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LIVER (S COTLER AND E KALLWITZ, SECTION EDITORS)

Treatment of Pruritus Secondary to Liver Disease

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Abstract

Purpose of Review Pruritus is a common extrahepatic symptom in various liver disorders, in particularly those with cholestatic features. This review summarizes epidemiology, pathophysiology, evidence-based therapeutic recommendations and currently investigated drugs for pruritus in hepatobiliary disorders.

Recent Findings Recent epidemiological data suggest pruritus as a common and relevant symptom in immune-mediated liver diseases, i.e., primary biliary cholangitis (PBC) with over 70% affected patients, up to 56% suffering from chronic pruritus. The better pathophysiological understanding of hepatic pruritus has led to the identification of novel therapeutic targets, addressed in drug trials using KOR agonists, PPAR agonists, and ileal bile acid transporter inhibitors.

Summary Hepatic itch remains among the most agonizing symptoms for affected patients and a clinical challenge for physicians. Therapeutic recommendations include a guideline-based stepwise approach starting with cholestyramine, followed by rifampicin, naltrexone, and sertraline. Bezafibrate and ileal bile acid transporter inhibitors represent promising future anti-pruritic treatment options.

Keywords Autotaxin · Bile salt · Cholestasis · Liver · Lysophosphatidic acid · Pruritus

Introduction

Chronic pruritus is a significant burden and disabling symptom in several systemic medical conditions [1•]. Approximately one out of five patients with generalized pruritus suffers from a systemic disease [2]. Hepatobiliary conditions, chronic kidney disease, and hematological disorders are the three most common systemic disease entities associated with chronic pruritus. The affected hepatobiliary disorders are characterized by an impairment of hepatocellular and/or cholangiocellular bile formation and flow. Intrahepatic cholestasis may be caused by pure hepatocyte secretory failure as observed in intrahepatic cholestasis of pregnancy (ICP), toxin- or drug-induced cholestasis, benign recurrent intrahepatic cholestasis (BRIC), progressive familial intrahepatic cholestasis (PFIC), and chronic viral hepatitis infections. Pruritus may also be due to intrahepatic bile duct damage and secondary hepatocyte secretory failure as observed in primary biliary cholangitis (PBC), primary and secondary sclerosing cholangitis (PSC/SSC), and pediatric cholestatic syndromes such as the Alagille syndrome. Extrahepatic cholestasis with compression of the biliary tree can be caused by obstructive tumors of the pancreatic head or enlarged lymph nodes located in the hilar region compressing the bile ducts. Intraductular obstruction can be induced by PSC/SSC, choledocholithiasis, cholangiocellular carcinomas, bile duct adenomas, and biliary atresia (Table 1). In general, pruritus secondary to liver diseases is more often seen in intrahepatic than extrahepatic cholestasis.

Epidemiology

Epidemiological data on chronic pruritus secondary to liver diseases are scarce. From clinical experience, it is evident that pruritus varies considerably between the different hepatobiliary diseases. It is the defining symptom in intrahepatic cholestasis of pregnancy (ICP) [3] and present in most patients with benign recurrent intrahepatic cholestasis (BRIC) or progressive familiar intrahepatic cholestasis (PFIC). Chronic pruritus is a pre-eminent symptom in chronic cholestatic disorders such as primary biliary cholangitis (PBC), primary or secondary sclerosing cholangitis

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Table 1 Therapeutic recommendations for pruritus secondary to liver disease

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)	Possible drug-drug interactions
6th line	Experimental approaches, e.g.,		
	Gabapentin	300–3600 mg/day (po)	Administration recommended only in specialized centers
	Phenobarbital	2–5 mg/day (po)	
	UVB light	1–2×/week	
	Albumin dialysis, nasobiliary drainage		

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

po, per os

(PSC/SSC) affecting up to 75% of cases at any time during the course of the disease [4, 5]. In a recently published series of 2194 PBC patients from the UK, 73.5% of patients reported on pruritus at some point of their disease with one-third of patients suffering from persistent pruritus [6]. In a survey from Germany, 577 PBC patients reported on a point prevalence of chronic pruritus of 56% with 69.2% suffering from pruritus for many years [7]. Obstruction of intra- or extrahepatic bile tracts is less frequently associated with pruritus. Itching was reported in up to 45% of patients with a malignant obstruction such as pancreatic head carcinoma and in 16% of patients with benign causes of obstruction of the bile system such a choledocholithiasis [8]. Chronic pruritus was also described in 5–15% of untreated patients with chronic hepatitis C virus infection while it is rarely seen in chronic hepatitis B virus–infected patients [9]. Similarly, patients with alcoholic or non-alcoholic fatty liver disease ((N)AFLD) or alcoholic or non-alcoholic steatohepatitis ((N)ASH) rarely report on pruritus even if cholestatic features are present [10].

Clinical Features

Itching in hepatobiliary diseases characteristically presents most intensely at the limbs, particularly at the palms and the soles, although pruritus might also generalize and affect other body parts [11]. It can result in serious consequences by inducing sleep deprivation as well as exhaustion, fatigue, and depression [12], especially as pruritus tends to follow a circadian rhythm with the most intense sensation present in the early evening and at night, which was convincingly demonstrated by measuring scratch activity in patients with PBC by piezoelectric electrodes attached to a fingernail [13]. Especially women with ICP commonly present with pruritus as the leading symptom [14]. But also women with other causes of hepatic pruritus struggle with increased symptoms in times of hormonal changes such as during late pregnancy or hormone replacement therapy [15, 16], indicating an impact of female sex hormones in pruritus in liver diseases. Opposite to pruritus in dermatological conditions, patients with hepatic itch do not present with primary skin lesions. Nevertheless, intense scratching activity may induce secondary skin alterations such as excoriations and prurigo nodularis, causing difficulties to distinguish hepatic itch from a primary dermatological condition.

Objective quantification of pruritus intensity is attempted in clinical practice and trials by different assessment scales, i.e., visual analogue scales (VAS) or numeric rating scales (NRS) [17•]. Although those are accepted standards, pruritus remains difficult to objectify as it is a subjective sensation that is influenced by various determinants and may even change significantly throughout in 1 day. Results of clinical trials addressing pruritus treatment and changes in itch intensity are difficult to compare as various assessment scales and varying primary end points have been chosen. This highlights the urgent need for standardization in clinical trial design for anti-pruritic therapies.

Pathogenesis

Molecular mechanisms including possible pruritogens, receptors, and pathways involved in chronic pruritus have been subject to elaborate research over the past years. In particular, animal-based models revealed novel insights into the signaling pathways of acute pruritus and itch transmission within the central nervous system. In contrast, detailed knowledge on the pathophysiological mechanisms of chronic pruritus in humans, among them pruritus secondary to liver disease, remains only partially elucidated.

Bile Salts

Bile salts have been discussed as potential agents in pruritus of cholestasis for many years [9, 18]. Ensuring adequate bile elimination from the body, e.g., by nasobiliary drainage, often results in a strong relieve of therapy-refractory hepatic itch [19, 20]. In cholestatic patients, serum bile salt levels were elevated and oral application of bile salts aggravated their pruritus [9]. On a molecular level, bile salts mostly bind upon the nuclear transcription factor farnesoid X receptor (FXR) or the transmembrane G protein-coupled receptor TGR5 [21], inducing the activation of transcriptional networks and intracellular signaling cascades. The synthetically modified bile salt obeticholic acid (OCA), a selective FXR agonist, has recently been used in several clinical studies for treatment of liver disorders. Patients with PBC [22••, 23] and NASH [24] experienced de novo or more intense pruritus as an adverse event after application of the drug, while surrogate markers of the respective conditions improved. The removal of potential pruritogens such as bile acids from the enterohepatic circulation represents an appealing treatment in pruritus secondary to liver diseases. The ileal bile acid transporter (IBAT) has therefore been considered a potential therapeutic target [25, 26]. IBAT inhibitors have demonstrated an itch attenuating effect in several clinical studies [27•, 28–30]. Still, there are other findings which suggest that bile salts are not the primary pruritogens in cholestatic itch. So far, no correlation between the intensity of hepatic pruritus and levels of bile salts in serum, urine, or skin could ever be shown [2, 31]. In ICP, pruritus is among the defining criteria of the condition but total serum bile salt (TBS) levels are only marginally elevated [14]. Patients with PBC frequently experience pruritus as a first symptom at an early stage of disease without significant cholestasis and increase in bile salt levels; if the condition advances further including liver cirrhosis with intense cholestasis, itching is often diminished [16]. Obstructive cholestasis is associated with increased TBS but much less with pruritus [32] and the modern anion exchange resin colesevelam reduced TBS levels by approximately 50% without being superior to placebo in ameliorating pruritus [33•]. Total serum bile salt levels therefore do not seem to represent the main pruritogens in cholestatic pruritus, although certain subspecies might contribute in a yet to be determined mechanism [11]. One mechanism might be the activation of the sub-receptor X4 of the Mas-related G protein-coupled receptor family, which is expressed on sensory neurons [34]. However, these intriguing findings in mice have to be confirmed in humans.

Bilirubin Component

Recently, bilirubin has been suggested to directly activate sensory neurons and to mediate itch in an animal model of cholestasis. Meixiong and colleagues could show that bilirubin activated subclasses of the Mas-related G protein-coupled receptor family which are expressed on sensory neurons [35]. This interesting finding is however in contrast to the clinical experience that numerous patients suffering from pruritus are not jaundiced and conversely, many icteric patients never report on pruritus. Thus, it is likely that a yet undefined molecule within the bilirubin fraction may trigger pruritus in cholestasis.

Endogenous Opioids

The involvement of endogenous opioids in the pathophysiology of cholestatic pruritus has been another main theory in the past [18]. It is well known that opioid treatment can cause itching as an adverse effect, particularly in case of epidural or spinal application [36]. Elevated concentrations of endogenous opioids were detected in rats with cholestasis after bile duct resection [37, 38] and also in PBC patients with cholestasis [39, 40]. In the liver of cholestatic rats, the expression of preproenkephalin mRNA was elevated [41] and Met-enkephalin immunoreactivity was seen in liver tissue of PBC and chronic hepatitis C patients [42, 43]. But there are important findings which contradict a major role of endogenous opioids in the pathogenesis of pruritus in cholestasis. Equally to bile salts, no correlation between the intensity of itch and endogenous opioid levels has even been established [39]; furthermore, in PBC patients, opioid concentrations rather correlated with the stage of disease than pruritus, as they were significantly elevated in advanced histological stages, at which pruritus usually improves [31, 39]. A comparable opioid activity in PBC patients with and without pruritus was observed as well as in women with ICP and pregnant controls [31]. The opioid system might therefore be a modulating factor in cholestatic pruritus, but endogenous opioids are unlikely to be the causal pruritogens.

LPA-ATX Axis

Lysophosphatidic acid (LPA) has been shown to be a significant neuronal activator in sera of pruritic patients with liver disease [31]. Serum concentrations of the enzyme autotaxin (ATX), hydrolyzing LPA from its precursor molecule lysophosphatidylcholine (LPC), were increased in pruritic patients compared with those without pruritus [44] and had a high accuracy to diagnose intrahepatic cholestasis of pregnancy [45]. ATX activity correlated with itch intensity and response to therapeutic interventions, which could not be demonstrated for other suspected pruritogens so far. In mice, intradermal injection of LPA dose dependently caused scratching behavior [31, 44]. In cultures of dorsal root ganglia, it has recently been shown that LPA mediates its effects via the activation of LPA receptor 1 on satellite glia cells [46]. LPA could also induce an itch sensation in humans upon focal

application (unpublished data). Interestingly, a molecular interplay between ATX-LPA signaling and natural bile salts was recently described, strengthening the association of ATX with conditions of increased systemic levels of bile salts [47]. Thus, the ATX-LPA axis represents an intriguing signal pathway for potential therapeutic interventions in patients with pruritus secondary to liver disease.

Treatment

Reliable data for treatment recommendations for pruritus in liver disease result from few randomized, placebo-controlled trials and several cohort studies [48]. Aside from systemic treatment, general advice regarding skin care should be given to the patient. This includes the usage of emollients and oatmeal extract to ameliorate inflammation and dry skin, regular usage of moisturizing and cooling topical agents (e.g., emollients containing 1–2% menthol), shortening of fingernails to prevent from severe skin damage, and applying cold water in situations pruritus is worsened by warmth, e.g., after a hot bath, sportive activity, or at night [49]. In case of addictive scratching, psychologic consultation might be considered. Other causes for chronic pruritus such as dermatological diseases should be excluded.

Drug treatment as well as interventional options for treating cholestatic pruritus results from several pathogenetic considerations [50]:

- To eliminate potential pruritogens from the enterohepatic cycle/body circulation by anion exchange resins such as cholestyramine, IBAT inhibitors (linerixibat, maralixibat, A4250), interventional approaches such as nasobiliary and transcutaneous drainage or external biliary diversion, plasmapheresis, or extracorporeal albumin dialysis in difficult cases
- To modify metabolism of potential pruritogens in the liver and/or intestine by inducers of hepatic biotransformation enzymes such as rifampicin or the peroxisome proliferator-activated receptor (PPAR) agonist bezafibrate
- To modulate the central itch/pain pathway by interfering with the endogenous opioidergic and serotoninergic system using opioid-modifying drugs and selective serotonin re-uptake inhibitors (SSRI), i.e., μ-opioid antagonists such as naltrexone, κ-opioid-agonists such as nalfurafine, and selective serotonin re-uptake inhibitors such as sertraline
- To change itch perception locally in the skin by UV-phototherapy

Of note, all mentioned drugs—aside of cholestyramine—represent "off label" use. Current European and American guidelines recommend to administer anti-pruritic therapies in a stepwise manner in order to efficiently alleviate hepatic pruritus (Table 1) [49, 51].

Treatment in Current Use

Ursodeoxycholic Acid

The bile acid ursodeoxycholic acid (UDCA) is used as beneficial baseline therapy in several cholestatic conditions such as PBC, PSC, ICP, and pediatric cholestatic syndromes by excreting anti-cholestatic properties, i.e., improved hepatobiliary secretory function and reduced bile toxicity [52]. UDCA treatment positively affects overall survival in PBC patients [48]. However, UDCA at dosages of 13–15 mg/kg/day convincingly attenuated itch intensity solely in women with ICP. Pruritus improved in 73% of ICP women as recently summarized in a meta-analysis of 11 randomized controlled trials [53]. For other chronic liver disorders such as PBC and PSC, no significant beneficial effect on pruritus could be proven in randomized, placebo-controlled trials [9].

Antihistamines

Although often prescribed in clinical routine, anti-histaminergic drugs are mostly ineffective in hepatic pruritus [7]. Furthermore, fatigue is an inherent feature especially in autoimmune-mediated liver disease, which can be worsened by the sedative component in particular of first-generation antihistamines. Thus, antihistamines should not be applied in pruritus secondary to liver disease.

Cholestyramine

The anion exchange resin cholestyramine currently remains the guideline-recommended first choice for treatment of pruritus in liver diseases [49]. Data on efficacy are based on small, non-placebo-controlled trials, in which itching was diminished over a period of 2 weeks [9]. The bile sequestrant can be applied in a dosage of a 4-g sachet, i.e., 1 hour before and after breakfast, which might be raised to 4 × 4 g/day. Patients should be instructed to take cholestyramine with a minimum time interval of 4 h to any other medication due to possible interference with their intestinal absorption [54]. From a clinical expert opinion, cholestyramine does not exert strong anti-pruritic effects in most patients. Furthermore, possible adverse effects are mainly in the gastrointestinal tract including bloating, abdominal discomfort, and malabsorption of fat and fat-soluble vitamins. In addition, the resin is often not well tolerated by patients due to its unpleasant taste. Colesevelam, another anion exchange resin, adsorbing bile salts more efficiently than cholestyramine, did not prove superior in a well-defined, randomized, placebo-controlled trial

[33•]. Although there could be differences between bile sequestrants for their potential to bind, yet to be specifically defined, pruritogens, this finding gives rise to doubt the role of exchange resins as first-line treatment in pruritus of liver diseases.

Rifampicin

The pregnane X receptor (PXR) agonist rifampicin is recommended as second-line treatment for pruritus secondary to liver disease. Its effect in reducing hepatic itch is suggested to be mediated via the induction of several biotransformation enzymes and transporters in the liver and intestine, altering metabolism and excretion of potential pruritogens. In addition, being an antibiotic drug, the intestinal and skin microbiome could also be modified by rifampicin. Although phenobarbital also acts as an inducer of CYP3A4 such as rifampicin, it proved inferior in the reduction of pruritus in a randomized controlled trial, suggesting that further mechanisms contribute to the anti-pruritic effect of rifampicin [55]. It should be noted that the expression of ATX was reduced in vitro by rifampicin at the transcriptional level via mediation of PXR [44]. Several randomized, placebo-controlled trials have proven that rifampicin at doses of 150–600 mg/d is an effective and safe treatment in pruritus in hepatobiliary disorders [56], which was confirmed in meta-analyses [57]. From a clinical perspective, rifampicin, if well tolerated, has the strongest anti-pruritic effect in hepatic itch and can be administered for a long period of time, up to many years. In the majority of cases, a dose of 150 mg/d is sufficient. Monitoring of laboratory is recommended after 6 and 12 weeks of therapy or dose changes, as hepatotoxicity has to be considered as a serious adverse effect [49]. In the real-life setting, hepatotoxicity is low and seen in approximately 5% of patients, for most cases in long-term treatment [58•]. Other adverse effects include nausea and loss of appetite as well as the harmless adverse effect of change in urine or tears to orange-red color.

Peroxisome Proliferator-Activated Receptor Agonists

Peroxisome proliferator-activated receptors (PPARs) represent intracellular transcription factors, which upon being bound by various physiological and pharmacological agents, regulate the expression of numerous genes, influencing body metabolism, cellular differentiation, and development of different organs such as the liver [59]. For many years, fibrates, acting as agonists of PPAR α, γ, and δ, have been used as therapeutics for hyperlipidemia, but recent findings suggest also anti-cholestatic effects. In an investigator-initiated, randomized placebo-controlled 2-year trial (BEZURSO trial), bezafibrate given at doses of 400 mg/day in PBC patients with incomplete response to UDCA [60••] resulted in laboratory normalization in 30% of patients. In retrospective analyses, bezafibrate also showed a reduction in pruritus in PBC patients [61]. In the BEZURSO trial, in which itch intensity was analyzed as a secondary outcome, patients treated with bezafibrate had a 75% reduction of pruritus. However, it has to be considered that the median baseline pruritus in bezafibrate-treated patients was one on a visual analogue scale [60••], suggesting a clinically insignificant level of pruritus [62, 63]. Currently, the placebo-controlled FITCH (Fibrates in Itch) trial investigates bezafibrate in PBC and PSC patients with moderate to severe itch to further analyze its anti-pruritic efficacy. It should be noted that bezafibrate is unavailable in the USA. Fenofibrate may be used as substitution. In summary, the combined anti-cholestatic and anti-pruritic effect of fibrates appears very attractive and is therefore already recommended as third-line regimen in this manuscript.

μ-Opioid Antagonists

The μ-opioid antagonist naltrexone is considered the fourth option in a stepwise therapeutic approach after bezafibrate. Naltrexone at doses of 25–50 mg/d was mildly effective in alleviating pruritus in some small placebo-controlled trials [64, 65]. In a meta-analysis, the anti-pruritic influence of naloxone and naltrexone was calculated with a standardized mean difference of − 0.68 (− 1.19 to − 0.17; 95% CI) which was significantly lower than that for rifampicin with − 1.62 (− 3.05 to − 0.18; 95% CI) [57]. Starting doses of naltrexone should be chosen low as opiate withdrawal reactions may occur. Alternatively, treatment can be started with increasing doses of intravenous naloxone before switching to oral naltrexone which is a suitable option in hospitalized patients [16]. As pruritus might reoccur during treatment with naltrexone as so-called breakthrough phenomenon, a pause in application of 1 or 2 days per week can be considered [66]. Various painful disorders such as back or joint pain may significantly limit the use of μ-opioid-receptor antagonists [67]. Further adverse events might include headache, nausea, vomiting, and dizziness.

Selective Serotonin Re-Uptake Inhibitors

Selective serotonin re-uptake inhibitors (SSRI), i.e., sertraline or paroxetine, may be considered the fifth-line option. A moderate itch-reducing effect was reported in a single placebo-controlled, cross-over trial using sertraline [68] and some case series [69] as well as a randomized controlled trial using paroxetine [70]. Dosages for sertraline should be chosen at 75–100 mg/day. Common adverse events mainly occur by influencing the central nervous system causing among others insomnia, agitation, and change in appetite.

Future Treatments

κ-Opioid Receptor Agonists

In 2015, the κ-opioid receptor agonist nalfurafine was licensed for the treatment of hepatic itch in Japan. Earlier, the drug was tested in a placebo-controlled trial with hemodialysis patients suffering from uremic pruritus with mild anti-pruritic effects [71], also confirmed in a meta-analysis of two placebo-controlled double-blind trials in chronic kidney disease-associated pruritus [72]. In a randomized, placebo-controlled trial including 318 patients with pruritus from various liver disease treatments with nalfurafine at dosages of 2.5 μg/d and 5 μg/d showed a significant but clinically questionable benefit after 4 and 12 weeks of therapy [73]. It has to be stated that a quite undefined and inhomogeneous patient cohort was investigated within this trial. Adverse events included somnolence, insomnia, and pollakiuria including nycturia and constipation. Nalfurafine is currently not available in Europe or the USA.

Further, κ-opioid receptor agonists are currently being evaluated in clinical trials as treatment options for chronic pruritus of various origins such as atopic dermatitis or chronic kidney disease. If these agonists proof higher efficacy, further trials in liver diseases are warranted.

Ileal Bile Acid Transporter Inhibitors

As mentioned above, the ileal bile acid transporter (IBAT) represents a highly selective target for interrupting the enterohepatic cycle, resulting in augmented excretion of bile salts with feces. Recently, the IBAT inhibitor linerixibat (= GSK2330672) was applied in a phase II cross-over, randomized, placebo-controlled trial in 21 patients with PBC at dosages of 90 mg/day for 3 days followed by 180 mg/day on days 4–14. The results showed a reduction of itch in 57% on the NRS scale after 14 days in linerixibat-treated patients compared with 23% in the placebo group [27•]. The major adverse event was bile salt-induced diarrhea. In a post hoc analysis, these PBC patients had elevated serum bile acid and autotaxin levels compared with PBC patients without pruritus and healthy controls which decreased after IBAT inhibitor treatment [28]. Linerixibat is further investigated in a currently running phase III trial (GLIMMER study) at different dosages (20 to 180 mg/day) to provide information on its long-term efficacy and safety in PBC patients.

In contrast, maralixibat (lopixibat, LUM001, SHP-625), another IBAT inhibitor, was not superior to placebo in a 13-week randomized, placebo-controlled phase II trial (CLARITY trial) in 55 PBC patients [30]. Recently, an open-label exploratory phase IIa study was conducted with nine PBC patients using A4250, a third IBAT inhibitor. An improvement in pruritus was seen in four patients who finished the protocol, whereas five patients dropped out of the trial early because of intestinal adverse events such as bile acid-associated diarrhea [29]. A4250 has also been investigated in pediatric cholestasis syndromes in a multiple dose, open-label trial. The attenuation of pruritus was however comparable with the effects of placebo in other trials using IBAT inhibitors.

The different outcomes of trials of these drugs may result from varying trial designs, non-standardized outcome variables for pruritus and drug dose as well as potency.

Expert Treatment Recommendation in Real-Life Setting

A step-by-step protocol is recommended in pruritus secondary to liver disease (Table 1). UDCA (13–15 mg/kg/day) should be chosen as first-line anti-pruritic treatment in ICP. Albeit UDCA exerts positive anti-cholestatic effects in chronic liver diseases, it has no significant impact on pruritus. In these disorders, the anion exchange resin cholestyramine represents the first choice for pruritus in liver diseases given as a 4-g sachet before and after breakfast. Patients should be advised to separate the intake of cholestyramine from UDCA and other drugs for at least 4 h. If no improvement is reported after 2–4 weeks, rifampicin should be considered with a starting dose of 150 mg/day. The low dose of 150 mg is sufficient in many patients, but rifampicin may be up-titrated to 600 mg/day. If patients do not respond to rifampicin within 2 weeks, bezafibrate at doses of 200–400 mg/day should be considered the third-line regimen. If itch is not attenuated within 4 weeks or adverse events occur, naltrexone is recommended as the fourth-line therapy. Starting dose should be chosen low, i.e., 12.5 mg/day with a stepwise increase every 3 days. Patients non-responsive to naltrexone within 4 weeks may be offered SSRI, i.e., sertraline at doses of 75 mg/day as the fifth-line option.

The majority of patient will respond to the suggested approach. Patients being unable to tolerate the above-mentioned drugs or experiencing insufficient therapeutic benefit are advised to be included in ongoing clinical trials or to be 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. It is advised against co-applying the different drugs to avoid interactions. Caution should be made in cirrhotic patients in particular those with decompensated liver disease. Rifampicin, bezafibrate, and fenofibrate may exert a significant increased toxicity potentially resulting in acute-on-cirrhosis liver failure.

Conclusions

Chronic pruritus is a burdensome and often underestimated symptom in various hepatobiliary diseases. Recent epidemiological data suggest a higher-than-expected prevalence

particularly in PBC patients. The better pathophysiological understanding has emerged new therapeutic targets, and novel drug classes are currently investigated in clinical trials, partly showing promising results. A stepwise guideline-based stepwise approach is effective in the majority of patients (Table 1). Further, findings of ongoing drug trials are awaited to provide more, better tolerated, and potentially causal therapeutic options to desperate patients. Experimental and interventional approaches should be reserved for otherwise intractable pruritus and performed at expert centers.

Compliance with Ethical Standards

Conflict of Interest Miriam M. Düll declares no conflict of interest. Andreas E. Kreme has received speaker fees from CymaBay, Falk Foundation, and Intercept and has signed advisory contracts with Beiersdorf, GSK, and Intercept. He further received unrestricted research grants from Intercept.

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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