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Newer Approaches to the Management of Pruritus in Cholestatic Liver Disease

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Abstract

Purpose of Review Chronic pruritus represents a burdensome symptom in cholestatic liver disease. This review recommends a stepwise therapeutic approach, alongside with providing information on epidemiology, pathophysiology, and novel drug targets.

Recent Findings Current epidemiological data emphasize chronic itch as a major symptom in immune-mediated liver diseases such as primary biliary cholangitis affecting up to 70% of patients with a significant number suffering from long-lasting and severe pruritus. κ-opioid receptor (KOR) agonists, PPAR agonists, and ileal bile acid transporter (IBAT) inhibitors are currently investigated for their anti-pruritic efficacy in clinical trials. Future therapies may target the autotaxin-lysophosphatidic acid-axis or the Mas-related GPCR MRGPRX4.

Summary Cholestatic pruritus still remains a challenging symptom for patients and physicians. Using a stepwise approach including cholestyramine, rifampicin, bezafibrate, naltrexone, and sertraline, pruritus is often adequately manageable. KOR agonists and IBAT inhibitors are currently the most promising anti-pruritic drugs for cholestatic pruritus in development.

Keywords Autotaxin · Bezafibrate · Bile salt · IBAT · Itch · Rifampicin · Opioid

Introduction

Various systemic diseases are associated with chronic pruritus. Up to 20% of patients with generalized pruritus suffer from systemic disease entities such as chronic kidney disease, hepatobiliary disorder, and hematological disorder [1, 2•]. Almost all hepatobiliary disorders may be accompanied by pruritus albeit this symptom is commonly seen in disorders with cholestatic features. These hepatobiliary diseases share the common pathophysiological aspect of impaired bile formation and/or flow on the hepatocellular and/or cholangiocellular level resulting in cholestasis [3]. Pruritus due to intrahepatic cholestasis caused by primary hepatocyte secretory failure is seen in intrahepatic cholestasis of pregnancy (ICP), toxin- or drug-induced cholestasis, benign recurrent intrahepatic cholestasis (BRIC), progressive familial intrahepatic cholestasis type (PFIC), and acute and chronic viral hepatitis. Cholangiocellular cholestasis may result from intrahepatic bile duct damage and secondary hepatocyte secretory failure as seen in primary biliary cholangitis (PBC), primary and secondary sclerosing cholangitis (PSC/SSC), or pediatric cholestatic disorders (e.g., Alagille syndrome). Pruritus due to obstructive cholestasis caused by obstruction of the intrahepatic or extrahepatic biliary system may occur in PSC/SSC, biliary atresia, choledocholithiasis, bile duct adenomas, cholangiocellular carcinoma, enlarged lymph nodes, or pancreatic head carcinoma (Fig. 1). Pruritus is more frequently seen in cases of intrahepatic than extrahepatic cholestasis. Aside fatigue, pruritus can represent a major agonizing symptom often resulting in a significant reduction of quality of life [4].

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Clinical Aspects of Pruritus in Cholestatic Liver Disease

Clinical Presentation

In particular patients with the immune-mediated cholestatic liver diseases, PBC and PSC experience pruritus most

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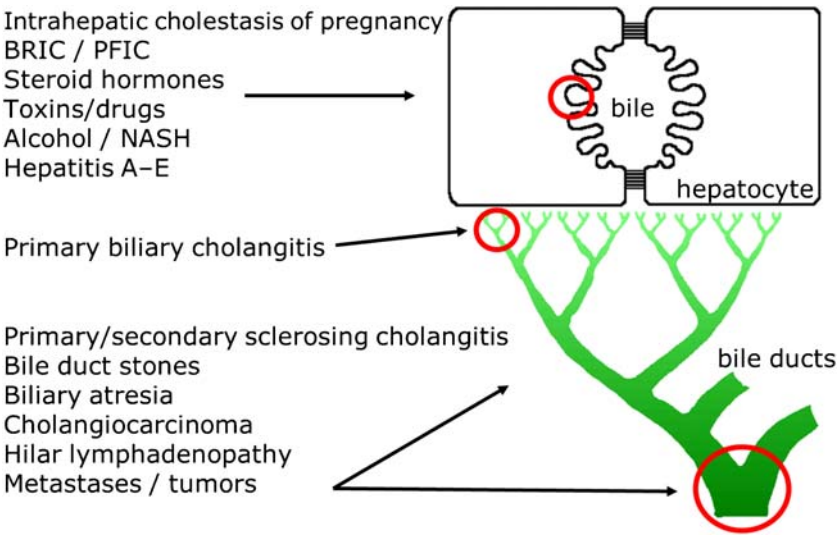

Fig. 1 Hepatobiliary diseases associated with cholestatic pruritus (modified from Kremer AE et al., Drugs 2008)

commonly at the extremities including the soles and the palms [5]. Pruritus may affect other body parts and generalize over time. In contrast to itch in dermatological conditions, cholestatic pruritus is not associated with primary skin lesion but might result in excoriations, prurigo nodularis, and even scars due to intense scratching [6]. These secondary skin lesions may be difficult to distinguish from dermatological or other conditions [7]. Chronic pruritus can cause severe sleep deprivation and exhaustion, resulting in fatigue, depression, and even suicidal ideas [4]. Thus, therapy-refractory persistent pruritus can represent an indication for liver transplantation, even in the absence of liver failure [8].

In a study, scratching activity of PBC patients was traced by attaching piezoelectric electrodes to the fingernails [9]. A diurnal rhythm was confirmed, with the highest scratching activity in the afternoon and early evening hours. Still, the intensity of pruritus does not correlate with severity of cholestasis [6]. While women suffering from ICP experience pruritus as their disease-defining symptom [10], female patients in general suffer from more severe cholestatic pruritus. This is particularly seen during alterations of female sex hormones, e.g., prior to menstruation, during advanced pregnancy, or during hormonal replacement therapy [11]. A role of female sex hormones in the pathophysiology of cholestatic pruritus therefore seems likely.

Visual analog scales (VAS) and numeric rating scales (NRS) are commonly applied in clinical settings and studies as objective evaluation tools of pruritus [12•]. Itch sensations are however very subjective, fluctuating impressions and therefore difficult to objectify. Additionally, in clinical drug trials addressing anti-pruritic treatment, diverse itch-assessing tools and primary end points are used, making intercomparability difficult. Standardized variables in clinical trials addressing pruritus should therefore be a long-term goal to improve data quality.

Epidemiological Data

There is only limited data available on the epidemiology of pruritus in the different hepatobiliary disorders. From clinical observations, prevalence and intensity of pruritus may vary considerably between the different liver diseases. In ICP, pruritus is one of the disease-defining criteria [13]. Patients with genetic biliary disorders such as BRIC or PFIC commonly suffer from cholestatic itch. Chronic pruritus is characteristic for the immune-mediated cholestatic disorders PBC, PSC, and SSC, with a lifetime prevalence of up to 70–80% [14, 15]. These numbers have recently been substantiated by a national cohort study from the UK assessing 2194 PBC patients, in which 73.5% experienced pruritus at some point during their disease, 34.5% reported on persistent pruritus, and 11.7% on severe pruritus [16]. Data from Germany, collected via a large online survey of 577 PBC patients, indicated a point prevalence of chronic pruritus of 56% of out of which almost 70% reported on persistent itch for many years [17].

Pruritus presents with a far lower frequency in patients with obstructive cholestasis. Around 45% of patients experience pruritus in case obstruction is caused by malignancies, e.g., pancreatic head carcinoma, and 17% of patients with non-neoplastic obstruction, e.g., by choledocholithiasis [18]. A total of 5–15% of patients with untreated chronic hepatitis C virus (HCV) infections report chronic itch [19], albeit pruritus is hardly observed in patients with chronic hepatitis B virus (HBV) infections and alcoholic or non-alcoholic fatty liver disease ((N)AFLD) [20]. However, a recently published interim analysis of the REGENERATE phase III study in non-alcoholic steatohepatitis (NASH) reported on 19% prevalence of pruritus within the placebo group which may indicate that pruritus may be a relevant symptom in non-cholestatic liver conditions [21••].

Pathophysiological Mechanisms of Cholestatic Pruritus

The molecular pathophysiology of itch has been intensely investigated in recent years. Cell- and animal-based models have given more insights into potential pruritogens, receptors, and pathways mainly involved in acute itch signaling. In contrast, detailed understanding of the underlying mechanisms of chronic pruritus in humans remains only partially elucidated. For cholestatic pruritus, several possible transmitters and mechanisms have been suggested including biliary components, endogenous opioids, and the autotaxin-lysophosphatidic acid (ATX-LPA) axis.

Biliary Components

"Prickly bile salts" were already implied as potential agents of pruritus in patients with jaundice more than 2000 years ago in ancient Greece by the physician Aretaeus of Cappadocia [3, 22]. Until today, there are aspects which argue in favor of this theory. Nasobiliary or transcutaneous drainage can significantly and quickly reduce otherwise refractory cholestatic itch [23, 24]. A less-invasive method to remove bile salts can be achieved by inhibitors of the ileal bile acid transporter (IBAT) which is responsible for the re-uptake of bile salts from the small intestine [25, 26]. So far, inhibition of IBAT showed a promising anti-pruritic effect in some clinical studies [27, 28•, 29, 30]. On a cellular level, the intracellular nuclear Farnesoid-X receptor (FXR) and the transmembrane G protein-coupled receptor TGR5 can be activated by bile salts, initiating potential transcriptional networks and signaling cascades resulting in itch sensation [31]. Data from clinical drug trials substantiated a role of bile salts in cholestatic pruritus. Although ameliorating biochemical and histological properties of the underlying condition, the semi-synthetic bile acid and selective FXR agonist obeticholic acid (OCA) caused de-novo or aggravated pruritus in PBC [32, 33••] and NASH patients [21, 34].

Still, no clear-cut correlation between itch intensity and levels of bile salts in serum, urine, or skin could be established so far [1, 35]. ICP is strongly associated with itch; still, total serum bile salt (TBS) levels are hardly increased in most cases [10]. Patients with cholestasis due to obstruction often have increased TBS but experience pruritus far less commonly [36]. TBS concentrations were significantly lowered by the anion exchange resin colesevelam without being superior to placebo concerning pruritus improvement [37•]. Recently, a new mechanism in which certain bile salt subspecies could induce itch via the sub-receptor X4 of the Mas-related G protein-coupled receptor family (MRGPRs) was proposed by three different research groups [38–40]. As no murine orthologue of MRGPRX4 could be identified, this mechanism may be solely relevant in humans or primates. The MRGPRX4-activating bile salt subspecies caused itch sensation upon intradermal injection in the forearm of healthy volunteers but no scratching behavior in mice. MRGPRs have been investigated in the context of non-histaminergic itch and are expressed in a subset of small-diameter sensory neurons which mediate in particular itch sensation [41]. Several known pruritogens have been shown to activate different MRGPRs [42]. In addition, bilirubin was also suggested to activate MRGPRX4 [43]. Although representing intriguing experimental data, this finding does not reflect clinical experience that the degree of icterus in patients is not correlated to the degree of pruritus, if at all present. In conclusion, evidence points to a potential role of certain bile subspecies contributing to cholestatic pruritus, but they seem unlikely to be the sole pruritogens in cholestatic itch. Still, MRGPRX4 represents an interesting target for anti-pruritic therapies in hepatobiliary disorders.

Endogenous Opioids

Endogenous opioids have been discussed as potential pruritogens in cholestatic liver disease for many years [44]. Elevated plasma opioid levels were seen in rats with surgically induced cholestasis [45, 46] and in a few cholestatic PBC patients [47, 48]. The expression of preproenkephalin mRNA, a precursor molecule of endogenous opioids, was elevated in livers of cholestatic rats [49], and Met-enkephalin immunoreactivity was detected in liver tissue of PBC and chronic hepatitis C patients [50, 51]. However, no convincing correlation between itch intensity and endogenous opioids has ever been demonstrated so far. Opioid activity did not significantly differ between pruritic and non-pruritic PBC patients, nor between women with ICP compared with pregnant controls [35]. A publication indicated an inverse correlation with increased concentrations of endogenous opioids at advanced histological stages of PBC, when pruritus may decline [35, 47]. Novel data came from a recent report suggesting bovine adrenal medulla (BAM) 8-22, an itch-inducing endogenous peptide, to be a potential pruritogen in cholestatic itch. Using a mouse model of surgically induced cholestasis, the authors showed increased BAM 8-22 levels which may cause scratch activity via MRGPRX1 [52]. Still, the endogenous opioid system might rather serve as a modulating factor than play a major causative role in cholestatic pruritus.

LPA and ATX

The small phospholipid LPA was identified as a component in sera of patients with cholestatic pruritus, activating neuronal cell lines [35]. ATX, the enzyme hydrolyzing LPA from its precursor molecule lysophosphatidylcholine (LPC), was found in higher concentrations in patients suffering from cholestatic pruritus compared with non-pruritic patients [53].

Additionally, ATX activity correlated with itch intensity and response to therapeutic interventions, which could not be shown for other suggested pruritogens in cholestasis [53], and proved a reliable marker to confirm the diagnosis of ICP [54]. Intradermal injection of LPA caused increased scratching in mice in a dose-dependent manner [35, 53]. Comparably, LPA induced a mild but significant itch sensation in healthy human subjects when applied focally to the skin [55]. In a recent publication using cultured dorsal root ganglia neurons, LPA activated the LPA receptor 1 on satellite glia cells [56]. Interesting data also suggested a possible molecular interaction linking natural bile salts and LPA signaling [57]. The ATX-LPA axis is therefore part of a signaling pathway for potential therapeutic interventions in patients with cholestatic liver disease.

General Approaches to the Management of Pruritus in Cholestatic Liver Disease

Established therapeutic approaches to pruritus in cholestatic liver diseases are mainly derived from some randomized, placebo-controlled trials and few cohort studies [58]. If itch is not adequately manageable upon those recommendations, experimental medical and interventional attempts have to be considered at specialized expert centers [3]. Additional practical advice towards general measures should be given to patients as basic care, addressing the following aspects [59]:

- Use of emollients and oatmeal extract for dry and inflamed skin
- Regular application of moisturizing and cooling topical agents (e.g., emollients containing 1–2% menthol)
- Showering with cold water to relieve exacerbations of pruritus
- Shortening of fingernails to evade severe skin damage
- Wearing light clothes made from natural fibers, such as cotton, in order to avoid skin irritation from friction
- Avoid clothing that is woolen or tight, and the use of overly scented detergents
- Psychologic intervention in case of addictive scratching/scratch dependence. Patients should also be screened for other or co-existing causes of chronic pruritus.

The anion exchange resin cholestyramine is still the only approved medication for cholestatic pruritus, while all other below-mentioned drugs are “off-label” recommendations. The current American and European guidelines suggest a stepwise approach to efficiently treat cholestatic pruritus which was modified within this review according to recent clinical results (Table 1) [59, 60].

Established Approaches to the Management of Pruritus in Cholestatic Liver Disease

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA) exerts anti-cholestatic properties among others by improved hepatobiliary secretory function and reduced bile toxicity [61•]. It is therefore used as baseline treatment in various cholestatic liver diseases including PSC, PBC, ICP, and pediatric cholestatic syndromes. PBC patients benefit from receiving UDCA, positively affecting overall survival rates [58]. Still, UDCA has not proven to attenuate pruritus in neither PBC nor PSC patients [3]. In women suffering from ICP however, UDCA (13–15 mg/kg/day) not only improved biochemical laboratory results and fetal outcome but also mildly reduced pruritus in a meta-analysis of 11 randomized controlled trials [62]. From clinical experience, pruritus is often only temporarily attenuated by UDCA in ICP women.

Antihistamines

Oral antihistamines are commonly prescribed to patients with cholestatic pruritus drugs but do not attenuate itching in most cases. As fatigue is an inherent extrahepatic symptom of chronic liver disease, in particular, sedating antihistamines are not recommended as they may potentiate fatigue.

Cholestyramine

Cholestyramine, an anion exchange resin and bile sequestrant, represents the only licensed drug and remains therefore the first-line guideline-recommended treatment for cholestatic pruritus [59]. In small, non-placebo-controlled trials, cholestyramine reduced pruritus over a period of 2 weeks [3]. From clinical experience, cholestyramine is often not sufficient in treating patients with considerable pruritic intensity and should be stopped after 2 weeks if inefficient.

Dosage recommendations include an intake of a 4-g sachet of the bile sequestrant, i.e., one before and one after breakfast. The dosage can be raised up to 4 × 4 g/day. Another important information for clinicians and patients is to keep a at least 4-h time period to the intake of other drugs, as cholestyramine might prevent their intestinal absorption [63]. Patients do often refuse to take this drug for longer periods due to its unpalatable taste. Most common adverse effects include abdominal symptoms such as bloating and malabsorption of fat and fat-soluble vitamins. Colesevelam represents an alternative option which exerts a higher adsorbing affinity for bile salts than cholestyramine. Still, colesevelam did not alleviate pruritus more efficiently than placebo in a well-defined, randomized, placebo-controlled trial [64]. In clinical routine, cholestyramine remains the first-line recommendation mainly due to justification to switch to below-mentioned off-label options rather than its efficacy.

Table 1 Stepwise approach for the treatment of pruritus in liver diseases

Approach	Drug[1]	Dose	Interactions/precautions
1st line	Cholestyramine	4–16 g/day (po)	Interference with intestinal absorption; 4-h interval to administration of other medication
2nd line	Rifampicin	150–600 mg/day (po)	Hepatic enzyme induction, altered metabolism of other drugs, hepatotoxicity
3rd line	Bezafibrate	200–400 mg/day (po)	Renal and hepatotoxicity, myopathy, and rhabdomyolysis
4th line	Naltrexone	25–50 mg/day (po)	Opioid withdrawal reactions, low starting dose; pain, confusion
5th line	Sertraline	75–100 mg/day (po)	QTc prolongation, malignant neuroleptic syndrome, drug-drug interactions
6th line	Experimental approaches, e.g., gabapentin phenobarbital UVB light Albumin dialysis, nasobiliary drainage	 300–3600 mg/day (po) 1–5 mg/kg/day (po) 1–2×/week	Administration recommended only in specialized centers

[1] Solely, cholestyramine is licensed for the treatment of hepatic pruritus; all other drugs are off-label use

po, per os

Rifampicin

The Pregnane-X receptor (PXR) agonist rifampicin is an inducer of phases I and II enzymes of biotransformation in liver and intestine. In this way, it may alter the metabolism and increase the excretion of potential pruritogens. Furthermore, rifampicin as an antibiotic drug could also affect the microbiome of the gastrointestinal tract and the skin. It is considered as a second-line treatment in cholestatic pruritus, as it proved efficacy and safety in several randomized, placebo-controlled trials at doses of 150–600 mg/day [65], also validated in meta-analyses [66]. In most patients, 150 mg/day is sufficient, and a benefit is reported by most patients within 1 to 2 weeks. Monitoring of laboratory should be performed after 2, 6, and 12 weeks of therapy or at dose changes. Hereby, potential hepatotoxicity, which has to be considered as a serious, but not common adverse effect, can be detected [59]. Patients might also experience gastrointestinal adverse effects such as anorexia, nausea, and changing the color of urine or tears to orange-red.

Although phenobarbital is a comparable inducer of the biotransformation enzyme CYP3A4, it did reduce pruritus less effectively than rifampicin in a randomized, controlled trial [67]. Still, it may be used in an experimental off-label application at doses of 1–5 mg/kg/day.

Peroxisome Proliferator-Activated Receptor Agonists

Peroxisome proliferator-activated receptors (PPARs) represent intracellular transcription factors with many physiological and pharmacological ligands. They are involved in the regulation of gene expression, body metabolism, cellular differentiation, and organ growth [68]. Fibrates are agonists of the subtypes PPAR α, γ, and δ, which are used to treat dyslipidemia. Besides lowering triglyceride and low-density lipoprotein (LDL) levels, recent data also suggest anti-cholestatic and anti-inflammatory properties of fibrates. In addition, bezafibrate was reported to reduce pruritus in PBC patients in cohort studies [69]. In the randomized, placebo-controlled BEZURSO trial, with 400 mg/day of bezafibrate applied in PBC patients with incomplete response to UDCA [70••], itch intensity was reduced by 75% in the verum group. A recent placebo-controlled trial (FITCH) investigated bezafibrate in PBC, PSC, and SSC patients with moderate to severe pruritus. A total of 45% of the patients experienced a 50% or higher reduction in itch intensity within 3 weeks of treatment [71]. Of note, severe hepatotoxicity may also occur under bezafibrate treatment, which may require steroid treatment as stated in the BEZURSO trial [70••]. Furthermore, kidney function can worsen which may represent a reversible effect for most cases. Fibrates may cause myopathy and rhabdomyolysis and should therefore not be combined with statins. Bezafibrate is currently unavailable in the USA; therefore, fenofibrate may be considered as an alternate. The coincident anti-cholestatic and anti-pruritic properties of fibrates appear especially appealing in immune-mediated liver diseases, and bezafibrate is therefore recommended as the third-line therapy in this review.

μ-Opioid Receptor Antagonists

As fourth option, the μ-opioid receptor antagonist naltrexone can be considered. Doses of 25–50 mg/day achieved mild itch-relieving effects in smaller placebo-controlled trials [72,

73]. A meta-analysis demonstrated a significant lower standardized mean difference for the treatment with opioid antagonists than rifampicin [66]. Dosages of naltrexone should be gradually increased over time to avoid opiate withdrawal reactions. Another option is to start hospitalized patients on intravenous naloxone with very low doses of 0.002–0.02 μg/kg/min with titration up to 0.4 mg/8h before continuing oral medication with naltrexone [6]. As a breakthrough phenomenon during naltrexone treatment is possible, application might be intermitted for 1 to 2 days per week [74]. Pre-existing pain syndromes might restrict the usage of μ-opioid receptor antagonists [75]. Especially, older patients can experience adverse events such as headache, nausea, abdominal pain, and dizziness. From clinical experience, the intravenous naloxone infusion can be a very helpful tool in decompensated liver cirrhosis or advanced malignancy stages for in-hospital patients. In contrast, pure oral treatment is often associated with limited benefit.

Selective Serotonin Re-Uptake Inhibitors

As a fifth-line option, selective serotonin re-uptake inhibitors (SSRI) can be applied. Sertraline and paroxetine demonstrated moderate anti-pruritic effects in placebo-controlled, cross-over trials [76] and a few case series [77] using sertraline and a randomized controlled trial with paroxetine [78]. Sertraline can be applied in doses of 75–100 mg/day. Adverse events might arise by the effects of SSRI on the central nervous system inducing, e.g., sleep disorders, restlessness, and loss of appetite.

Newer Approaches to the Management of Pruritus in Cholestatic Liver Disease

κ-Opioid Receptor Agonists

Another approach to modulate the endogenous opioid system is the κ-opioid receptor agonist nalfurafine, which has been approved in Japan for treating cholestatic pruritus since 2015. In an earlier placebo-controlled trial with patients suffering from chronic kidney disease-associated pruritus, nalfurafine induced a mild anti-pruritic effect [79]. In a later randomized, placebo-controlled trial, 318 patients with pruritus from different liver diseases were included. Nalfurafine was applied at doses of 2.5 μg/day and 5 μg/day and reduced pruritus in the statistical analysis, although the clinical relevance of this effect remains disputable [80]. Main adverse effects consisted of pollakiuria including nycturia, constipation, somnolence, and insomnia. Of note, nalfurafine is neither licensed for treatment in Europe nor the USA. Further studies with other κ-opioid receptor agonists are currently conducted in terms of treatment of pruritus due to atopic dermatitis or chronic kidney disease and might also be studied in cholestatic pruritus in the future in case of positive results.

Ileal Bile Acid Transporter Inhibitors

The IBAT represents an interesting therapeutic target for the interruption of the enterohepatic cycle, thereby increasing the secretion of bile salts via the intestinal tract. The IBAT inhibitor linerixibat (= GSK2330672) showed promising results in a phase II cross-over, randomized, placebo-controlled trial in 21 PBC patients at dosages of 90 mg/day for 3 days followed by 180 mg/day on days 4–14. After 2 weeks, itch intensity declined by 57% on a NRS scale in the verum group compared with 23% in patients receiving placebo [28]. Bile salt-induced diarrhea presented the most common adverse event. Significantly more elevated TBS and autotaxin concentrations were found in pruritic vs non-pruritic PBC patients, which decreased on linerixibat [81]. A currently conducted phase IIb trial (GLIMMER trial) and its extension study further investigate linerixibat in multiple doses (20–180 mg/day) for long-time effects and safety in PBC patients.

Maralixibat (Lopixibat, LOM001, SHP-625) represents a further IBAT inhibitor, which was applied in a parallel, randomized, placebo-controlled phase II trial (CLARITY trial). In contrast, it did not improve pruritus more effectively than placebo in 66 PBC patients [33••]. Here, the Adult Itch Reported Outcome (ItchRO™) scale spanning between 0 (no pruritus) to 70 (maximal pruritus) was chosen as primary efficacy outcome. A total of 10 and 20 mg/day of maralixibat reduced pruritus intensity on the ItchRO scale (− 25.6 and − 27.3) in a similar range as placebo (− 23.4).

Odevixibat (A4250), again another IBAT inhibitor, was tested in an open-label exploratory phase IIa study including 9 PBC patients. Doses of 0.75 or 1.5 mg/day were applied for 1 week with a following increase to 1.5 or 3 mg/day for 3 weeks. Only four patients finished the 4-week protocol and also reported a decrease in pruritic intensity. Five patients stopped their participation in the study early due to diarrhea and abdominal discomfort [27]. Odevixibat has also been investigated in pediatric cholestasis syndromes in a multiple dose (10–200-μg/kg bodyweight/day), open-label trial. Although difficult in pediatric patients, placebo-controlled trials are warranted to proof the benefit of IBAT inhibitors above the placebo level. Long-term experience and safety data are not yet available for IBAT inhibitors.

Conclusions

A stepwise treatment approach should be applied for pruritus in cholestatic liver disease (Table 1). We propose cholestyramine as first choice, e.g., a 4-g sachet before and after breakfast. It is important to mind a 4-h interval to the intake of other

oral drugs including UDCA. In case pruritus is not ameliorated within the next 2 weeks, rifampicin represents the second option, starting with a dose of 150 mg/day. Although often already effective at this low dose, rifampicin might be uptitrated to 600 mg/day. Bezafibrate at doses of 200–400 mg/days is recommended as the third-line choice, if rifampicin fails to improve pruritus over a time of 2 to 4 weeks. In case of insufficient reduction of pruritus over 4 weeks or adverse events, naltrexone can be considered as the fourth-line regimen. Here, a gradual dose increase with low starting doses of 12.5 mg/day and a subsequent dose increase every 3 days is favorable. SSRI might be offered to patients with an inadequate treatment response to naltrexone, i.e., sertraline at doses of 75 mg/day as the fifth-line option. Following this approach, a majority of patients will respond with adequately controlled pruritus. In case of intolerance or inefficacy of the guideline-based recommendations, patients should be included in ongoing clinical trials or referred to specialized centers for experimental approaches such as UVB phototherapy, molecular adsorbent recirculating system (i.e., MARS®, Prometheus®), nasobiliary drainage, plasmapheresis, plasma separation, or anion absorption. Co-applications of different drugs are possible but should be restricted to expert centers.

Pruritus in cholestasis remains a challenging and often commonly trivialized symptom in many chronic hepatobiliary diseases. Unraveling further underlying molecular targets has recently led to the development of several novel drug classes, among which are ATX inhibitors and MRGPRX4 antagonists. Clinical trials have to prove their efficacy in humans; however, they represent a glimmer of hope for causal anti-pruritic therapies in hepatobiliary disorders.

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Compliance with Ethical Standards

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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