</td>
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<td>IBAT inhibitors</td>
<td>Linerixibat (GSK2330672)</td>
<td>20 mg, 90 mg, 180 mg po qd</td>
<td>II (GLIMMER)</td>
<td>Primary end-point not met, 40 mg and 90 mg bid most effective doses</td>
<td>NCT02966834</td>
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<td></td>
<td></td>
<td>40 mg, 90 mg po bid</td>
<td>III (GLISTEN)</td>
<td></td>
<td>NCT04950127, EudraCT: 2021-000007-21</td>
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<tr>
<td></td>
<td></td>
<td>n.a.</td>
<td>Open-label extension</td>
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<td></td>
<td>Maralixibat (SHP625, LUM001, lopixibat)</td>
<td>10 or 20 mg po qd</td>
<td>II</td>
<td>Not superior to placebo</td>
<td>Mayo MJ, Hepatol Commun 2019, PMID: 30859149</td>
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<td></td>
<td>FDA approval to treat pruritus in Alagille syndromea</td>
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<tr>
<td></td>
<td>Volixibat (SHP626, LUM002)</td>
<td>20 mg po bid or 80 mg po bid</td>
<td>II (VANTAGE)</td>
<td>Separate volixibat study for PSC patients</td>
<td>NCT05050136</td>
</tr>
<tr>
<td>MRGPRX4 inverse agonist</td>
<td>EP547</td>
<td>Single and multiple doses po</td>
<td>I</td>
<td>Healthy subjects and patients with CKDaP equally included</td>
<td>NCT04510090</td>
</tr>
</tbody>
</table>

**Abbreviations:** bid, twice daily; CKDaP, chronic kidney disease-associated pruritus; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IBAT, ileal bile acid transporter; KOR, κ-opioid receptor; MRGPRX4, mas-related G protein-coupled receptor X4; po, per os; qd, once a day.

a Dose recommendation for pruritus in Alagille syndrome: day 1 to 7: 190 mg/kg po (solution) qd; from day 8 on: increase to 380 mg/kg if tolerated.
in PBC and also found an antipruritic activity in affected patients. The randomized, placebo-controlled BEZURSO phase III study followed with application of bezafibrate 400 mg qd in 100 patients with PBC with incomplete response to UDCA according to Paris-2 criteria, of whom 66% reported about pruritus, and found a 75% reduction in itch intensity in the bezafibrate-receiving group. Moreover, the Japanese PBC registry revealed a significant improved overall survival in patients with PBC on bezafibrate compared with a matched control group. The recently completed placebo-controlled FITCH trial investigated bezafibrate in 70 patients with PBC or PSC/secondary sclerosing cholangitis (SSC) for treatment of moderate to severe disease-associated pruritus. Bezafibrate was superior to placebo (55 vs 11%) in reducing the intensity of moderate or severe pruritus intensity by at least 50%. Bezafibrate is currently not available in all countries, for example, the United States. Fenofibrate may be used as an alternate; however, its antipruritic properties are less well established. Fenofibrate exhibits different pharmacologic properties with preferential affinity to PPAR-\(\alpha\), compared with the broader receptor binding of bezafibrate, which calls for more studies to directly compare the efficacy of both drugs. Hepatotoxicity has to be taken into consideration as a serious adverse effect of fibrates, as reported in the BEZURSO study, in which 3 (6%) patients in the Bezafibrate group had an increase in aminotransferase levels over 5 times of upper limit normal. Two of these patients had to receive steroid treatment for normalization of aminotransferase levels within 3 months, and the drug was discontinued in 2 patients. Serum creatinine levels might increase mildly during intake of bezafibrate as found in the BEZURSO and FITCH trials and should be monitored throughout fibrate therapy. Fibrates commonly cause myopathy and in severe cases rhabdomyolysis. As statins may potentiate this risk, a concomitant therapy with fibrates should be prescribed with caution. Taking clinical history for muscle weakness and/or pain and laboratory assessment of creatinine kinase and myoglobin is recommended during fibrate therapy.

*Modulators of the endogenous opioid system*

\(\mu\)-opioid receptor antagonists (naltrexone, naloxone). The \(\mu\)-opioid receptor antagonist naltrexone at dosages of 25 to 50 mg qd exerted a mild effect on itch intensity of patients with cholestatic pruritus in some smaller placebo-controlled trials, which was less pronounced compared with rifampicin in a meta-analysis. Some patients may benefit from even higher dosages of up to 150 mg/d. In-patients might profit from an intravenous nalofoxone infusion starting at very low doses of 0.002 to 0.02 \(\mu\)g/kg/min with a subsequent uptitration to 0.4 mg/8 hours and later switch to oral naltrexone. From clinical experience, the infusion of naltroxone represents a very effective treatment option for patients with severe pruritus, especially in hospitalized patients with complications from the underlying disease, for example, decompensated cirrhosis. Of note, naltrexone dosages should be augmented slowly, as it otherwise bears the risk of opioidlike withdrawal symptoms. To avoid a previously described breakthrough phenomenon of pruritus during otherwise effective treatment with naltrexone, it might be paused for 1 or 2 days a week. Concurrent chronic pain symptoms due to other underlying causes might exacerbate and should be monitored during administration of \(\mu\)-opioid receptor antagonists. Further adverse effects can include gastrointestinal symptoms, dizziness, and headaches.

\(\kappa\)-opioid receptor agonists (nalfurafine, difelikefalin). Nalfurafine, a \(\kappa\)-opioid receptor agonist, represents another drug affecting the endogenous opioid system. In Japan, it was licensed to treat CKDaP, after positive results in some placebo-controlled trials. Nalfurafine was later also approved for treatment of cholestatic pruritus in
Japan. An inhomogeneous patient collective of 318 patients with pruritus due to different hepatic diseases was treated with nalftofareine at dosages of 2.5 \( \mu g \) qd and 5 \( \mu g \) qd in a randomized, placebo-controlled study. Pruritus intensity assessed on a VAS scale was statistically significant reduced by 8 mm compared with the placebo group at 4 and 12 weeks of administration of nalftofareine but the clinical relevance of this slight difference remains questionable. In Europe and the United States, the drug was not approved by legal authorities. In terms of adverse effects, nalftofareine can cause sleep disturbances, constipation, and nocturia.

Since 2021, the peripheral \( \kappa \)-opioid receptor agonist difelikefalin represents the first Food and Drug Administration–approved and licensed drug to treat moderate to severe CKDaP for adults undergoing hemodialysis treatment. Difelikefalin exerts significantly less central adverse events due to its restricted peripheral mode of action. Although it is intravenously applied in this condition, a current phase II trial is investigating the effect of an oral formulation of difelikefalin on pruritus in patients with PBC. (see Table 3)

**Ileal bile acid transporter inhibitors**

The IBAT mediates the reuptake of bile acids from the small intestine into the enterohepatic circle. This receptor seems as an interesting target for the interruption of the enterohepatic circulation, as it was hypothesized and demonstrated that removal of potential pruritogens from this circulation ameliorates pruritus. Inhibition of IBAT results in increased elimination of bile acids with feces.

Several IBAT inhibitors have been and are currently still investigated in various hepatobiliary disorders for their efficacy in reducing pruritus. The IBAT inhibitor linerixibat was initially applied in a phase IIa cross-over, placebo-controlled, randomized study in 21 patients with PBC at dosages of 90 mg qd for 3 days, with an increase to 180 mg qd from day 4 to 14. Linerixibat reduced baseline NRS itch scores by 57% after 14 days of therapy compared with 23% in the placebo group. In a post-hoc data analysis of this study, patients with pruritic PBC exhibited higher serum bile acid and ATX levels compared with patients with PBC without pruritus and healthy controls with a significant reduction after the linerixibat treatment period. The phase IIb GLIMMER trial investigated linerixibat at different dosages (20–180 mg/d) in 147 patients with PBC across 66 centers in 10 countries for dose response, safety, and tolerability. Albeit the primary endpoint was not met, preliminary positive results were presented for the 40 mg twice daily application of linerixibat in patients with moderate to severe pruritus. In 2021, the follow-up Global Linerixibat Itch Study of Efficacy and Safety (GLISTEN) in patients with PBC started as a 2-part, randomized, placebo-controlled, double-blind, multicenter, phase III trial to evaluate the efficacy and safety of linerixibat. Bile acid–induced diarrhea represents the main adverse effect of IBAT inhibitors.

In 2021, the IBAT inhibitor maralixibat was approved in the United States for the treatment of pruritus in Alagille syndrome for patients of 1 year of age or older. In contrast, maralixibat was not superior to placebo in reducing pruritus in a phase II study in patients with PBC. Odevixibat, a further IBAT inhibitor, was licensed for pruritus in Progressive familial Intrahepatic Cholestasis Europe and the United States the same year.

**Selective serotonin reuptake inhibitors**

SSRIs demonstrated mild to moderate antipruritic effects in cholestatic pruritus. Sertraline reduced itch intensity in patients with various hepatobiliary disorders in a randomized, placebo-controlled cross-over trial and case series. Paroxetine may represent an alternative drug, as it was effective in a randomized trial of patients with various systemic causes of pruritus. The recommended dose for sertraline is 50 to 100 mg qd and
20 mg qd for paroxetine. Common adverse effects of SSRI may include hyponatremia, sleep disorders, reduction in appetite, and restlessness.

**SUMMARY**

Pruritus remains an agonizing and sometimes difficult-to-treat symptom in patients suffering from PBC. In general, greater awareness among physicians and patients is needed to achieve the best possible treatment and symptom control. After ruling out other factors that trigger chronic pruritus and applying basic care, several systemic drug therapies are available to efficiently treat pruritus in many patients with PBC (see Table 1).

*Practical Approach to Treat Pruritus in Patients with Primary Biliary Cholangitis*

Cholestyramine often still represents the first-line therapy as licensed drug to treat cholestatic pruritus, with a starting dose of 4 to 8 g qd that may be increased to 12 to 16 g qd. All other mentioned drugs represent an off-label use. In case of insufficient pruritus control within 2 to 4 weeks, the authors recommend either rifampicin at 150 mg qd or bezafibrate at (200–)400 mg qd. Rifampicin is mostly effective at 150 to 300 mg qd, and the maximum daily dose of 600 mg is rarely required. Attention should be paid in regard to augmented drug metabolism of co-administered drugs such as oral contraceptives, anticoagulants, or antiepileptic drugs. The risk for hepatotoxicity is comparable for both rifampicin and bezafibrate (see Table 1). Transaminases should be controlled at 2, 6, and 12 weeks after start of therapy or in case of dose change. Bezafibrate exerts additional anticholestatic properties and should therefore be considered especially in patients with an incomplete response to UDCA and moderate to severe pruritus. In OCA-treated patients with PBC suffering from pruritus both bezafibrate and rifampicin efficiently attenuate itch intensity. If symptom control is insufficient with either drug within 4 weeks or adverse effects occur, patients can be started on naltrexone. Withdrawal-like symptoms can be avoided by starting with intravenous naloxone or low doses of 12.5 mg qd and a subsequent increase in dosage every 3 days. Mostly 25 to 50 mg qd are recommended; however, some patients benefit from higher doses up to 150 mg qd. Alternative drugs are sertraline at doses of 75 to 100 mg qd or gabapentin 100 to 3600 mg qd (see Table 1).

In most patients with PBC, this approach will successfully attenuate chronic pruritus. Patients, unresponsive or with intolerable adverse effects to the presented drugs, should be referred to expert centers for inclusion in clinical trials or undergo experimental medical or interventional approaches, for example, ultraviolet B phototherapy, molecular adsorbent recirculating system (ie, MARS, Prometheus), external or nasobiliary drainage, plasmapheresis, plasma separation, or anion absorption (see Table 2). IBAT inhibitors such as linerixibat and volixibat are currently investigated in clinical trials and seem to be promising future treatment options for pruritus in PBC (see Table 3). Research into the molecular pathophysiological mechanisms of pruritus in cholestatic liver disorders has provided further targets for development of new therapeutics such as ATX inhibitors and MRGPRX4 antagonists, which still have to be proved beneficial in clinical trials in humans.

**CLINICS CARE POINTS**

- Patients with PBC should be actively monitored for pruritus as a potentially burdensome symptom.
Basic measures such as applying hydrating skin care can already improve especially low-intensity pruritus.

Cholestyramine is often not well-tolerated and effective in treating pruritus in PBC.

Bezafibrate might also exert anti-cholestatic and anti-inflammatory effects besides its positive effect on pruritus. Still, especially transaminases levels should be closely monitored during therapy.

IBAT inhibitors represent promising new drugs for treating pruritus in PBC, but the results of ongoing clinical trials have to be awaited.

DISCLOSURE

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