Cholestatic pruritus : an update

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Abstract

Pruritus is a common, troublesome symptom in patients with cholestatic liver diseases, especially frequent in intrahepatic cholestasis of pregnancy (ICP) and in primary biliary cholangitis (PBC). Cholestatic associated pruritus can have profound effects on the quality of life. The underlying mechanism is still poorly understood. Severe potential pruritogens have been discussed, such as bile salts, opioids, steroid and lysophosphatidic acid (LPA), but none of these are considered as key mediators. Because of this unraveling pathophysiology the treatment of hepatogenic pruritus often represents a clinical challenge. The EASL guidelines have suggested a step-wise approach, starting with elimination of pruritogens by bile acid sequestrants (cholestyramine), in second line managing the metabolism of pruritogens (rifampicin) and in third-line and fourth- line by modifying the itch perception with μ-opioid antagonist or selective serotonin reuptake inhibitors (SSRI). In treatment-refractory pruritus interruption of the enterohepatic cycle by molecular absorbent recirculating system (MARS), nasobiliairy drainage or experimental therapy such as Ultraviolet B light therapy can be considered. Liver transplantation may be reserved for intractable pruritus. Clinical trials with novel agents are ongoing, potentially providing efficacious options in the future. (Acta gastroenterol. belg., **2019**, 82, **75-82**).

Keywords : Cholestasis, pruritus, itch, LPA, Autotaxin, Rifampicin

Introduction

Cholestatic liver disease can be complicated by extrahepatic manifestations such as pruritus, fatigue, osteoporosis and fat malabsorption (1). Pruritus is a burdensome symptom which can be severe, sometimes leading to sleep deprivation, emotional disturbances (including suicidal ideation in some patients) and disruption of the quality of life (2).

Pruritus may develop in any cholestatic disease, caused by decreased hepatocellular secretion (hepatocellular cholestasis), intrahepatic bile duct damage (cholangiocellular cholestasis) or extrahepatic/ intrahepatic bile duct obstruction (2,3). The prevalence of pruritus varies depending on the underlying liver disease (3). It is especially frequent in intrahepatic cholestasis of pregnancy (ICP) (100%) and in primary biliary cholangitis (PBC) (up to 80% at any time during the course of their disease) (3). In malignant biliary obstruction up to 45% have pruritus, while in benign obstructions only 16% complains of itch (3). Also in chronic hepatitis C infections 5-15% of the patients has pruritus, while patients with chronic hepatitis B infections, alcoholic or non-alcoholic steatohepatitis or non-alcoholic fatty liver disease rarely suffer from pruritus even when cholestasis is present (3,4,5). Pruritus is more frequently seen in intrahepatic than in extrahepatic cholestasis (2).

In this article, we will review the clinical manifestations, diagnosis, pathogenesis and management of cholestatic pruritus.

Methods

Articles were searched in pubmed, in English, from 1970 till 2018, with search terms: cholestatic pruritus, pathogenesis, treatment or management. Also the European Association for the study of the liver (EASL) guidelines about PBC and about management of cholestatic liver disease were used in this review. Especially all the articles from the authors specialized in the domain of cholestatic pruritus were read, such as Kremer AE, Beuers U, Hirschfield GM, Jones D, Corbechot C, Lindor KD, Pares A and Chazouilleres O. The ethic commission of UZ Leuven gave its approval for this review.

Clinical manifestations

Cholestatic pruritus may be generalized or localized at the limbs (mostly at the palms of the hands and soles of the feet) (2,5). It can occur at any stage of the disease and may lessen with the development of end-stage liver disease (1,6).

Fluctuations are characteristic for cholestatic pruritus over time during the course of the disease and in one day, it shows a typical circadian rhythm with a peak in the evening and early night (2,3,5). Once pruritus occurs, the severity can diminish over time (7). The intensity of pruritus may also be exacerbated by psychologic stress, heat and contact with wool (7,8,9). Cool temperatures often lead to improvement.

Furthermore, pruritus is more common in women than in men. Female cholestatic patients may also experience worsening of pruritus in the progesterone phase of the menstrual cycle, in the late pregnancy or during hormone replacement therapy, suggesting a role for female sex hormones (2,3).

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Diagnosis

Quantifying the severity of pruritus can be difficult, because the perception differs individually (2). But it is important to know the impact of pruritus on people's life and to evaluate the efficacy of medical therapy (9). The visual analogue scale (VAS), scoring from 0-10, is one of the most commonly used methods for pruritus severity assessment and helps to estimate the response to interventions (9,10). Also patients' questionnaires, such as the itch severity scale or the 5-D itch questionnaires are an easy but subjective way to score itch (9). The 5-D itch scale was developed as a single-page multidimensional questionnaire which has been validated in patients with chronic pruritus to detect changes over time (9,10). This 5-D itch scale is assessing the extent of itch and its impact in terms of 5 domains: duration (hours of itching in one day), degree (intensity), direction (getting worse or better over 2 weeks), disability (impact on activities such as sleep, work, leisure and housework) and distribution (affecting skin sites) (11). In PBC the disease specific quality of life assessment tool, PBC-40, scoring 6 domains of typical PBC symptoms (fatigue, itch, cognition, emotional, social and other symptoms) can be used (9). A more accurate method to objectify itching is using the scratching activity monitoring system, by attaching piezo-electric crystals to a fingernail, allowing for recording of scratching behavior independent from gross body movement (because of the high cost, this system is little used as a research tool) (2,8,12). Although the VAS and questionnaires are unreliable subjective methods to asses itch, it can be used in practice because itch is a subjective feeling and pruritus therapy aims in the first place to improve patients well-being and quality of life, which can only be measured subjectively (2,12,13).

A presumptive diagnosis of cholestatic pruritus can be made in patients with cholestasis complaining of itch. There is a long list of differential diagnosis for causes of pruritus, such as skin disorders, systemic disorders (uremia, lymphoma), psychogenic itch, neurological itch and iatrogenic itch (2). At least skin examination to look for dermatologic disorders (other than scratch marks) and a lab to rule out myeloproliferative diseases or uremic pruritus in end-stage renal disease should be done (9).

Pathogenesis

The precise pathogenesis of pruritus in cholestasis still remains unsolved. There is still no substance that is considered as causative pruritogen in cholestasis (9). The perception of itch depends on a complex interplay of pruritogens, receptors, neuronal and cerebral pathways (2). Itch and pain are highly associated perceptions and involve the activity of the same receptor (transient receptor potential cation channel subfamily V member 1 (TRPV1)); however itch is transmitted by itch-specific unmyelinated C-fibers, transmitting signals from the skin to the spinal cord, to the thalamus, activating the cortex, leading to scratch (14,15). The possible ligands and receptors for the itch sensation remain unclear and the question remains whether sensory neurons exist exclusively mediating itch sensation (14). Probably the itch-causing molecules in cholestasis are (biotrans) formed in liver and/or gut, are secreted into bile, accu-

Table 1. — **The precise pathogenesis of pruritus in cholestasis still remains unsolved, several hypotheses as underlining mechanism have been proposed, including bile acid accumulation, increased endogenous opioids, and elevations in lysophosphatidic acid levels**

Pruritogen	Pro	Contra
1. Bile acids	-In cholestasis serum bile acid levels are elevated - In healthy volunteers pruritus develops after intradermal application of bile acids (19) - Relief or pruritus after nasobiliairy drainage (3,18) - Antipruritic effect of Cholestyramine	- No correlation between bile salt levels and itch intensity (2,20) - In PBC pruritus is often the first symptom when bile acid concentration is low (3) - ICP patients have mild increase of bile salts, yet all suffer from pruritus (21) - Liver failure: itching disappears although bile salts reach maximum concentrations (2) - Inefficacy of bile sequestrant colesevelam (22)
2. Endogenous opioids	- Endogenous opioid levels are elevated (via an uncertain mechanism) (12) - Opioid antagonists have beneficial effects in cholestatic pruritus (25) - Intrathecal administrations of morphine lead to pruritus (12).	- No strict correlation between itch perception and serum levels of opioids (24).
3. LPA / ATX	- After intradermal injection of LPA dose-dependent scratch movements are seen in mice (27,28,29). - Increased serum concentrations of LPA and ATX in patients with cholestasis-associated pruritus (27,29). - ATX correlates with the grade of cholestatic pruritus (3,10,14). - Nasobiliary drainage markedly decrease itch intensity and ATX activity (3). - Rifampicin leads to a reduction in ATX expression at transcriptional level (14)	- The source of the circulating ATX level is unknown (14). - An undefined element in the enterohepatic circulation may be responsible for increased serum ATX levels because ATX is not secreted into bile (14). - The molecules involving the ATX gene expression regulation are unknown (14). - How LPA activates itch selective neurons is another unsolved issue (14).

mulate in the systemic circulation and do centrally also affect the endogenous opioid and serotoninergic system (16). Several hypotheses as underlying mechanism have been proposed, including peripheral mechanism such as bile acid accumulation, progesterone metabolites and central mechanism such as increased endogenous opioids and elevations in lysophosphatidic acid levels (Table 1) (17). The current understanding of the potential pruritogens is mirrored by the success of the different therapeutic approaches (18). But not all patients with cholestasis report pruritus, so there may also be a subject-dependent factor, such as a genetic factor, like a polymorphism for multidrug resistance associated protein 2 (MRP2) (12).

Elevated levels of *bile acids* were thought to act as a pruritogens in the first hypothesis, although they probably don't play a primary role in pruritus (Table 1). Pruritus in healthy volunteers can be caused by intradermal injection of bile salts (19) and relief of pruritus is common after removing bile acids by resins, by ileal exclusion surgery or by biliary drainage (3,18). Although, the main argument against a key role for bile salts is the lack of correlation between the level of bile acids in blood, skin or urine and the presence or severity of pruritus (2,14,15,20). The intensity of itch doesn't correlate with the severity of cholestasis (2,3). Severe pruritus is often the initial sign in patients with PBC and ICP, however bile acid concentrations are then predominantly low (3,21). In addition, in terminal liver failure itching often disappears although bile salts reach a maximum concentration (2). The fact that bile acids doesn't play a key role is also underlined by the therapeutic approaches. For instance Colesevelam efficiently decreases bile salt concentrations, but are no better than placebo in reducing pruritus (18,22). However, a shift in the bile salt metabolism has been described in women with ICP (23). A related hypothesis implicates that bile acids play an indirect role by altering the hepatocyte membranes (maybe by activating (taurine G-coupled protein receptor 5 (TGR5)), permitting leakage of hepatocyte contents (some of which are pruritogens) into the bloodstream (2,9,14,18).

Progesterone may be a cofactor in development of cholestatic pruritus, explaining the female predilection (2,3). ICP typically occur in the third trimester of the pregnancy, when steroid hormones and their metabolites reach the highest serum levels (2,3,21). After delivering, serum liver tests normalize and pruritus rapidly disappears, correlating with normalization of the steroid hormone levels (2,3). In a cohort of ICP patients the intensity of pruritus correlates with urinary levels of disulphated progesterone metabolites before and after treatment with ursodeoxycholic acid (UDCA) (2,3,23). Steroid hormones might modulate neuronal excitability in cholestatic patients (3,5,18).

Histamine, the main mediator in allergic reactions, is unlikely to represent a causative factor in cholestasis-associated pruritus because antihistamines are ineffective for cholestatic pruritus and bile salt-induced histamine release from mast cells occurred at much higher concentrations of bile salt than those generally observed in cholestatic patients (2,3). The typical histamine-induced skin alternations such as erythema, urticarial or flares are lacking in patients with cholestasis (18).

The second hypothesis in the pathogenesis of cholestatic pruritus is an elevated level of *endogenous opioids*, such as Met-enkephalins (Table 1) as a central mechanism of pruritus (2,12). In patients with chronic liver diseases endogenous opioid levels are elevated (via an uncertain mechanism) and a series of reports have shown a beneficial effect of opioid antagonists in cholestatic pruritus, although there is no strict correlation between itch perception and serum opioid levels (12,24,25,26). It is also described that intrathecal administrations of morphine lead to pruritus (12). A possible explanation for the working mechanism is the intimate interaction between itch and pain; pain has a strong negative modulating effect on itch (hence the scratch), and the transmission of both involve the receptor TRPV1 (2,16,26).

Recent studies suggest that *lysophosphatidic acid (LPA)*, a potent neuronal activator, may have an important function in cholestatic pruritus (Table 1) (16). The enzyme autotaxin (ATX) forms LPA by cleaving a choline group of lysophosphatidylcholine (27). Intradermal injection of LPA causes dose-dependent scratch movements in mice (27,28,29). Kremer et al showed a significantly increased serum concentration of LPA and ATX activity in patients with cholestasis-associated pruritus compared with nonpruritic controls (27,29). ATX is the only variable identified so far that correlates with the severity of cholestatic pruritus (3,10,14). ATX is a more reliable parameter to use in studies, because LPA is unstable and can vary after blood sampling depending on processing and storage (16,17,27). ATX serum activity can also mirror treatment response, for instance nasobiliary drainage markedly decrease itch intensity and ATX activity (3). Also rifampicin leads to a reduction in ATX expression at transcriptional level, partly explaining the antipruritic effect (14,16,29). But there are several concerns about ATX in the pathogenesis of cholestatic itching: 1) the source of the circulating ATX level is unknown. 2) An undefined element in the enterohepatic circulation may be responsible for increased serum ATX levels because ATX is not secreted into bile. 3) The molecules involving the ATX gene expression regulation are unknown (14). Steroids may cause induction of ATX expression, explaining the female predilection (16). Also how LPA activates itch selective neurons is an unsolved issue (14).

There are maybe also *genetic, environmental and dietary factors* in the pathogenesis of cholestatic itch. The interindividual differences in susceptibility for cholestatic pruritus and the genetic background for ICP advocate genetic factors that contribute to itching (17). Consumption of specific food leads to aggravation of itch

in some patients, suggesting influence of environmental and dietary factors in pathogenesis (17).

Management

The unknown pathogenesis of cholestatic pruritus also precludes the development of effective therapy (26). The treatment options are limited and do not yet provide relief for all patients (9). A step by step recommendation is based on the EASL guidelines.

The first step in treating patients with cholestatic pruritus is to *treat the underlying hepatobiliary disease* and to exclude bile duct obstruction (1). In biliary obstruction endoscopic, radiological or surgical correction must be obtained, such as endoscopic treatment of dominant strictures in PSC or bile duct stenting in malignant extrahepatic biliary obstruction (2). In drug-induced cholestasis discontinuation of offending medication is the treatment of choice (12).

In ICP and in PBC ursodeoxycholic acid (*UDCA*), a naturally occurring dihydroxy bile acid is the first treatment option, in a dose of 10-15 mg/kg/daily (7). UDCA is a disease-modifying therapy, but there is no evidence that UDCA has any effect on pruritus, except in ICP (1,30,31). In PBC it improves biochemical parameters, delays progression to liver cirrhosis and enhances survival (2,32). Also in ICP UCDA is associated with decreased levels of endogenous bile acids, normalization of alanine aminotransferase levels, and improved fetal outcomes (2,33). The working mechanism of UDCA may be explained by competition for intestinal absorption, by increasing hepatic clearance of endogenous bile acids or due to bile detoxification or an anti-apoptotic effect (2). Still about 40% of the PBC patients don't respond to UDCA (34). New pharmacological approaches for non-responders are reported, such as obeticholic acid (OCA) and fibrates, targeting nuclear receptors which regulate the intracellular concentration of biliary constituents (Figure 1). OCA is a semi-synthetic hydrophilic bile acid analogue that is selective for Farnesoid X receptor (FXR) (Figure 1). FXR represses bile acid uptake (by inhibiting sodium taurocholate co-transporting polypeptide NTCP), represses bile acid synthesis (by inhibiting cholesterol-7alpha-hydroxylase CYP7A1), stimulates biliary secretion (via induction of canalicular transporters), leads to detoxification and has antifibrotic effects (35). OCA leads to significant improvement in serum alkaline phosphatase in PBC (6), but it can exacerbate pruritus in a dose dependent relationship by an unknown mechanism (10). Another option is adding fibrates to UDCA, which has an anti-cholestatic, anti-inflammatory, anti-fibrotic and anti-pruritic effect, through the activation of peroxisome proliferator-activated receptors (PPAR) by stimulating FXR, promoting bile acid secretion (by multidrug resistance protein 3 (MDR3) expression), downregulation of bile acid synthesis and regulating detoxification (Figure 1) (6,34,35). Particularly bezafibrate 400mg/day, a PPAR agonist, leads to biochemical improvement, improvement of the noninvasive measures of liver fibrosis and alleviation of pruritus and fatigue (34,36,37). In the placebo-controlled trial, recently published in the New England, one third of the patients in the bezafibrate group compared with no one in the placebo group reached normal levels of the main biochemical markers of the disease at 24 months (36). Increase in serum creatinine and myalgia are described as adverse events (36). Longer and larger trials will be required to assess the effect of bezafibrate on hard outcomes such as liver transplantation and death and to know the side effects on the long term (9,36).

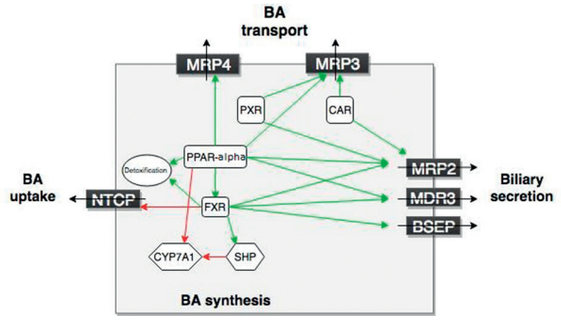

Fig. 1. — (adapted from the figure of Zollner (35), and figure of Chazouilleres (63)) : Regulation of hepatocellular bile formation and transport: Bile acid uptake by sodium taurocholate co-transporting polypeptide (NTCP). Bile acid secretion into bile by 3 transporters: multidrug resistance associated protein 2 (MRP2), multidrug resistance protein 3 (MDR3) and bile salt export pump (BSEP), Bile transport into systemic circulation by multidrug resistance associated protein 3 and 4 (MRP3 and MRP4). Expression of hepatobiliary transporters is tightly regulated by nuclear receptors. Nuclear receptors (Farnesoid X receptor (FXR), peroxisome proliferator-activated receptors (PPAR), Pregnane X receptors (PXR), Constitutive androstane receptor (CAR)) controls the intracellular concentration of biliary constituents and are good targets for therapy. 1. Obeticholic acid is a FXR agonist; it represses bile acid uptake (by inhibiting NTCP), represses bile acid synthesis (by inhibiting CYP7A1), stimulates biliary secretion via induction of canalicular transporters), leads to detoxification and has antifibrotic effects. 2. Fibrates are PPAR agonists; stimulating FXR, biliary excretion, biliary transport, detoxification, suppressing bile acid synthesis (by inhibiting CYP7A1) and having an anti-fibrotic effect. 3. Rifampicin is a PXR agonist; stimulating biliary secretion by MRP2 an biliary transport by MRP3. (legend: green arrow= stimulating, red arrow= inhibiting, CYP7A1= cholesterol-7alpha-hydroxylase, SHP= small heterodimer partner).

General measures (e.g., cold water, emollients with menthol or aqueous cream) may be helpful for pruritus, though studies evaluating their efficacy are lacking (6,9). In cholestasis-associated pruritus antihistamines are mostly ineffective and should not be prescribed, however antihistamines are frequently used because of sedative effects in patients with nocturnal pruritus (9,12,38).

If the underlying hepatobiliary disease can't be corrected, starting systematic treatment focusing entirely on pruritus itself in a stepwise approach should be

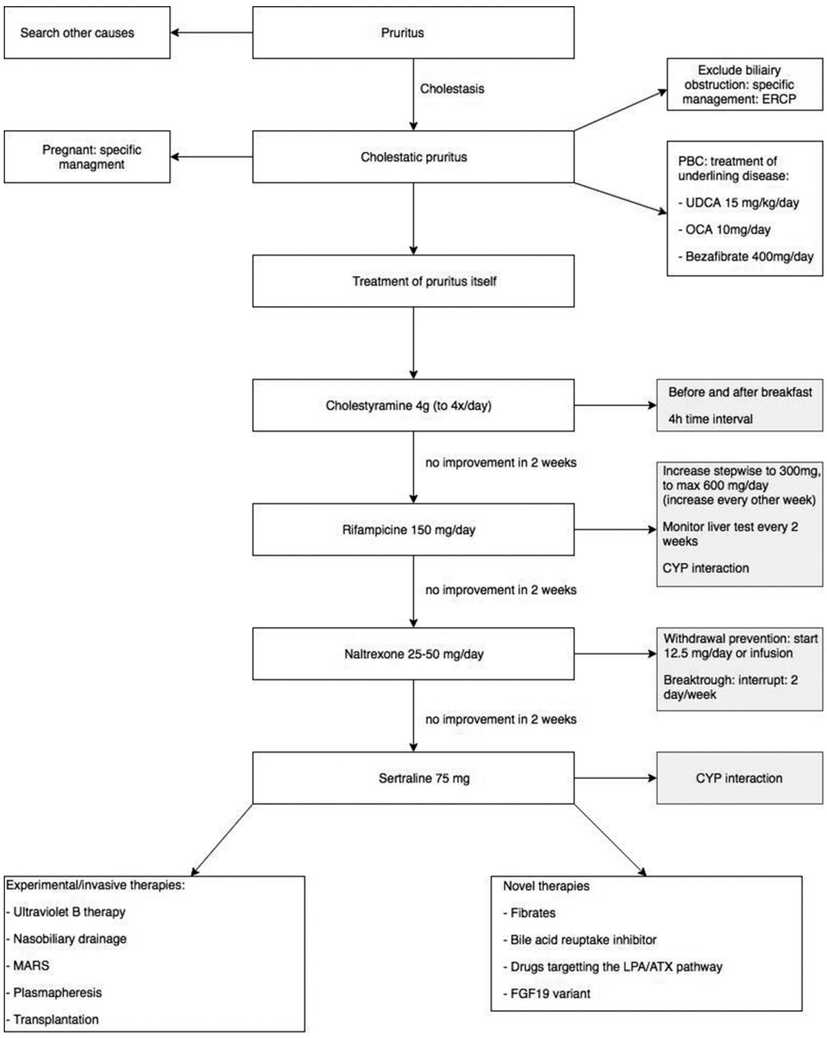

Fig. 2. — Adapted from the EASL guidelines (1) and the figure of Kremer (2): A stepwise approach for treatment of cholestatic pruritus is suggested in de EASL guidelines. Furthermore there are some invasive and experimental therapy and also novel therapies under development.

considered, as suggested in the recommendations of 2009 EASL guidelines for the management of pruritus in cholestatic patients (1). There are four goals in the therapy for cholestatic pruritus. The first goal is removing pruritogens from the enterohepatic cycle by bile acid sequestrants (cholestyramine). Managing the metabolism of pruritogens by the Pregnane X-receptor (PXR) agonist, rifampicin, an enzyme-inducer is the second goal. The third and fourth goal is influencing the itch perception with μ-opioid antagonist or selective serotonin reuptake inhibitors (SSRI) (1) (Figure 2, Table 2). In treatment-refractory pruritus elimination of possible pruritogens from the systemic circulation with MARS or plasmapheresis can be attempted (1,14).

The widely used first-line treatment are non-absorbable anion exchange resins *cholestyramine*, a ratio 4 gram up to four times daily, based on their bile salt binding properties, preventing the reuptake in the terminal ileum (1,2). It is the first-line treatment despite its limited evidence. It was already widespread before the era of evidence based medicine. Its beneficial effect is reported in small uncontrolled case series (14,39,40). Resins should be spaced away at least 4 hours from other drugs to prevent binding and drug interactions and

Table 2. — **(adapted from the table from Kremer (2) : Current therapeutic recommendations of the EASL guidelines for the management of cholestatic pruritus. Categories of evidence : I : randomized controlled trial, II-2 : cohort or case-control analytic studies. Evidence Grading : A: high quality. B : Moderate quality, further research may change the estimate. C : low quality: further research is likely to change the estimate. Recommandation :1 : strong, 2 : weak**

Approach	Therapy	Dosage	Evidence
1st line	Cholestyramine	4-16g/day	II-2/B1
2nd line	Rifampicin	300-600 mg/day	I/A1
3rd line	Naltrexone	25-50 mg/day	I/B1
4th line	Sertraline	75-100 mg/day	II-2/C2

morning dose is preferred (2,5,7). Poor tolerance is often an issue due to bad taste and complains as constipation and bloating (2,6). Colesevelam (Cholestagel) is a novel and often better tolerated bile sequestrant, with higher affinity for bile salts. However, a placebo-controlled trial revealed 50% reduction in bile salts concentration without improvement of pruritus (2,22).

If resins are ineffective, the second-line treatment is *rifampicin*, a pregnane X-receptor (PXR) agonist and potent inducer of key enzymes in the hepatic and intestinal detoxification machinery (such as CYP3A4, CYP2D, UGT1A1, SULT2A1) and export pump MRP2 (2). It stimulates excretion of pruritogens, detoxification and alters the intestinal metabolism by an antimicrobial effect (2,5). In vitro studies also found that rifampicin reduce ATX expression at the transcriptional level in human hepatoma cells by a PXR dependent mechanism (29). Rifampicin is the only proven drug in randomized placebo-controlled trials and in two meta-analyses (41-44). In the meta-analysis of Tandon et al, four clinical trials with variable quality with a total of 57 patients were included (43). The other meta-analysis included a total of 61 participants from 3 double-blind randomized prospective studies and 2 randomized controlled cross-over trails (44). Both meta-analyses concluded that rifampicin was safe and effective, leading to a relief of pruritus in up to 77% of the patients as compared with placebo or alternatives (43,44). Low dose initiation (150 mg) with serial monitoring of serum liver tests and blood count before dose escalation (up to maximum of 600 mg daily) is recommended (1), because of drug-induced hepatitis and significant liver dysfunction is reported in up to 12% of patients with cholestasis (42,45). In a recent retrospective review with 105 patients under rifampicin, only 5% developed hepatitis, recovering after drug cessation, so it can be concluded that in 95% rifampicin is safe and drug cessation in rifampicin-induced hepatitis is effective (46). Even in patients with jaundice and advanced liver disease rifampicin was safe (46). Rifampicin can also affect vitamin K metabolism, increasing the INR in icteric patients (6). Other side effects as hemolytic anemia, thrombocytopenia, renal impairment and many drug interactions are reported (7,43). Patients should be informed about the occurrence of discoloration of urine, tears and other body secretions when initiating this therapy (1,2).

If rifampicin is ineffective or intolerable within 2 weeks, *oral opioid antagonist*, such as naltrexone, is proposed as next agent (1), reducing itch at a dose of 50 mg daily (43,47). Naltrexone should be started at low dose of 12.5 mg increasing by a quarter every 3-7 days or this oral therapy should be preceded by Naloxone intravenous for 3 days because of the self-limited withdrawal-like syndrome in the first days of treatment (1,2,4,7,9,48). Since naloxone ejects the opioids from their receptors in the brain, causing a withdrawal-like syndrome. To prevent a break-through phenomenon during long term therapy, interrupting the treatment for 2 days a week has been suggested (49). Following the liver biochemistry on naloxone therapy is also recommended because naltrexone hepatotoxicity is uncommon but has been reported (7).

The selective serotonin reuptake inhibitor (SSRI), *Sertraline,* may be considered as fourth-line treatment for patients resistant to above mentioned treatments, starting at 25 mg daily, increasing gradually to 75-100 mg daily (50). SSRIs probably act by altering neurotransmitter-concentrations within the central nervous system (51). The uncommon adverse events are dry mouth, nausea, dizziness, diarrhea, visual hallucinations or fatigue (6,9)

Other therapies have also been tried. The use of Ondansetron, Phenobarbital and Propofol (in hypnotic dose 15 mg intravenously) are not recommended because of lack of efficacy and side-effect profile (1,2,7,12,52,53).

In therapy-refractory pruritus, *Ultraviolet B photo-therapy* can be considered, presumably working by influencing the itch-specific nerve endings or by chemical modification of pruritogens in the skin (54). It is a well-tolerated and promising therapy in hepatogenic pruritus, but further studies are needed (54).

Also invasive physical approaches can be considered, for example alleviating pruritus by transient therapeutic interruption of the enterohepatic circulation, such as *MARS* (molecular adsorbents recirculating system), an extracorporeal albumin dialysis capable of removing albumin-bound molecules (55,56). Furthermore, *plasma-pheresis* (57-59) and *bile duct drainage* (60,61) have been reported to remove pruritogens accumulating in the plasma or bile (1). The temporary success of these therapies is their main limitation, but supports that the putative pruritogens in cholestasis accumulates in the blood and undergo an enterohepatic circulation (2).

Intractable pruritus may become an indication for *liver transplantation* when all the previous therapeutic efforts have failed (12), even in the absence of liver failure (2). Transplantation is highly effective to control cholestatic itch with rapid reduction (frequently within 24 hours) (62).

There is a lot of active research in cholestatic pruritus, with several experimental agents and approaches being developed (6,63). Rifampicin, a PXR agonist, remains the most evidence-based treatment for cholestatic pruritus (34). *Drugs targeting nuclear receptors* (Figure 1) involved in regulation of bile formation, bile acid homeostasis and defense pathways may lead to new treatment options, such as FXR ligands (Obeticholic acid), PPAR ligands (Fibrates), GR/PXR ligands (budesonide) (35,64). *Fibrates*, especially targeting PPAR-alpha, are an attractive treatment option for PBC because of the antipruritic and anticholestatic effects, but long-term placebo controlled studies are still needed (34,65). A study with the Seladelpar, a selective PPAR-delta agonist, improves alkaline phosphatase, but increases aminotransferases, leading to early discontinuation of the study (66). Novel therapies including *bil*e acid

reuptake inhibitors and drugs targeting the autotaxin/lypophosphatidic acid pathway, are in development (9). In a cross-over fase 2a study bile acid transporter inhibitor GSK2330672 in PBC patients showed good results on pruritus and is well tolerated (most common adverse event is diarrhea) (67). A protein variant of Fibroblast growth factor 19 (FGF19) from the ileum, NGM282, suppressor of bile acid synthesis is also under study (65).

Conclusion

Pruritus is a difficult-to-treat symptom associated with various cholestatic diseases. Its complex pathogenic mechanism is not unraveled yet with remaining controversies concerning the role of possible pruritogens such as bile salts, opioids, steroids and LPA. A stepwise approach in EASL guidelines is suggested with cholestyramine, PXR agonist rifampicin, oral opioid antagonist naltrexone and SSRI sertralin. Efficacy and side-effect profile are disappointing. Rifampicin is the only proven drug in randomized placebo-controlled trials and in meta-analyses. In therapy resistant pruritus experimental therapy such as UV therapy or invasive therapy such as MARS, nasobiliary drainage or plasmapheresis could be considered. Liver transplantation can form a final solution in selected patients. Further studies are needed to identify the key pruritogen, possibly leading to development of more efficacious treatment strategies. Bile transporter inhibitors and Fibrates are under investigation as potential therapeutic options for cholestatic pruritus.

Conflict of interest

I, Charlotte De Vloo have no conflict of interest. Co-author, Frederik Nevens HAS a consultancy agreement with Intercept, but also no conflict of interest.

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