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Advances in Pathogenesis and Management of Pruritus in Cholestasis

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Abstract
Chronic pruritus is a burdensome feature of numerous hepatobiliary disorders such as primary biliary cirrhosis, primary sclerosing cholangitis, cholangiocarcinoma, inherited forms of cholestasis and intrahepatic cholestasis of pregnancy. Bile salts, μ-opioids, serotonin, histamine and steroids have been controversially discussed in the pathogenesis of cholestatic pruritus. However, for these substances neither a correlation with itch severity nor a causative link has ever been established. Recent findings indicate that the potent neuronal activator lysophosphatidic acid and autotaxin, the enzyme forming lysophosphatidic acid, may play a key element in the pathogenesis of cholestatic pruritus. Serum activity of autotaxin correlated with itch intensity and response to antipruritic treatment in patients with cholestatic pruritus, but not other forms of pruritus. Autotaxin activity thereby represents the first biomarker for pruritus and had a positive predictive value of 70% in differentiating cholestatic pruritus from other forms of pruritus. Treatment options for patients with cholestatic pruritus include the anion exchange resin colestyramine, the PXR agonist rifampicin, the μ-opioid antagonist naltrexone, and the serotonin reuptake inhibitor sertraline. These drugs are recommended by evidence-based guidelines as a stepwise therapeutic approach. Patients unresponsive to these drugs should be referred to specialized centers to receive experimental approaches such as UVB phototherapy, albumin dialysis, plasmapheresis or nasobiliary drainage. This review discusses pruritogen candidates in cholestasis, gives novel insights into the neuronal signaling pathway of pruritus and summarizes evidence-based treatment options for patients suffering from pruritus in cholestasis.

Introduction

Chronic pruritus is a sensory phenomenon accompanying a broad range of systemic disorders including metabolic and endocrine diseases, hematologic and lymphoproliferative disorders, solid tumors, and infectious diseases [1, 2]. In hepatobiliary diseases, pruritus particularly accompanies those disorders with cholestatic features [3–5]. In these disorders, cholestasis may be caused by a pure hepatocellular secretory failure (hepatocellular cholestasis), cholangiocellular cholestasis

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with intrahepatic bile duct damage or cholestasis due to obstruction of the intrahepatic or extrahepatic bile duct system [3, 6]. Interestingly, the prevalence of pruritus varies considerably between these hepatobiliary disorders. Pruritus is the defining symptom of women suffering from intrahepatic cholestasis of pregnancy (ICP) [7] and is experienced by up to 70–80% of patients with primary biliary cirrhosis (PBC) and primary sclerosing cholangitis at any time during the course of their disease [8–11]. In contrast, pruritus is less frequently reported by patients with obstructive cholestasis [12], or chronic hepatitis C infections [13–15]. Noteworthy, itch is not or only 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 [(N)AFLD], or alcoholic or non-alcoholic steatohepatitis [(N)ASH] even if cholestasis is present [16].

Clinical Picture

Although often undervalued by clinicians, pruritus represents a major burden of cholestatic patients and can dramatically reduce quality of life. Pruritus may be mild and tolerable, but does in some patients limit daily life activities, cause severe sleep deprivation resulting in lassitude, fatigue, depressed mood and even suicidal sensation. In rare cases, intractable pruritus may become a primary indication for liver transplantation [17–20].

One characteristic feature of cholestatic pruritus is its circadian rhythm with patient's reporting the highest intensity in the evening hours and early at night [6]. A diurnal variation of itch intensity has been objectified by measuring the scratching intensity in PBC patients using piezo-film technology [10]. Another specific feature is its localization at the limbs and in particular at the palms and soles, but cholestatic pruritus is often reported to be generalized [10, 21]. Female cholestatic patients commonly report pruritus worsening during the progesterone phase of the menstrual cycle, in late pregnancy, and during hormone replacement therapy [6, 22]. In multivariate analysis, serum alkaline phosphatase and the Mayo risk score were found to be independent indicators for the occurrence of pruritus in PBC patients [23].

In contrast to dermatological pruritus, primary skin lesions are not detectable in these patients; however, intense scratching activity may cause secondary skin alterations such as excoriations and prurigo nodularis [24]. 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 leukonychia may help to identify the underlying cause.

Pathogenesis

In spite of the growing knowledge of receptors and pathways responsible for acute itch signaling in mice, rats and other species [25–27] as outlined below, the responsible ligands and receptors for itch sensation in human beings remain unsolved for most disorders associated with chronic pruritus [28]. The pathogenesis of pruritus in cholestasis remains likewise enigmatic. Several potential itch-causing substances including bile salts, endogenous μ-opioids, histamine, serotonin and steroids have been controversially discussed. However, for these substances neither a correlation between serum and/or tissue concentrations and itch severity nor a causative link have ever been established [5, 23]. Thus, these substances rather seem not to be direct itch-causing molecules, although some might modulate the neuronal signaling cascade leading to the desire to scratch. For detailed rationale in favor or against these substances, the reader is referred to previous reviews [5, 29]. The current review highlights novel insights in the bile salt G-protein-coupled receptor TGR5 and lysophosphatidic acid (LPA) as well as the neuronal itch signaling pathway.

Potential Pruritogens

Clinical and experimental observations indicate that the itch-causing molecules in cholestasis accumulate in the systemic circulation as suggested by attenuation of pruritus after treatment with plasmapheresis or albumin dialysis. The pruritogens are secreted into bile as indicated by rapid relief of severe, treatment-refractory pruritus after nasobiliary drainage. Furthermore, the itch-inducing substances are (biotrans)formed in liver and/or gut as indicated by effective treatment with the potent pregnane X receptor (PXR) agonist rifampicin. Finally, the pruritogens of cholestasis affect the endogenous opioidergic and serotoninergic system as suggested by moderate antipruritic activity of μ-opioid antagonists and selective serotonin reuptake inhibitors [3, 5]. It was our hypothesis that itch-causing molecules during cholestasis

accumulate in serum, which should be capable of activating neuronal cells. We therefore screened sera of cholestatic patients with and without pruritus 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 [30]. The main neuronal activator could be unraveled as a potent lipid mediator, LPA. LPA levels were increased in women with ICP compared to gestation-matched women with uncomplicated pregnancy [30]. Intradermal injection of LPA caused a dose-dependent scratching behavior in mice confirming a previous mouse study [30, 31].

Extracellular LPA is mainly synthesized from its precursor molecule lysophosphatidylcholine (LPC) by the lysophospholipase D, also named autotaxin (ATX) [32, 33]. LPC is present in high micromolar concentrations in plasma and LPA levels largely depend on the amount of ATX as shown in heterozygous mice ($ATX^{+/-}$) [34]. 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 compared to lysophospholipids [35]. 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 [36]. Our studies have added a role of ATX in cholestatic pruritus. Serum ATX activity and ATX protein content were markedly increased in sera of ICP women compared to gestation-matched pregnant controls and in sera of cholestatic patients with compared to those without pruritus [37]. Furthermore, in contrast to other putative pruritogens such as serum bile salt levels or serum μ-opioid activity, serum ATX activity correlated with the actual itch intensity in these patients [37]. Also, 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 [38]. ATX activity again returned to higher levels when pruritus relapsed in patients weeks to months after cessation of MARS therapy or nasobiliary drainage [38, 39]. Rifampicin was found to reduce ATX expression at the transcriptional level in human liver-derived cell lines by a PXR-dependent mechanism, possibly explaining the strong antipruritic effect of rifampicin in clinical practice at least in part [38].

Serum ATX activity was higher in patients with pruritus of cholestasis compared to patients with pruritus due to chronic kidney disease, Hodgkin's disease or atopic dermatitis [38]. Autotaxin activity had a positive predictive value of 70% in differentiating cholestatic pruritus from pruritus associated with atopic dermatitis, uremia and Hodgkin lymphoma. Thus, ATX represents the first biomarker for a chronic itch condition and might represent a useful diagnostic tool for those cases in whom chronic pruritus remains unclassified [38].

These novel insights into the pathogenesis of cholestatic pruritus raise new questions. First of all, the source of the circulating ATX levels remains to be elucidated. Interruption of the enterohepatic circulation by nasobiliary drainage caused a rapid drop of circulating levels of ATX concomitant with relief of pruritus [30, 38]. As ATX is not secreted into bile [30], a factor within the enterohepatic circulation may be responsible for the increased serum ATX levels. Preliminary data from our laboratory point to the human small intestine as source of ATX [Bolier et al., in preparation]. Which molecules are involved in the regulation of ATX gene expression is an unresolved question. In that regard, steroids may play a role as autotaxin gene expression was upregulated in the hippocampus of ovariectomized rats upon treatment with estrogen [40]. Intake of oral contraceptives was associated with increased serum ATX levels in healthy female individuals [Kremer et al., in preparation]. Thus, steroids may particularly in pregnancy and ICP be responsible for increased ATX levels. A further issue is the molecular mechanism of LPA-induced scratching behavior as outlined below.

Bile salts have been implicated in the pathogenesis of cholestatic pruritus almost since their discovery [5, 41]. Bile salts mediate their effects via the nuclear transcription factor farnesoid X receptor (FXR) or the transmembrane G-protein-coupled receptor TGR5 [42]. Upon binding to these receptors, bile salts are capable of activating complex transcriptional networks and intracellular signaling cascades. Activation of FXR has proven various beneficial effects in different pathophysiological states including cholestasis, liver fibrosis, non-alcoholic steatohepatitis and hepatocellular carcinoma [42, 43]. 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 [44]. This drug exerted beneficial anticholestatic effects in PBC; however, it caused pruritus particularly at high doses [44]. The underlying mechanism remains elusive. Recently, TGR5 was suggested to play a role in bile salt-me-

diated pruritus and analgesia [45]. TGR5 was detected in peptidergic neurons of mouse dorsal root ganglia, pointing out a possible role in sensory circuits. Indeed, intradermal injection of high concentrations of the bile salts deoxycholate and lithocholate induced scratching behavior which was attenuated in TGR5$^{-/-}$ mice and augmented in TGR5 transgenic mice [45]. However, the applied concentrations of these hydrophobic bile salts were far beyond the pathophysiological levels observed in cholestatic disorders such as PBC or ICP which are associated with pruritus. These disorders are characterized by a depleted deoxycholic acid (DCA) pool size [46] with barely detectable concentrations of unconjugated DCA in serum and bile. Still, other agonists of TGR5 such as neurosteroids might be capable of activating this receptor leading to itch sensation. Notably, progesterone has recently been shown to activate TGR5 in placental tissue in a dose-dependent manner [47].

Neuronal Itch Signaling

Itch sensation depends on a complex interplay of pruritogens, their receptors on peripheral sensory nerve fibers, intraspinal and cerebral neural pathways, as well as cerebral processing of the stimuli. The discovery of sensory nerve fibers responsive to histamine but insensitive to certain algesic stimuli such as mechanical pain revolutionized pruritus research 15 years ago [48]. Still, these neurons can be activated by the algogen and TRPV1 agonist capsaicin. Thus, the question remained whether sensory neurons exist that exclusively mediate itch sensation. Only recently, a very elegant study presented evidence that a small subpopulation of sensory neurons expressing the Mas-related G-protein-coupled receptor subtype A3 (MrgA3) could represent such neurons [49]. Ablation of these MrgA3-positive neurons strongly attenuated scratching behavior in mice to most intradermally applied pruritogens. In mice lacking the TRPV1 channel, re-expression of TRPV1 only in MrgA3-positive neurons revealed that the algogen capsaicin largely caused scratching behavior but hardly any pain-related wiping [49]. Thus, irrespective of the modality of activation, these neurons seem to induce itch sensation but no pain. Still, pain and itch signaling are closely intertwined processes: activation of pain neurons abrogates itch sensation, e.g. by scratching, cooling or heating of the skin [1, 50]. Analgetics may induce itch sensation, e.g. by epidural or intrathecal application of opioids or anesthetics [51–53]. This can be explained by an itch circuitry which is under a tonic inhibitory control of mechanosensitive neurons (fig. 1). Evidence for such an inhibitory control was supported by the observation of spontaneous intense scratching behavior in mice lacking certain inhibitory, Bhlbh5- and Prdm8-expressing interneurons [54, 55]. These interneurons are believed to be activated by glutamate. Deletion of the glutamate transporter VGLUT2 caused increased spontaneous and induced scratching behaviors after application of pruritogens which underlined this hypothesis [56, 57].

Beside Mas-related G-protein-coupled receptor subtype A3 (MrgA3) which is activated by chloroquine [58], other receptors have been implicated in the onset of pruritus. Among these are the MrgD for β-alanine [59], the μ-opioid receptor 1D for morphine-induced pruritus [60], endothelin-A receptor for endothelin-1 [61], as well as the interleukin-13 [62] and interleukin-31 receptor [63]. Activation of these receptors results in opening of transient receptor potential (TRP) receptors such as the vanilloid-1 receptor (TRPV1) or ankyrin-1 channel (TRPA1) on sensory neurons [49, 64]. Primary sensory neurons signal to the dorsal horn of the spinal cord where secondary neurons are activated by release of glutamate and neuropeptide natriuretic polypeptide b (Nppb) [65]. Secondary neurons express natriuretic peptide receptor A (NprA, 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) [65–67]. Ablation of either the NrpA or GRP receptor expressing neurons by intrathecal application of a toxin bound to the respective signaling molecule largely abolished scratching behavior after intradermal application of various pruritogens [65, 67]. Noteworthy, pain responses were unaltered after ablation of these neurons, indicating that a selective itch pathway exists on spinal cord level [65, 67].

The molecular mechanisms of LPA-induced scratching behavior still remain to be elucidated. LPA is synthesized by ATX and may act via at least six G-protein-coupled receptors for LPA ($LPA_{1–6}$) [35, 68]. These receptors are present in various tissues including the nervous system. LPA can induce neuropathic pain via LPA_1, LPA_3 and LPA_5 receptors [69]. LPA was recently suggested to also directly activate the transient receptor potential vanilloid receptor subfamily V1 (TRPV1) and may thereby mediate neuropathic pain [70]. Intracellularly applied LPA activated TRPV1 considerably faster and stronger than extracellular LPA via an intracellular binding site on TRPV1 [70]. As LPA contains a charged phosphate group, it cannot easily cross the plasma membrane and it remains to be shown how relevant this type of activation is with regard to extracellularly generated LPA.

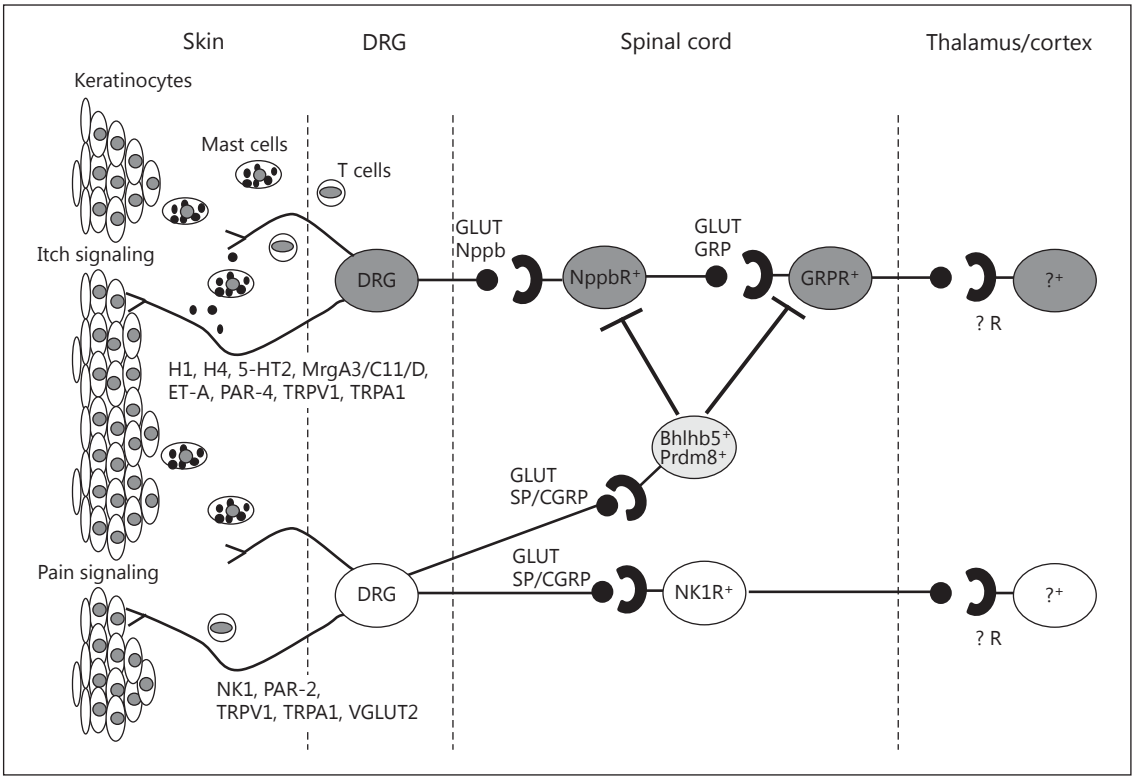

Fig. 1. Neuronal itch signaling. Simplified scheme of pain and itch signaling pathways from the peripheral to the central nervous system and their interaction. Itch- and pain-causing molecules bind to specific receptors on sensory nerve endings in the epidermis or dermis. Among the established receptors for itch signaling are histamine (H1, H4), serotonin (5-HT2), Mas-gene-related G-protein-coupled receptors (MrgA3, MrgC11, MrgD), endothelin (ET-A), protease-activated receptor (PAR-4), and interleukin-31. These neurons also express transient receptor potential (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 natriuretic polypeptide b (Nppb). Gastrin-releasing peptide (GRP) and GLUT may be involved in signal transmission to the tertiary neuron. The neuronal itch signaling 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 (NK1) for substance P (SP) or protease-activated receptor 2 (PAR-2) 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 GLUT, SP, and calcitonin gene-related peptide (CGRP).

Which LPA receptor and intracellular signaling pathway is required for LPA-induced pruritus warrants further investigation.

Management

Current treatment recommendations for pruritus in cholestasis are based on only a few well-designed, randomized, placebo-controlled trials and several cohort studies [3]. The rationale for medical and interventional therapeutic approaches is (i) to remove the 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 desperate 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 signaling by influencing the endogenous opioidergic and serotoninergic system via μ-opioid antagonists and selective serotonin re-uptake inhibitors (SSRI), respectively, or (iv) to remove the potential pruritogen(s) from the systemic circulation by invasive methods such as anion absorption, plasmapheresis or extracorporeal albumin di-

Table 1. Therapeutic recommendations for the management of pruritus in cholestasis [3]

Approach	Drug/therapy[a]	Dosage	Evidence
ICP only	UDCA[b]	10–15 mg/kg/day (p.o.)	I/B1[b]
1st line	Cholestyramine	4–16 g/day (p.o.)	II-2/B1
2nd line	Rifampicin	300–600 mg/day (p.o.)	I/A1
3rd line	Naltrexone	50 mg/day (p.o.)	I/B1
4th line	Sertraline	100 mg/day (p.o.)	II-2/C2

Categories of evidence[c]

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

p.o. = Peroral.

[a] It should be noted that except for cholestyramine, all recommended drugs to treat pruritus of cholestasis have an 'off label use' character.

[b] Recommendation and evidence grade for ICP only.

[c] Categories of evidence according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system.

alysis if pruritus is intractable (table 1) [3]. It should be noted that except for cholestyramine, all recommended drugs to treat pruritus of cholestasis have an 'off label use' character.

Ursodeoxycholic acid (UDCA, 10–15 mg/kg/day) exerts beneficial anticholestatic effects [71] and represents therefore a baseline therapy for several cholestatic disorders including PBC, cystic fibrosis-associated liver disease, pediatric cholestatic syndromes and ICP. Several case series reported UDCA to effectively attenuate pruritus in some pediatric cholestatic disorders [72–74]. In ICP, UDCA convincingly improved pruritus and serum liver tests in several randomized, placebo-controlled trials and is regarded as first-line treatment [3, 75]. This well-tolerated drug has been studied in several other chronic cholestatic disorders, but never with regard to itch as primary endpoint [23, 76].

In pruritus of all other forms of intrahepatic cholestasis and extrahepatic forms in which bile flow cannot be restored by invasive procedures, anion exchange resins are recommended as first-line treatment. Beneficial effects for cholestyramine have been reported in several small uncontrolled case series [77–84]. Cholestyramine is recommended as a 4-gram sachet 1 h before and after breakfast and may be extended to 16 g/day. Resins should be taken at least 4 h prior to any other medication as they may interfere with their intestinal absorption. In a recent randomized, placebo-controlled trial, colesevelam, which has a higher binding affinity for bile salts than cholestyramine, failed to be superior to placebo [85]. 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 underline the importance of randomized, placebo-controlled trials.

If resins are ineffective, the PXR agonist, rifampicin, is regarded as second-line treatment (table 1). Four prospective, randomized, placebo-controlled trials have proven the antipruritic efficacy of rifampicin [86–89]. Rifampicin is a safe short-term therapy of cholestatic pruritus; however, hepatotoxicity may occur in up to 13% of patients after treatment for several weeks or months [89] requiring the monitoring of serum transaminase levels at regular intervals. If rifampicin is ineffective within 2 weeks, the μ-opioid antagonist naltrexone is recommended as third-line treatment. Naltrexone moderately improved pruritus at doses of 25–50 mg/day in four small placebo-controlled trials [90–93]. Adverse effects may include withdrawal-like reactions, particularly during the first days of therapy. Therefore, naltrexone should be administered at low doses of 12.5 mg/day or intravenous infusion of naloxone followed by a stepwise dose increase. The selective serotonin uptake inhibitor sertraline (75–100 mg/day) can be administered as fourth-line therapy. A single placebo-controlled crossover trial [94] and a case series [95] reported moderate antipruritic effects. Coadministration of several drugs at the same time is not recommended due to the risk of drug-drug interactions.

Using this stepwise approach pruritus will improve in most patients. Experimental approaches such as UVB phototherapy, albumin dialysis, plasmapheresis or nasobiliary drainage may be considered in those patients not adequately responding to standard care and should be performed in specialized medical centers. Only if all evidence-based and experimental therapies have failed liver transplantation can be regarded as the very last desperate therapeutic step.

Conclusion

Cholestatic pruritus is a debilitating symptom of various hepatobiliary disorders. We still scratch on the surface of the complex molecular mechanisms responsible for this enigmatic symptom. Further insights into the signaling cascade of itch sensation in cholestasis will open new avenues for the development of more effective treatment strategies among which LPA receptor antagonists and ATX inhibitors may be of significance.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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