Pruritus in Primary Sclerosing Cholangitis: New Insights into Cause and Treatment

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Introduction

Pruritus is a common complaint among patients with cholestatic liver diseases. Specifically, pruritus is a distinct and profound symptom associated with intrahepatic cholestasis of pregnancy (ICP) and benign recurrent intrahepatic cholestasis (BRIC). Moreover, pruritus is commonly encountered in patients with primary biliary cholangitis (PBC), affecting up to three-fourths of PBC patients to some degree [1]. In patients with PBC, itch can also be severe, significantly impairing patient quality of life (QOL) leading to depression, social withdrawal, and even suicidal ideation. In rare cases, severe itch can even be an indication for liver transplantation [1, 2].

In contrast, the prevalence and impact of pruritus in PSC patients are less well understood. The prevalence of pruritus in PSC patients at the time of diagnosis has been reported for a number of well-characterized patient cohorts. In Scandinavia, in a cohort of 305 patients with PSC, 30% had pruritus at the time of their diagnosis [3]. However, in a cohort of PSC patients followed at the Mayo Clinic in Rochester, Minnesota [4], pruritus was almost twice as common at the time of diagnosis (59%) compared to the frequency reported by Broome et al. [3]. This discrepancy likely reflects the specialized referral pattern for PSC patients seen at the Mayo Clinic. Moreover, among the Mayo patient cohort, 75% of the patients who were symptomatic at diagnosis reported pruritus [4]. In another Scandinavian study, 65 PSC patients were provided with daily diaries and asked to report symptoms over a 3-year period [5]. A majority of patients (84%) reported the occurrence of symptoms during this period, including pruritus, however these symptoms were typically intermittent and transient (lasting 1–2 days). In these patients, pruritus correlated closely with serum alkaline phosphatase levels [5]. Berquist et al. [6] examined a cohort of 246 PSC patients and divided them into those diagnosed before ($n=185$) and after ($N=61$) 1998. At the time of PSC diagnosis, 20% of patients complained of pruritus. Interestingly, pruritus in these patients was significantly more common in women (28%) than in men (16%), a finding paralleling observations from PBC patients where women are more likely to be pruritic than men [7]. These observations are suggestive of hormonal regulation of pruritus in cholestasis and are consistent with the common clinical observation that pruritus in PBC patients often worsens around the time of menses. Perhaps not surprisingly, pruritus was reported in 25% of patients diagnosed with PSC by endoscopic retrograde cholangiopancreatography (ERCP), compared to 5% of patients diagnosed using magnetic resonance cholangiopancreatography (MRCP). The frequency of pruritus at the time of diagnosis

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was similar in patients diagnosed before and after 1998 (22% vs 15%, respectively) [6].

In general, pruritus in cholestatic patients can have a profound effect on their health-related quality of life (HRQOL) [1, 2]. Similar findings of a pruritus-related detriment in HRQOL have been reported in patients with PSC. Gotthardt et al. administered HRQOL questionnaires to 113 PSC patients (SF-36 and Patient Health Questionnaire) and found that more frequent pruritus was associated with considerable reductions in HRQOL, as reflected by scores obtained in most of the QOL scales tested [8]. Moreover, pruritus was the most prominent factor affecting HRQOL and was associated with higher depression scores [8]. Similar findings were reported by Benito de Valle et al. in 182 patients with PSC [9]. Interestingly, in this group of patients, systemic symptoms such as pruritus were associated with lower HRQOL scores, whereas diseases severity was not [9].

The Pathophysiology of Itch

Pruritus is defined as an irritating skin sensation which leads to a desire to scratch. To better understand pruritus as it relates to cholestatic liver diseases, including PSC, it is important to appreciate the neural pathways that initiate and regulate itch. Pruritus may originate from diseases occurring within the CNS (e.g., stroke, tumors); however, more commonly pruritus has a peripheral origin that results from a pruritogen acting at the level of the skin to activate cutaneous "itch" nerve endings. Signals generated by activation of these cutaneous itch nerve endings are carried in unmyelinated C-fibers, through the dorsal root ganglion, to ultimately synapse with and activate spinal neurons within the dorsal horn of the spinal cord. Within the dorsal horn, itch-selective neurons carry the itch signal to the contralateral spinothalamic tract which relays the itch signal to the thalamus and ultimately to a number of itch-responsive areas of the brain [10]. An important role for the brain in regulating itch is routinely demonstrated by the observation that the itch sensation can be provoked in non-itchy people, simply by watching a person scratch an itch – a process termed "contagious itch" [11].

Much of our current understanding of itch comes from studies of *acute* itch induced by the application of a pruritogen. In contrast, pruritus associated with systemic disease, including cholestatic liver disease, is most commonly *chronic* in nature. The sensations of pain and itch are closely related but are distinct sensations subserved by separate nerve pathways [12]. Interestingly, painful stimuli (including scratching) often improves acute itch but is less effective in ameliorating chronic itch [13]. Based on relatively recent pioneering studies in models of acute itch, two types of peripheral C-fiber nerve pathways carrying itch signals from the skin to the spinal cord have been defined (Fig. 10.1):

(i) The *histaminergic itch pathway* involving mechanically insensitive C-fibers, as defined by Schmelz et al. [14].
(ii) The *non-histaminergic itch pathway* which is a histamine-independent pathway involving mechanically sensitive polymodal C-fibers, as originally described by Namer et al. [15].

Importantly, the histaminergic and non-histaminergic itch pathways activate distinct populations of dorsal horn spinothalamic tract neurons within the spine (Fig. 10.1) [16]. Therefore, the itch sensation can be driven by either of these two pathways, although it is generally believed that itch related to chronic systemic disease (e.g., cholestasis) *involves mainly the non-histaminergic itch pathway* [17], consistent with routine clinical observations that cholestasis-related itch is poorly relieved by antihistamines.

Four histamine receptors have been identified (H1R–H4R), with H1R being implicated as the major receptor involved in histamine-induced itch via activation of transient receptor potential cation channel V1 (TRPV1) [18]. In addition, H4R has been linked to chronic itch [19], although the pathways involved remain unclear. Cowage, a protein extract isolated from the legume *M. pruriens*, is commonly used experimentally to activate the non-histaminergic itch pathway. Cowage contains a cysteine protease

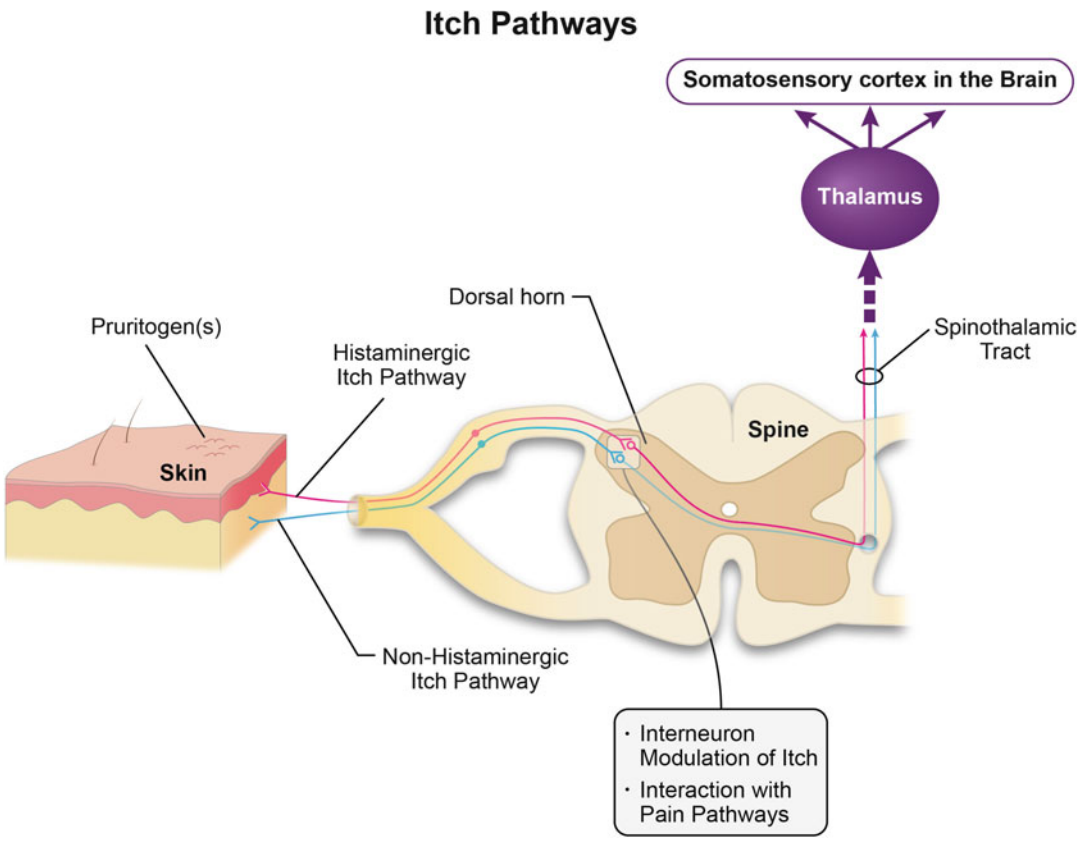

Fig. 10.1 Itch pathways. The two main peripheral itch pathways include the histaminergic pathway (*red line* stimulated by histamine) and the non-histaminergic pathway (*blue line* stimulated by a number of agents, including a protease contained in cowhage). The pruritogen present in cholestatic PSC patients is presumed to activate receptors located in the dermis of the skin to generate signals which are carried in polymodal C-fibers of the non-histaminergic itch pathway. These nerve fibers synapse with secondary neurons in the dorsal horn of the spinal cord where the itch signal can be modulated by input from neurotransmitters released from a variety of spinal interneurons and by interactions with pain pathways. Secondary afferent nerves carry the itch signal in the contralateral spinothalamic tract and synapse in the thalamus from which nerves project to a number of somatosensory areas within the brain

(mucunain) which activates protease-activated receptors 2 and 4 (PAR-2 and PAR-4) [20]. PAR-2 and PAR-4 have been implicated in the development of non-histaminergic itch [21], and PAR-2 specifically appears to be important in chronic itch [22, 23]. Interestingly, PAR-2 activation has been linked to transient receptor potential ankyrin 1 (TRPA1), a channel modulated by cold and cannabinoids [21, 24], with implications with regard to potential therapeutic approaches for treating itch. PAR-2 is co-expressed with TRPV1, and PAR-2 agonists increase afferent nerve signaling by sensitizing TRPV1 which in turn induces sensory nerve endings to become more responsive to other non-histaminergic pruritogens [25], an effect likely relevant in chronic itch syndromes.

At the level of the spinal cord, a close interplay between the histaminergic and non-histaminergic itch pathways appears to occur, through the activation of similar receptors (including G-protein-coupled receptors) and downstream messengers, as well as with pain-signaling pathways [17]. Both itch pathways activate phospholipase C and TRPV1 within the spinal dorsal root ganglion. Moreover, pain and itch pathways are in turn cross regulated through excitatory and inhibitory interneurons within the spinal cord that modulate

the activity of each other. In addition, descending modulatory neural pathways from the brain also profoundly regulate both pain and itch pathways [17]. Within the dorsal horn of the spinal cord, a number of neurotransmitters and associated receptors have been implicated in the regulation of itch pathways. These include calcitonin gene-related peptide (CGRP), substance P, glutamate, gastrin-releasing peptide (GRP), glycine, and gamma-aminobutyric acid (GABA) [10, 17]. Gastrin-releasing peptide receptor (GRPR) activation has been strongly implicated in the generation of itch [26]; however, it is unclear whether GRPR is activated predominantly by GRP or by glutamate in the spinal cord to invoke itch [27]. In contrast, the neurotransmitters glycine and GABA [28], as well as a subset of inhibitory interneurons termed "Bhlhb5" neurons [29], have been implicated in the inhibition of itch.

Acute histaminergic and non-histaminergic itch pathway stimulation in healthy individuals results in neuronal signaling which is carried within specific spinal cord neural pathways and results in activation of neurons within the thalamus and subsequently activates numerous areas of the brain that are involved in the regulation of perception, emotion, motor control, pain regulation, attention, and motivation [10]. In contrast, this distinct representation of activation of different brain regions involved in acute itch processing induced by these two pathways is blurred in the context of diseases associated with chronic itch [30]. Interestingly, in uremic pruritus, increased PAR-2 expression in the skin, leading to chronic overstimulation of the PAR-2-mediated itch pathway, has been implicated in altered responses to acute activation of non-histaminergic itch pathways in these patients [30].

Summary

Chronic itch, as commonly experienced by PSC patients, likely involves non-histaminergic peripheral nerve pathways from the skin, where the pruritogen(s) in PSC is postulated to act, to the dorsal horn of the spinal cord where these nerves synapse with other neurons (Fig. 10.1). Pruritogenic stimuli carried in this pathway may in turn be significantly modulated in the spine by interactions with stimuli carried in the histaminergic and pain nerve pathways, from itch-modulating spinal interneurons involving a number of neurotransmitters and receptors and/or from descending inhibitory neural pathways from the brain. Therefore, itch is a very complex sensory response that is even more challenging to understand in the context of a chronic disease such as PSC, which in turn has its own complex pathophysiology. However, the multiple levels through which pruritogenic nerve stimuli can be modulated would seem to offer a significant number of potential targets for therapeutic interventions designed to ameliorate itch in PSC patients.

What Causes PSC Patients to Itch?

The peripheral and central pathways involved in the generation of cholestatic itch, and its regulation, are poorly understood. Moreover, a specific pruritogen(s) has not been identified in cholestatic patients; however, the accumulation or creation of the cholestasis-related pruritogen must in some way be related to an impairment of bile flow into the gut lumen as this is by definition a central component of the cholestatic syndrome. In addition, it is quite possible that different pruritogenic pathways may be primarily responsible for the generation of itch in different cholestatic syndromes (e.g., ICP, BRIC, PBC, PSC). Many studies have been published examining different therapeutic approaches to cholestatic itch. Unfortunately, no single effective therapy for all patients with cholestatic itch has been identified to date. However, these studies, when evaluated together, do provide insight into the pathophysiology of cholestatic itch and allow for the generation of novel hypotheses that can be tested which may lead to therapies that are more specific and effective for cholestatic patients in general and PSC patients specifically.

Cholestasis is associated with elevated circulating histamine levels [31], suggesting that mast cells are likely activated in cholestatic patients.

However, cholestatic itch is not associated clinically with a classical histamine-related wheal and flare reaction in the skin, and antihistamines are poorly effective in treating cholestatic itch [1, 2]. Mast cells are a rich source of histamine, but also secrete proteases (e.g., tryptase) which are strong activators of PAR-2 [32] which, as outlined earlier, plays an important role in modulating the activity of the non-histaminergic itch pathway. Therefore, it is plausible that mast cell stabilizers may be beneficial in treating cholestatic itch by decreasing mast cell release of PAR-2 activating proteases and warrants further study.

Bile acids have historically been most commonly implicated as the causative pruritogen in cholestasis. However, serum and skin bile acid levels correlate poorly with itch in cholestatic patients, and in PBC patients with advanced disease, pruritus often decreases or disappears completely despite the persistence of high serum bile acid levels [2]. Cholestyramine is widely used to treat cholestatic itch, presumably based on its ability to bind bile acids in the gut lumen [33]. However, the highly potent oral bile acid sequestrant colesevelam was not effective in treating cholestatic itch (including 14 patients with PSC) [34]. These findings suggest that the clinical efficacy of cholestyramine in treating cholestatic itch is likely distinct from its ability to bind bile acids and is consistent with cholestyramine potentially binding some other unknown pruritogen or pruritus-regulating substance in the gut lumen. Furthermore, obeticholic acid, a bile acid that is a strong farnesoid X receptor (FXR) agonist, induces itch but reduces levels of circulating bile acids in PBC patients [35]. Therefore, circulating bile acids do not appear to be primary mediators of cholestatic itch. Recently, a role for bile acids in cholestatic itch was supported by the finding that the TGR5 receptor, which is expressed in primary sensory neurons, can be activated by bile acids to induce itch through activation of TRPA1 channels [36, 37]. In contrast to the suggestion that bile acids are acting as pruritogens in cholestatic patients, another possibility is that altering the bile acid composition within the gut lumen, as part of the cholestatic syndrome or after treatment with obeticholic acid or cholestyramine, in turn alters the gut microbiota in such a way to either enhance or reduce specific bacterial species within the gut that facilitate or inhibit the generation of a pruritogenic substance. The concept that the pruritogen in cholestasis is secreted in the bile has led to other approaches to divert bile flow away from the gut, in an attempt to treat cholestatic itch. Nasobiliary drainage has been used in this regard and has been highly effective in treating refractory cholestatic itch in patients with BRIC and to a lesser extent in patients with PBC [38, 39]. However, it remains unclear whether nasobiliary drainage is an effective therapy for intractable itch associated with PSC.

The concept of a potential gut-derived pruritogen as a driver of cholestatic itch, which is created as a result of cholestasis-related changes in the gut microbiota, is supported by a number of other clinical observations. Specifically, rifampin is an antibiotic widely used to effectively treat cholestatic itch, including patients with PSC [40, 41]. Although the mechanism whereby rifampin alleviates cholestatic itch remains unknown, it is clear that rifampin has broad spectrum antimicrobial properties, and therefore ingestion of rifampin likely profoundly alters the gut microbiota [42]. Consistent with this possibility, treatment of PSC patients with high doses of the antibiotic metronidazole significantly decreased pruritus [43, 44]. The bile acid obeticholic acid is a powerful FXR agonist, and its administration to both cholestatic and non-cholestatic patients causes itch [35]. However, it is clear that FXR activation also strongly induces the production of a number of antimicrobial peptides [45], significantly altering the gut microbiome [46]. These FXR-mediated effects could potentially drive the gut microbial community to generate more pruritogenic substances. In contrast to the antipruritic effects of antibiotics, treatment of PSC patients with a probiotic mixture did not improve pruritus [47].

Lysophosphatidic acid (LPA) has recently been implicated as a potential mediator of cholestatic itch [48], and LPA is formed through the action of the enzyme autotaxin. Interestingly, LPA also stimulates basophils to release histamine, and this has recently been implicated

in the development of itch in a patient with PSC [49]. Importantly, autotaxin activity in the serum is increased in cholestatic patients with pruritus and is decreased in cholestatic patients who have been effectively treated with antipruritic regimens, including nasobiliary drainage and rifampin [48, 50]. Indeed, Kremer et al. have suggested that the antipruritic effect of rifampin in cholestasis can be explained, at least in part, by rifampin-related activation of pregnane X receptor (PXR) which inhibits autotaxin expression at the transcriptional level [50]. However, other clinical observations do not support this hypothesis. Bezafibrate has been increasingly used as a treatment for patients with PBC, in part, due to its effects as a PXR agonist [51, 52]. However, bezafibrate has no effect on PBC-related pruritus [40, 52]. Moreover, autotaxin activity is highest and correlates most closely with itch in women with intrahepatic cholestasis of preagnancy (ICP); however, ursodeoxycholic acidhep (UDCA) therapy is highly effective in relieving itch in ICP patients but is without effect for itch in PBC and PSC patients [1, 2, 53, 54]. Moreover, LPA has a very short biological half-life and is highly lipophilic, and its receptors are located intracellularly making the case for a significant role for LPA in cholestatic itch challenging [2]. Interestingly, serum autotaxin activity is also often significantly increased clinically in a number of non-cholestatic clinical syndromes but is not associated with the development of itch [2].

Opioids have historically been closely linked to both pain and itch pathways, as administration of opioids (e.g., morphine) relieves pain but often induces itch. Endogenous opioids accumulate in the serum of cholestatic patients [55] and have been shown to modulate pain pathways in cholestasis by acting at peripheral opioid receptors located on cutaneous nerve endings [56]. Moreover, blockade of opioid receptors with naloxone, naltrexone, or nalmefene is clinically effective in treating some patients with cholestatic itch [40, 57–59]. However, the induction of an opioid withdrawal-type reaction in pruritic cholestatic patients treated with opioid receptor blockers suggests that endogenous opioids may be acting centrally, to modulate the perception of itch, and not peripherally to generate itch [57, 59].

Inflammatory mediators, including cytokines, can modulate pain and itch pathways. In particular, TNFα can activate nociceptive primary afferent nerve fibers [60], and topical application of TNFα to peripheral nerves causes mechanical hyperalgesia [61]. In addition, TNFα modulates spinal cord dorsal horn pain-related synaptic activity [62], and TNFα increases the expression of the TRPV1 receptor in the spinal dorsal root ganglia [63]. Inhibition of TNFα using etanercept reduces pain-related behaviors in a model of neuropathy [64]. A potential role for TNFα in modulating cholestatic itch is supported by a number of clinical observations. Circulating TNFα levels are increased in cholestatic patients, and treatment of profoundly pruritic cholestatic patients with MARS is associated with a significant reduction in serum TNFα levels [65]. In addition, thalidomide treatment (which inhibits TNFα production) decreased itch in PBC patients [66]. In contrast, treatment of PSC patients with pentoxifylline (also inhibits TNFα production) did not alter pruritus; however, the patients included in this study were not significantly pruritic at the start of treatment [67]. In another study, treatment of PSC patients with the TNFα inhibitor etanercept resulted in a reduction in pruritus [68]. Activated B cells produce significant amounts of TNFα [69], and we have shown that elimination of B cells with rituximab in PBC patients resulted in a significant improvement in pruritus, without altering serum indicators of cholestasis severity [70]. These observations suggest that targeting TNFα may be a novel approach to treat pruritus in PSC patients and may be linked to therapeutic approaches for inflammatory bowel disease (IBD) which commonly coexists in these patients.

The cutaneous itch signal is transmitted to secondary neurons within the spinal cord. These secondary neurons can be extensively modulated by input from excitatory and inhibitory interneurons (Fig. 10.1) and by descending inhibitory neural pathways from the brain [10, 17]. Itch signal processing and regulation within the spinal cord and brain therefore represent potential targets for

therapeutic modulation of cholestatic itch. Cannabinoids are widely used clinically for their ability to modulate pain and decrease nausea, most likely by acting on receptors within the CNS. A pilot study in three cholestatic patients with treatment refractory itch, treated with the cannabinoid dronabinol, showed an improvement in itch [71]. Interestingly, histamine-induced itch is attenuated by a peripherally administered cannabinoid receptor agonist [72]. These findings suggest that cannabinoids may be beneficial in cholestatic itch by acting both peripherally and centrally. Serotonin also regulates itch, and a role for serotonin in cholestatic itch is supported by the well-documented clinical efficacy of the selective serotonin reuptake inhibitor (SSRI) sertraline in treating patients with cholestatic itch, including patients with PSC [73]. However, it remains unclear whether the clinical effect of sertraline in improving itch in these patients is due to the effects on serotonergic neurotransmission within the brain, spinal cord, or skin. One serotonin receptor in particular, the 5-HT3 receptor, has been examined as a potential driver of cholestatic itch. However, a number of studies have been performed using 5-HT3 antagonists in patients with cholestatic itch, but no significant beneficial effects could be consistently documented [40, 74].

Rational Approach to Treating Pruritus in PSC Patients

(i) *Defining the severity and impact of pruritus*: Evaluating patients in the clinic with regard to the severity of pruritus and its impact on their HRQOL (including physical, emotional, and social impacts) should be addressed at each visit. This evaluation can include simple to administer methods such as asking a patient to score their pruritus using a visual analog scale (VAS) [73, 75] or by asking the patient to rate their itch using a simple subjective-descriptive numerical scale, as previously described [67, 76].

(ii) *Dominant strictures and endoscopic therapies*: In PSC patients, the new onset or worsening of pruritus, especially when coupled with clinical deterioration of serum markers of cholestasis, suggests the possible development of a dominant stricture (benign or malignant) or a worsening of their overall disease. Dominant strictures occur commonly in PSC patients, occurring at a frequency ranging from 36 to 57% over 10 years of follow-up [77]. Benign strictures can often be managed effectively endoscopically with an associated relief of, or improvement in, associated pruritus (Fig. 10.2).

(iii) *Medical management of pruritus in PSC patients*: As outlined earlier, since the specific cause of pruritus in PSC patients remains unknown, therapeutic approaches to treat itch in these patients must therefore remain somewhat empiric. However, in general, the therapeutic medical approach outlined in Fig. 10.2 is a useful framework for treating pruritic PSC patients and will be effective to satisfactorily ameliorate pruritus in the majority of these patients. Choosing a second-line therapy for treatment (Fig. 10.2) often comes down to personal preference, as there have been no head-to-head comparison studies of these therapies, and none of these treatments work in every pruritic patient. Therefore, therapy often needs to be individualized. In my own practice, I typically choose rifampin as my first choice, followed by sertraline and then naltrexone. For patients who are refractory to these first- and second-line therapies for pruritus, phototherapy, plasmapheresis, and/or albumin dialysis (MARS) can be considered; however, their potential utility is based on anecdotal experience and/or reports from small groups of cholestatic patients of with diseases of mixed etiology.

(iv) *Surgical management of pruritus in PSC patients*: In general, surgery has almost no role in the treatment of PSC-related pruritus. However, if pruritus is intractable and is due to advanced stricturing disease that is not amenable to endoscopic intervention, liver transplant should be considered as a therapeutic option.

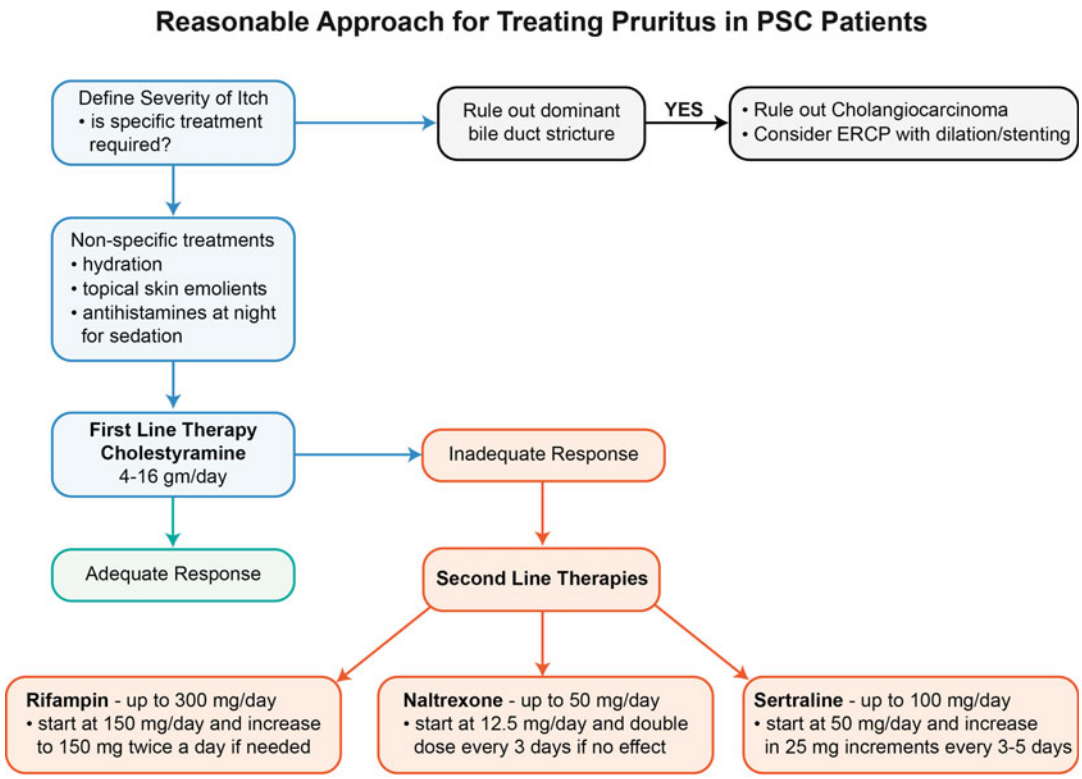

Fig. 10.2 Reasonable approach for treating pruritus in PSC patients. A reasonable approach to an itching PSC patient should include an assessment of itch severity (which can be quantitative or qualitative) to determine the impact of itch on quality of life. If the impact is minor, only nonspecific treatment may be indicated. It is important that in any PSC patient with new onset of significant pruritus, or a rapid worsening of pruritus, especially when serum cholestatic indices also deteriorate, a dominant stricture needs to be ruled out (and specifically dealt with). If pruritus is significant, first-line therapy consists of cholestyramine. If response is inadequate, then second-line therapies can be tried (instituted one at a time) and consist of either rifampin, naltrexone, or sertraline. If one of these does not work, it is reasonable to try another

Closing Remarks

Pruritus is a complex and poorly understood symptom that commonly affects patients with PSC and has a significant negative impact on their HRQOL. As we gain increasing insight into the pathways that cause and regulate itch, it is likely that more effective therapies will be developed in the near future to treat itch in PSC patients. However, for the time being, a rational stepwise approach to managing these patients can be followed that will benefit the majority of these patients.

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