Primary Sclerosing Cholangitis

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Pathogenesis and Management of Pruritus in PBC and PSC

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Abstract
Pruritus is a preeminent symptom in patients with chronic cholestatic liver disorders such as primary biliary cirrhosis and primary sclerosing cholangitis. More than two-thirds of these patients experience itching during the course of their disease. This symptom is also frequently observed in patients with other causes of cholestasis such as cholangiocarcinoma, inherited forms of cholestasis and intrahepatic cholestasis of pregnancy, but may accompany almost any other liver disease. The pathogenesis of pruritus of cholestasis remains largely elusive. Increased concentrations of bile salts, histamine, serotonin, progesterone metabolites and endogenous opioids have been controversially discussed as potential pruritogens. However, for these molecules, neither a correlation with itch intensity nor a causative link could be established. The G protein-coupled receptor for bile salts, TGR5, has been shown to be expressed in dorsal root ganglia and give rise to itch in rodents, albeit upon stimuli with suprapathological concentrations of bile salts. The potent neuronal activator lysophosphatidic acid (LPA) and its forming enzyme, autotaxin (ATX), could be identified in the serum of patients with cholestatic pruritus. ATX activity correlated with itch severity and effectiveness of several anti-pruritic therapeutic interventions in cholestatic patients. Thus, the ATX-LPA-axis may represent a key element in the pathogenesis of this agonizing symptom. Treatment options for pruritus of cholestasis remain limited to a few evidence-based and several experimental medical and interventional therapies. The current guideline-based recommendations include the anion exchange resins colestyramine, the pregnane X receptor-agonist and enzyme inducer rifampicin, the μ-opioid antagonist naltrexone, and the selective serotonin reuptake inhibitors sertraline. Still, a considerable part of patients is unresponsive to these drugs and requires experimental approaches including phototherapy, plasmapheresis, albumin dialysis or nasobiliary drainage. This review outlines the current knowledge on pathogenesis of cholestatic pruritus and summarizes evidence-based and experimental therapeutic interventions for cholestatic patients with itch.

Introduction

From an evolutionary perspective, itching serves as an alarm signal to protect the body against potentially harmful environmental threats such as parasites, noxious

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plants or other irritants. The scratch response helps to remove these harmful agents from the skin and ameliorates the itch sensation. Acute pruritus largely arises from degranulation of skin mast cells and is likely mediated by histamine-responsive sensory neurons in the skin that are relatively insensitive to mechanical pain stimuli but also respond to noxious chemicals such as capsaicin [1]. In contrast, chronic pruritus can be a seriously debilitating symptom accompanying various cutaneous and systemic disorders [2–4], but may also be caused by drugs such as the anti-malaria drug chloroquine or the volume expander hydroxyethyl starch [5]. Antihistamines do not alleviate itching in most of these conditions, indicating that the itch sensation is mediated via histamine-independent pathways. Recently discovered receptors involved in itch signalling of rodents such as the Mas-related G protein-coupled receptors (Mrg) for chloroquine, bovine adrenal medulla 8–22 and β-alanine [6, 7], the μ-opioid receptor (MOR) 1D (MOR1D) for morphine-induced pruritus [8], endothelin-A-receptor for endothelin-1 [9], as well as the toll-like receptors 3 and 7 (TLR3 and 7) [10–12], interleukin-13 [13] and heterodimeric receptor consisting of the IL-31 receptor α (IL-31RA) and the oncostatin M receptor (OSMR) for IL-31 [14] have been shown to mediate itch sensation in a histamine-independent fashion. To which extent these receptors and associated signalling pathways play a role in numerous human disorders associated with chronic pruritus remains to be elucidated.

Chronic pruritus, which is defined by a duration of more than 6 weeks, also accompanies many hepatobiliary diseases, particularly those disorders with cholestatic features [15–17]. Here, cholestasis may either be caused by hepatocellular cholestasis due to hepatocellular secretory failure, cholangiocellular cholestasis with intrahepatic bile duct damage or obstructive cholestasis of the intrahepatic or extrahepatic bile duct system [15, 18].

This review highlights the current knowledge on putative pathomechanisms and currently available treatment strategies of pruritus due to primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

Prevalence, Localization and Influencing Factors of Cholestatic Pruritus

The prevalence of cholestatic pruritus varies considerably in terms of the different hepatobiliary disorders. While pruritus is a defining symptom of intrahepatic cholestasis of pregnancy (ICP) [19], it is a pre-eminent symptom in 25–80% of patients with chronic cholestatic liver disorders such as PBC and PSC and experienced by 80% of patients at any time during the course of their disease [20–23]. Obstructive cholestasis is less frequently accompanied by pruritus and was reported to occur in 16% of patients with benign biliary obstruction such as choledocholithiasis and up to 45% of those with malignant obstruction such as carcinoma of the head of the pancreas [24]. In patients with chronic hepatitis C infection, pruritus was noted in 5–15% of patients [25–27], whereas it is rarely associated with chronic hepatitis B infection, parenteral nutrition-induced cholestasis, biliary hamartomas, Caroli syndrome, congenital liver fibrosis, alcoholic or non-alcoholic fatty liver disease, or alcoholic or non-alcoholic steatohepatitis (NASH) even if cholestasis is present [28].

Besides fatigue, chronic pruritus represents a major burden of patients with PBC or PSC and can dramatically reduce the quality of life [29]. In these patients, itching may be mild and tolerable, but in some patients, it does limit daily life activities, cause severe sleep deprivation resulting in lassitude, fatigue, depressed mood and even suicidal tendencies. In rare cases, intractable pruritus may become a primary indication for liver transplantation [30–33].

Pruritus of cholestasis is characterized by a circadian rhythm with patients reporting the highest intensity in the evening and early at night [18], but it should be mentioned that chronic pruritus in general tends to increase with warmth and at night. A predilection site of pruritus in PBC and PSC patients is the limbs and in particular the palms and soles [22, 34], although generalized pruritus is reported by many patients. Patients may report that scratching barely alleviates itch sensations and that pruritus is accompanied with other sensations such as stinging and burning. Furthermore, female cholestatic patients commonly report pruritus worsening during the progesterone phase of the menstrual cycle, in late pregnancy, and during hormone replacement therapy [18, 35]. In multivariate analysis, serum alkaline phosphatase and the Mayo risk score were found to be independent indicators for the occurrence of pruritus in 335 PBC patients [36]. The Mayo risk score is derived from an equation containing clinical variables including patient age, serum total bilirubin, albumin, prothrombin time, and the presence/absence of oedema or ascites.

In contrast to pruritus in dermatological disorders, primary skin lesions are not detectable in cholestatic patients; however, intense scratching activity may cause secondary skin alterations such as excoriations and prurigo nodularis [37]. Although secondary skin lesions may be

difficult to discriminate from primary skin disorders, if no scratch tools are used, the so-called butterfly sign points to a non-dermatological cause of chronic pruritus. This sign is defined as unaffected skin at the upper patient's back due to difficulties to manually reach that part of the body. Furthermore, typical skin signs of chronic liver disorders such as jaundice, spider naevi, palmar erythema or leuconychia may help to identify the underlying cause.

It is common experience that intensity of pruritus may be temporarily affected by parenteral, oral or local application of a placebo. Hence, randomized, placebo-controlled and double-blinded trials are needed to validate new antipruritic treatment strategies.

Pathogenesis of Pruritus in Cholestasis

In recent years, the knowledge on receptors and pathways involved in acute and chronic itch signalling in rodents has grown remarkably [38–41]. In contrast, the underlying ligands and receptors for chronic pruritus in human beings remain unsolved for most dermatological and systemic disorders [42]. Likewise, the pathogenesis of pruritus in PBC and PSC remains largely elusive. Various substances, among which are histamine, serotonin, bile salts, endogenous opioids and progesterone metabolites, have been proposed but with limited evidence as pruritogens in the past. It is therefore likely that these substances do not represent the direct neuron activating molecules, but modulate or sensitize sensory neurons, thereby contributing to the itch sensation. The reader is referred to previous reviews [17, 43] for detailed rationale in favour of or against these substances. Recently, we could identify the potent neuronal activator lysophosphatidic acid (LPA) as potential pruritogen in cholestasis [44]. Still the detailed molecular mechanisms of cholestatic pruritus remain to be unravelled.

This review summarizes novel insights into the recently described G protein-coupled receptor TGR5 on sensory neurons, the autotaxin (ATX)-LPA-axis and the neuronal signalling pathways, which likely play a role in chronic pruritus.

Itch Signalling Pathways

Almost a century ago, itch was regarded as a mild form of pain induced by the weak activation of nociceptive nerve fibres [45]. However, substances such as histamine and the spicules of the tropical fruit mucuna pruriens, cowhage, induce itch even at high concentrations, whereas weak pain stimuli often do not induce itch [46, 47]. In 1997, Schmelz et al. [1] provided evidence for primary afferent neurons specific for histamine in cutis and subcutis of human beings. These itch-specific unmyelinated C-fibers are insensitive to mechanically induced pain stimuli and transmit their signals from the skin through the dorsal root ganglia to a second neuron in lamina I of the dorsal horn of the spinal cord. These observations indicated that itch and pain are transmitted via itch-selective and pain-selective neurons, respectively [47–49]. Interestingly, itch signals induced by histamine and cowhage are transmitted by mutually exclusive populations of neurons in the spinal cord [50], supporting the existence of different classes of pruritoceptive nerve fibres, as also known for nociceptive neurons. It was postulated that itch sensation evoked by a given stimulus modality would depend on a specific neuronal pathway, the itch-specific 'labelled-line' [51]. However, this theory is contradicted by the observation that these itch-selective neurons can also be activated by the algogen and transient receptor potential (TRP) vanilloid receptor subfamily V1 (TRPV1) agonist capsaicin [52]. An elegant animal study indicated that a small subpopulation of sensory neurons expressing the Mrg subtype A3 (MrgA3) could represent itch-selective neurons [53]. Scratching behaviour in mice was strongly attenuated to most intradermally applied pruritogens after ablation of these MrgA3 positive neurons. In a second step, mice lacking the TRPV1 channel were used and TRPV1 was re-expressed only in MrgA3 positive neurons. In these mice, the algogen capsaicin largely caused scratching behaviour but hardly any pain-related wiping [53]. Thus, irrespective of the modality of activation, these neurons seem to induce itch sensation but no pain. Still, the itchy spicules of cowhage activated every single polymodal nociceptor tested in human microneurography [54]. The cowhage enigma remains and seems to be incompatible with the labelled-line hypothesis, unless the highly focal stimulus of these spicules is taken into account. The spatial contrast theory may explain this paradox by stating that itch arises from a sharp contrast between individual nociceptors that are firing and their surrounding neighbour remain silent. Pain sensation occurs if the overlapping receptive fields are more homogenously activated [55].

Although there might be subsets of neurons selectively mediating itch and pain signals, both pathways are closely intertwined processes: activation of pain neurons abrogates itch sensation, for instance, by scratching, cooling or heating of the skin [2, 56]. Analgesics may induce itch sensation, for example, by epidural or intrathecal application of opioids or anaesthetics [57–59]. These phe-

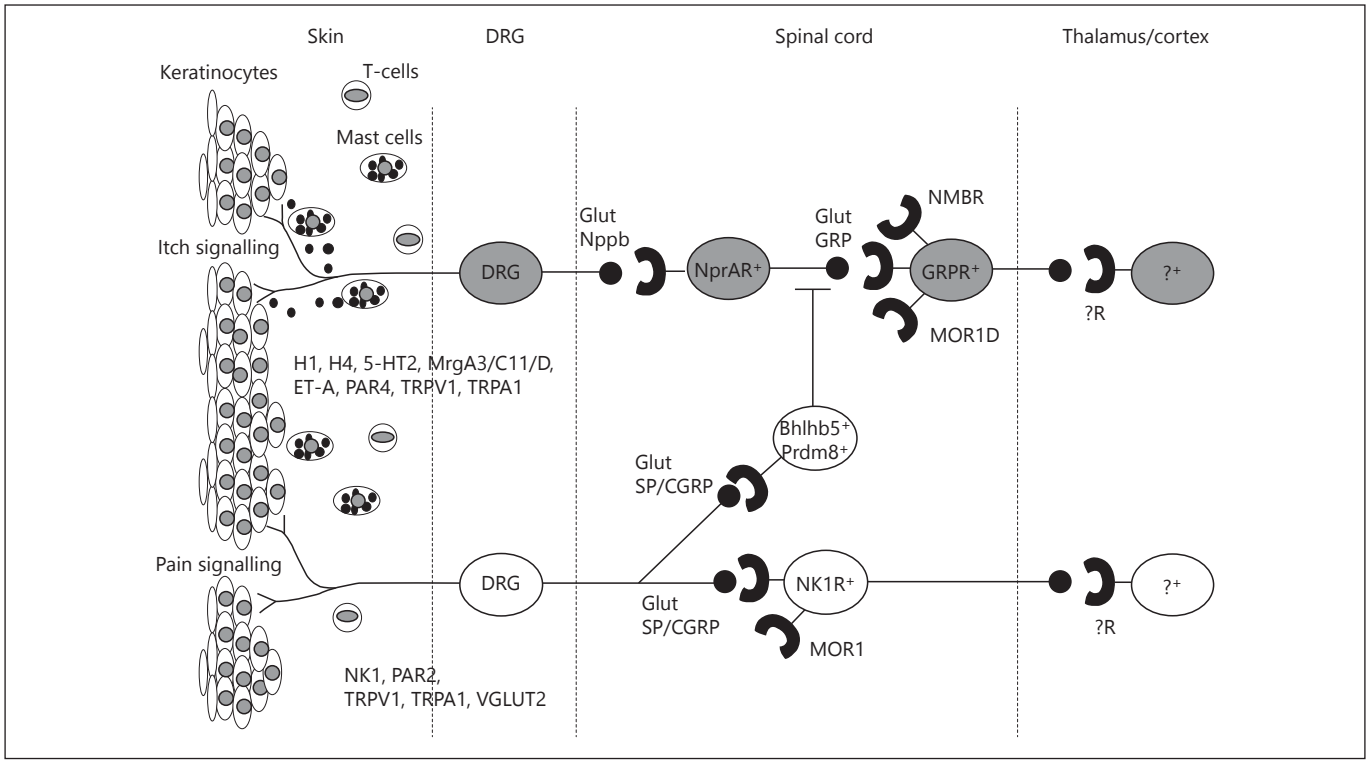

Fig. 1. Neuronal itch signalling. Simplified scheme of pain and itch-signalling pathways from the peripheral to the central nervous system and their interaction. Itch- and pain-causing molecules bind to specific receptors on sensory nerve endings in the epidermis or dermis. Among the established receptors for itch signalling are histamine (H1, H4), serotonin (5-HT2), MrgA3, MrgC11, MrgD, endothelin (ET-A), PAR4, TLR3 and TLR7, and heterodimeric receptor consisting of the IL-31RA and the OSMR. These neurons also express TRP receptors such as TRPV1 and TRPA1. Pruritus may also be initiated or potentiated by LPA receptors. Synaptic signal transmission from the peripheral sensory neuron to the secondary neuron in the dorsal horn of the spinal cord is mediated by glutamate (Glut) and Nppb. GRP and glutamate may be involved in signal transmission to the tertiary neuron. The neuronal itch-signalling pathway is under inhibitory control of the pain signals (as indicated by the Bhlhb5- and Prdm8-expressing interneurons). Pain sensation is similarly perceived by receptors on peripheral sensory neurons including neurokinin-1 for substance P or PAR2 for proteases. Synaptic signal transmission from the peripheral sensory neuron to the secondary pain neurons and interneurons in the dorsal horn of the spinal cord is presumably mediated by glutamate (Glut), substance P (SP), and calcitonin-gene related peptide (CGRP).

nomena may be explained by an itch circuitry, which is under a tonic inhibitory control of mechano-sensitive neurons (fig. 1). Evidence for such an inhibitory control was supported by the observation of spontaneous intense scratching behaviour in mice lacking certain inhibitory, Bhlbh5- and Prdm8-expressing interneurons [60, 61]. These interneurons are believed to be activated by glutamate. Interestingly, deletion of the glutamate transporter VGLUT2 also strongly augmented spontaneous and induced scratching behaviours after the application of pruritogens, which supports this hypothesis [62, 63].

Several receptors have been implicated in the onset of itch sensation [64]. The group of Mrgs represents a family of GPCRs consisting of more than 50 members in the mouse genome. Several of these Mrgs are specifically expressed in small-diameter sensory neurons in dorsal root and trigeminal ganglia, indicating their important role in somatosensation [65]. Recently, several of Mrgs have been unravelled as receptors that mediate non-histaminergic itch: the anti-malaria drug chloroquine was shown to activate MrgA3 [6]. The bovine adrenal medulla 8–22 peptide, which induces non-histaminergic itching when injected into human skin binds to MrgC11 [6], whereas β-alanine is a selective agonist of MrgD [7]. Thus, members of the Mrg family serve as pruriceptors, detecting different pruritogens on primary sensory neurons.

Other receptors involved in itch signalling have been protease-activated receptors 2 and 4 (PAR2 and 4), which have been shown to be activated by cathepsin S or mucunain, the active ingredient of cowhage [66, 67]. Intrader-

mal injection of SLIGRL-NH_2 the unmasked N-terminus (tethered ligand) of PAR2, induced robust scratching behaviour in mice and itch sensation in humans. It was believed that this peptide is hydrolyzed by proteases and induces itching upon activating PAR2. However, intradermal injections of SLIGRL-NH_2 exhibited comparable scratching behaviour in wild-type mice and PAR2 mutant mice, suggesting that PAR2 is not required for itch sensations mediated by SLIGRL-NH_2 [68]. In contrast, Liu and colleagues could show that SLIGRL-NH_2 mediates itching by the direct activation of MrgC11 [68]. This indicates that the unmasked N-terminus of PAR2, after cleavage by a protease, is capable of activating MrgC11 if present in the same neuron or a neighbouring cell.

The TLR3 has been implicated to play a role in pruritus [10]. The TLR3 agonist polyinosinic: polycytidylic acid directly activated primary sensory neurons and evoked a scratching behaviour in a TLR3-dependent manner. Interestingly, $TLR3^{-/-}$ mice exhibited a reduced scratching behaviour not only for a specific TLR3 agonist but also for many other pruritogens, indicating that TLR3 may also be involved in mediating itch sensations in the central nervous system [10]. Another toll like receptor, TLR7, has been shown to be expressed in sensory neurons. Two independent groups reported that imiquimod, a TLR7 agonist, induced scratching behaviour in mice [11, 12]. However, these groups presented conflicting data about whether the action of imiquimod is directly or indirectly mediated by TLR7.

Other important receptors in itch signalling are the splicing variant of the MOR, MOR1D, for morphine-induced pruritus [8], endothelin-A-receptor for endothelin-1 [9], the interleukin-13 receptor for IL-13 [13], and the heterodimeric receptor consisting of the IL-31RA and the OSMR for IL-31 [14]. Activation of these receptors results in the opening of TRP receptors such as the TRPV1 or ankyrin 1 channel (TRPA1) on sensory neurons [53, 69]. Primary sensory neurons signal to the dorsal horn of the spinal cord, where secondary neurons are activated by the release of glutamate and neuropeptide natriuretic polypeptide b (Nppb) [70]. Secondary neurons express natriuretic peptide receptor A (the receptor for Nppb) and were suggested to release gastrin releasing peptide (GRP), which activates the GRP receptor of a third neuron in the spinal cord (fig. 1) [51, 70, 71]. Ablation of either the NrpA- or GRP-receptor expressing neurons by intrathecal application of a toxin bound to the respective signalling molecule largely abolished scratching behaviour after the intradermal application of various pruritogens [51, 70]. Noteworthy, pain responses were unaltered after ablation of these neurons, indicating that a selective itch pathway exists at the spinal cord level [51, 70].

Pruritogenic Substances in Cholestasis

From a clinical and experimental perspective, the pruritogenic substances in hepatobiliary disorders are metabolized in the liver, excreted into bile, undergo an enterohepatic circulation and as a result of cholestasis accumulate in various tissues [72, 73]. The presence of direct or indirect pruritogens in the enterohepatic circulation is highlighted by the dramatic effects of interruption of this circulation either by nasobiliary drainage, which usually relieves itch within 24 h [74, 75]. We hypothesized that pruritogens accumulate in circulation and tissues during cholestasis, and that these molecules should be capable of activating neuronal cells. To identify these pruritogens, sera of cholestatic patients, with and without pruritus, were screened for the capacity of neuronal activation. Indeed, in a human neuroblastoma cell line, sera of cholestatic patients caused a dose-dependent transient rise in cytosolic free calcium concentrations [44]. The main neuronal activator could be unravelled as a potent lipid mediator, LPA. LPA levels were increased in PBC patients with pruritus compared to PBC patients without pruritus or healthy controls [44]. Intradermal injection of LPA caused a dose-dependent scratching behaviour in mice, confirming a previous mouse study and indicating that LPA is indeed a pruritogen [44, 76]. Furthermore, LPA is also capable of inducing the itch sensation in humans upon intradermal application (unpublished data). LPA acts via at least 6 different G protein-coupled receptors (LPA_{1-6}) [77, 78]. These receptors are present in various tissues including the peripheral and central nervous system. It has been shown that LPA can induce neuropathic pain via LPA_1-, LPA_3- and LPA_5-receptors [79]. Recently, LPA was suggested to also directly activate the TRPV1 and may thereby mediate neuropathic pain [80]. Intracellularly applied LPA-activated TRPV1 is considerably faster and stronger than extracellular LPA via an intracellular binding site on TRPV1 [80]. In contrast, in primary sensory neuron cultures, LPA activated a subset of neurons not responding to capsaicin. Furthermore, this subset of activated wild-type neurons was comparable to that of TRPV1 knock-out mice (unpublished data). These contradictory results may be explained by different modes of action of intracellular and extracellular LPA. As LPA contains a charged phosphate group, it cannot easily cross the plasma membrane. Therefore, it remains to be shown whether the LPA-mediated activation of TRPV1

is relevant for extracellularly generated LPA. Which LPA-receptor and intracellular signalling pathway are required for LPA-induced pruritus warrants further investigation.

Extracellular LPA is mainly synthesized from its precursor molecule lysophosphatidylcholine by the lysophospholipase D, also named ATX [81, 82]. Lysophosphatidylcholine is present in high micromolar concentrations in plasma, and LPA levels largely depend on the amount of ATX as shown in heterozygous mice ($ATX^{+/-}$) [83]. The enzyme ATX is the second member of the family of ectonucleotide pyrophosphatases/phosphodiesterases (ENPP) and also entitled as ENPP2. The affinity of ATX for nucleotides is however much lower when compared to lysophospholipids [77]. ATX plays a critical role in diverse physiological conditions such as vascular and neuronal development, during pregnancy or for lymphocyte migration. Furthermore, ATX influences several pathophysiological states including neuropathic pain, cardiovascular diseases, pulmonary fibrosis, cancer development and formation of metastases [84]. Our studies have added a role of ATX in cholestatic pruritus. Serum ATX activity and ATX protein content were markedly increased in sera of PBC and PSC patients with pruritus compared to patients without pruritus [85]. Serum ATX activity correlated with the itch intensity in these patients, in contrast to other putative pruritogens such as serum bile salt levels or serum μ-opioid activity [85]. In addition, the decline in ATX levels correlated with treatment efficacy of several medicinal and invasive therapeutic interventions such as colesevelam, rifampicin, molecular adsorbents recirculating system (MARS®) therapy and nasobiliary drainage [86]. ATX activity again returned to higher levels when pruritus relapsed in patients weeks to months after the cessation of MARS® therapy or nasobiliary drainage [44, 86]. Rifampicin was found to reduce ATX expression at the transcriptional level in human liver-derived cell lines by a pregnane X receptor (PXR)-dependent mechanism, possibly explaining the strong antipruritic effect of rifampicin in clinical practice at least in part [86]. Steroids have been implicated in the pathogenesis of cholestatic pruritus; however, the mode of action on itch perception remains to be determined. Of note, intake of oral contraceptives was associated with increased serum ATX levels in healthy female individuals [87]. Thus, steroids, particularly in pregnancy and ICP, may be responsible for increased ATX levels.

Recently, it could be shown that serum ATX activity and protein levels were also increased in patients with atopic dermatitis [88, 89]. Furthermore, increased levels of LPA and ATX have been described in a mouse model of atopic dermatitis [90]. Thus, the ATX-LPA-axis may not only represent a key element in pruritus of cholestasis but also in other forms of chronic pruritus such as atopic dermatitis.

For decades, bile salts have been held responsible for cholestatic itch [17, 91]. Bile salts mediate their effects via the nuclear transcription factor farnesoid X receptor (FXR) or the transmembrane G protein-coupled receptor TGR5 [92]. Upon binding to these receptors, bile salts are capable of activating complex transcriptional networks and intracellular signalling cascades. Activation of FXR has proven various beneficial effects in different pathophysiological states including cholestasis, liver fibrosis, NASH and hepatocellular carcinoma [92, 93]. The semisynthetic bile salt obeticholate (6-ethyl-chenodeoxycholate) is a selective FXR ligand, which is currently studied in clinical trials in patients with PBC and NASH [94]. This drug exerted beneficial anti-cholestatic effects in PBC as well as anti-inflammatory and anti-fibrotic effects in NASH; however, it caused pruritus particularly at high doses [95]. The underlying mechanism, however, remains elusive. Alemi et al. [96] suggested in a recent study that cholestatic pruritus may be mediated by TGR5, which was detected in peptidergic neurons of mouse dorsal root ganglia. Indeed, intradermal injection of high concentrations of the bile salts deoxycholate and lithocholate induced scratching behaviour that was attenuated in $TGR5^{-/-}$ and augmented in TGR5 transgenic mice [96]. However, the applied concentrations of these hydrophobic bile salts were far beyond the pathophysiological levels observed in PBC or PSC patients even in severe cholestasis. The same group further showed that TGR5 coexpressed with TRPA1 and unconjugated bile salts caused scratching behaviour by the coactivation of TRPA1. DCA-induced itching was reduced by antagonists of TRPA1 or in $TRPA1^{-/-}$ mice [97]. Of note, unconjugated DCA is present only in trace amounts in humans [98]. Still, other agonists of TGR5 such as neurosteroids might be capable of activating this receptor leading to the itch sensation. Notably, progesterone has recently been shown to activate TGR5 in placental tissue in a dose-dependent manner [99].

Management of Cholestatic Pruritus

Treatment recommendations for cholestatic pruritus in PBC and PSC patients are based on only a few well-designed, randomized, placebo-controlled trials and several cohort studies [15]. The rationale for medical and interventional therapeutic approaches is (i) to remove the

Table 1. Therapeutic recommendations for the management of pruritus in PBC and PSC [15]

Approach	Drug[1]	Dosage	Evidence
1st line	Cholestyramine	4–16 g/day (po)	II-2/B1
2nd line	Rifampicin	300–600 mg/day (po)	I/A1
3rd line	Naltrexone	50 mg/day (po)	I/B1
4th line	Sertraline	100 mg/day (po)	II-2/C2
5th line	Experimental treatments[2]		
Categories of evidence[3]			
I	Randomized controlled trials		
II-1	Controlled trials without randomization		
II-2	Cohort or case-control analytic studies		
II-3	Multiple time series, dramatic uncontrolled experiments		
III	Opinions of respected authorities, descriptive epidemiology		
Evidence grading			
A	High quality; further research is very unlikely to change our confidence in the estimate of effect		
B	Moderate quality; further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate		
C	Low quality; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain		
Recommendation			
1	Strong; factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost		
2	Poor; variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption		

po = Peroral. [1] Except for cholestyramine all recommended drugs to treat pruritus of cholestasis have an 'off label use' character. [2] For details see text. [3] Categories of evidence according to the grading of recommendations assessment development and evaluation (GRADE) system.

pruritogen(s) from the enterohepatic cycle by non-absorbable, anion exchange resins such as cholestyramine in mild pruritus or invasive interventions such as nasobiliary and transcutaneous drainage or external biliary diversion in severe cases; (ii) to alter the metabolism of the presumed pruritogen(s) in the liver and/or the intestine by inducers of the hepatic biotransformation machinery such as rifampicin; (iii) to modulate central itch and/or pain signalling by influencing the endogenous opioidergic and serotoninergic system via μ-opioid-antagonists and selective serotonin re-uptake inhibitors, respectively; or (iv) to remove the potential pruritogen(s) from the systemic circulation by invasive methods such as anion absorption, plasmapheresis or extracorporeal albumin dialysis if pruritus is intractable (table 1) [15, 72]. It should be noted that except for cholestyramine all recommended drugs to treat pruritus of cholestasis have an 'off label use' character.

All patients with cholestatic pruritus should be advised to use moisturizing and cooling (i.e. menthol-containing) ointments twice a day. Furthermore, it should be recommended to shorten fingernails to avoid unnecessary secondary skin lesions, which keep the vicious cycle of itching and scratching ongoing.

Antihistamine drugs that are widely prescribed to treat chronic pruritus of systemic disorders, however, do not alleviate itching in most of these conditions. The nonspecific antipruritic effect observed in a few patients may result from their sedative properties [100]. However, dryness of mucous membranes is a common adverse effect of antihistamines, which further limits its use in PBC patients with sicca symptoms.

Ursodeoxycholic acid (UDCA, 13–15 mg/kg/day) exerts beneficial anti-cholestatic effects [101] and represents a baseline therapy for patients with PBC and PSC [15]. In PBC, alkaline phosphatase and bilirubin represent the best surrogate markers to predict outcome (liver transplantation and death) [102]. Studies with extended follow-up have demonstrated that PBC patients responding to UDCA have improved overall survival [103–105]. Although UDCA convincingly ameliorated pruritus and serum liver tests in women with ICP as shown by several randomized, placebo-controlled trials [15, 106], it did not

significantly alleviate itching in chronic cholestatic disorders such as PBC and PSC [36, 107].

In jaundiced PSC patients, pruritus may be attenuated or relieved by endoscopic biliary stenting of extrahepatic biliary obstructions. For PSC patients without biliary obstruction and PBC patients, the first-line drug treatment is cholestyramine (table 1). This anion exchange resin has been reported to alleviate pruritus in several small uncontrolled case series [108–115]. Cholestyramine is recommended as a 4 g sachet 1 h before and after breakfast and may be extended to 16 g/day. Patients should be carefully advised to take cholestyramine at least 4 h prior to any other medication, as it may interfere with the intestinal absorption of various drugs such as UDCA, digoxin, warfarin, propranolol, oral contraceptive hormones or fat-soluble vitamins. In a recent randomized placebo-controlled trial, colesevelam, which has higher binding affinity for bile salts than cholestyramine, failed to be superior to placebo [116]. Although cholestyramine may theoretically bind the 'real' itch-causing molecules more efficiently in the gut lumen than colesevelam, these results weaken the position of resins in the treatment recommendations and stress the importance of well-defined randomized, placebo-controlled trials.

If cholestyramine is not tolerated or ineffective, the PXR agonist, rifampicin, is recommended as second-line treatment (table 1). Four prospective, randomized, placebo-controlled trials demonstrated the anti-pruritic efficacy of rifampicin [117–120]. Rifampicin is a safe short-term therapy of cholestatic pruritus. However, hepatotoxicity has been reported to occur in up to 13% of patients after treatment for several weeks or months [120], requiring the monitoring of serum transaminase levels at regular intervals. Patients should be informed that rifampicin changes the colour of body fluids such as urine and tears to orange-red, a benign but sometimes frightening adverse effect.

If rifampicin does not alleviate pruritus within 2 weeks, the μ-opoid antagonist naltrexone is regarded as third-line treatment. Naltrexone moderately alleviated pruritus at doses of 25–50 mg/day in 4 small placebo-controlled trials [121–124]. Adverse effects may include withdrawal-like reactions, particularly during the first days of therapy. Therefore, opioid antagonists should be started at very low doses such as 12.5 mg/day. Alternatively, treatment could be initiated with intravenous naloxone at sub-therapeutical doses (e.g. 0.002 μg/kg/min), then gradually increased before switching to oral naltrexone [125]. Pruritus may recur during long-term opioid antagonist therapy, possibly due to drug-induced upregulation of MORs. This breakthrough phenomenon may be prevented by interrupting treatment for 2 days of the week [121]. Long-term treatment of opioid antagonists has been associated with a chronic pain syndrome limiting its use [126].

The selective serotonin re-uptake inhibitor sertraline (75–100 mg/day) can be administered as fourth-line therapy. A single placebo-controlled cross-over trial [127] and a case series [128] reported moderate anti-pruritic effects.

Using this stepwise approach, pruritus will resolve in a majority of PBC and PSC patients. From clinical experience, both opioid antagonists and selective serotonin re-uptake inhibitors exert limited antipruritic effects, underlining the importance of fully exploring the treatment with cholestyramin and rifampicin. There are case series to support the use of gabapentin and fibrates such as bezafibrate in PBC and PSC patients [129, 130]. Co-administration of several drugs at the same time is not recommended due to the risk of drug–drug interactions.

Patients not adequately responding to standard care should be transferred to specialized hospitals in which experimental approaches are performed. UVB phototherapy may represent an option to alleviate refractory pruritus as outlined in an uncontrolled case series [131]. Furthermore, a beneficial effect of invasive therapeutic procedures such as plasmapheresis [132, 133], MARS® or Prometheus® therapy [134–137], plasma separation and anion absorption [138], and nasobiliary drainage [75] with otherwise uncontrollable pruritus has been reported in case series. However, none of the studies was placebo controlled and the techniques are invasive, very elaborate, and too expensive for routine use. These methods should therefore be considered for otherwise intractable pruritus in desperate patients. Only if all evidence-based and experimental therapies have failed, liver transplantation may be regarded as the very last desperate therapeutic step. But this raises issues of organ allocation priority and risk in patients who would not otherwise require transplantation [15].

Conclusion

Chronic pruritus represents a tantalising symptom in many patients with PBC and PSC. Although there are novel insights into the pathogenesis of cholestatic pruritus, several parts of the complex molecular mechanisms remain to be elucidated. In spite of patients being efficiently treated following the current guidelines, further insights into the signalling cascade of itch sensation in cholestasis are awaited to enable the development of more effective causal treatment strategies.

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None of the authors has any conflicts of interest to disclose with regard to this work.

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