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New insights into the pathophysiology and treatment of chronic itch in patients with End-stage renal disease, Chronic liver disease and Lymphoma

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Introduction

Chronic itch associated with systemic diseases continues to be one of the most bothersome dermatological symptoms accompanying end-stage renal disease (ESRD), chronic liver diseases, and lymphoma. The International Forum for the Study of Itch has recently issued a consensus paper on different types of chronic pruritus, including pruritus in systemic diseases that can present with or without secondary skin changes.¹ Various types of itch have been described based on the origin of the itch, which could be skin-related, neuropathic, systemic, or psychogenic.² At any given time patients with these systemic diseases may have more than one origin, for example, patients with end-stage renal disease (ESRD) could have neuropathic itch due to nerve fibers damage, as well as itch associated with skin inflammation such as perforating folliculitis. Itch adversely affects quality of life of patients, leading to sleep deprivation and depression that further augment itch. Chronic itch associated with systemic diseases range from mild to intractable, which is defined as a chronic itch state in which the cause cannot be removed or treated, and no relief or cure has been found in the generally accepted course of medical practice.³ In the last decade, there are significant advances in our understanding of specific itch neuronal pathways, mediators and relevant receptors, opening the field for development of new antipruritic strategies. The purpose of this review is to highlight the new findings related to the pathophysiological mechanisms and the treatment of itch associated with the most common systemic diseases including ESRD, chronic liver disease and lymphoma.

Epidemiology

A recent study estimated that approximately one in five dermatology outpatients with generalized pruritus with no obvious dermatologic cause may have an underlying systemic cause.⁴ This result underscores the significance of ruling out potential underlying systemic diseases when seeing a patient with generalized itch.

Chronic itch remains as one of the most common symptoms in patients with ESRD, particularly in hemodialysis (HD) patients. Although the prevalence of itch has decreased in the last 30 years, itch remains a major problem in ESRD. The overall prevalence of pruritus in a recent study in US was 57%.⁵ The largest study so far analyzed data from 18,801 HD

patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS) (1996–2004) and indicated that 42% of HD patients experienced moderate to extreme pruritus.⁶ Several smaller studies found that significant itch affects 15%–49% of patients with chronic renal failure and 50%–90% of the dialysis population.⁷ Most of these studies showed ESRD-associated itch being independent of gender, age, ethnicity and types of dialysis. The prevalence of chronic kidney disease has increased in the last decades and is predicted to continue to rise worldwide,⁸ suggesting that chronic itch associated with ESRD will remain as a major health problem in this population.

Pruritus is common in chronic cholestatic liver disease. It is more common in intrahepatic than extrahepatic cholestasis. Intrahepatic cholestatic itch is associated with chronic viral hepatitis B and C, cholestasis of pregnancy, primary biliary cirrhosis and Alagille syndrome which is a pediatric cholestatic syndrome. Extrahepatic cholestatic itch may be caused by obstructive tumor in the pancreatic head and primary sclerosing cholangitis. It seems that prevalence of itch in primary biliary cirrhosis (PBC) is much higher than in other liver diseases. Itch is the most common symptom associated with PBC. According to a recent Internet survey,⁹ 69% of patients with PBC reported itch, and itch preceded the diagnosis of PBC in 75% of these cases and worsened at night in 65%.

Prevalence of chronic itch has been reported decades ago as 30% in patients with Hodgkin's disease.¹⁰ A recent small-scale study showed that approximately 15% of patients with non-Hodgkin's disease suffered from generalized pruritus.¹¹ According to a retrospective study recently conducted at MD Anderson,¹² the incidence of itch is about 19% in patients with Hodgkin's disease who were referred to dermatology.

Impact on the quality of life

The intensity of itch associated with ESRD ranges from sporadic discomfort to complete restlessness during day and night. It could be intermittent or persistent.^{7,13} It was found in DOPPS that HD patients with moderate to extreme pruritus were more likely to feel drained and have poor sleep quality, depression, and lower mental and physical composite scores of quality of life than patients with no or mild pruritus. Moreover, pruritus in HD patients is associated with a 17% higher mortality risk and this effect is no longer significant after adjustment for measures of sleep quality.⁶ A recent study showed that there was significant association between the intensity of itch and the quality of life of HD patients, and incremental increase in itch intensity was associated with decrements in health-related quality of life.¹⁴

Pruritus associated with chronic liver disease is usually generalized and intermittent. Its negative impact on quality of life of PBC patients is marked. The cholestatic pruritus could range from mild to severe; it could disturb regular sleep, limit activities of daily life and reduce quality of life, resulting in depression, and in extreme cases, suicidal ideation.¹⁵

Severe intractable itch has been reported in lymphoma patients. Some of the most severe pruritic cases in our practice suffer from lymphoma, however there is limited published data on its effect on quality of life of lymphoma patients.

Clinical characteristics of chronic itch

Secondary skin lesions as a result of the malicious itch-scratch cycle are excoriations, hyperpigmentation or hypopigmentation, lichenification, prurigo nodules and scars. In all types of chronic itch, itch usually becomes more intense during nighttime. Meanwhile, there are unique clinical characteristics of itch associated with specific systemic disease. Of note, itch can be severe in systemic diseases without skin signs.

The characteristics of itch in ESRD patients vary over time and among individual patients. Itch could last only a few minutes per day or persist continuously throughout the day. The common exacerbating factors include dry skin, stress and heat. Itch could be generalized in 25% to 50% of patients, and it predominantly affects the back (70%), abdomen (46%), head (44%), and arms (43%).^{5,13} There are several primary skin lesions that can cause extreme itch in patients with ESRD such as perforating folliculitis.¹⁶ Nephrogenic systemic fibrosis related with gadolinium exposure was recently reported to cause severe itch and pain in ESRD patients.¹⁷

The unique feature of cholestatic pruritus is that the itch initially starts and is most intense in the palms and soles, which is usually not reported in other diseases.¹⁸⁻¹⁹ Several studies indicated that females with cholestatic pruritus usually reported worse itch premenstrually, during hormone replacement therapy and in late pregnancy.¹⁵ Intractable itch in chronic liver disease could be an indication for liver transplantation even in the absence of liver failure.^{20,21}

Itch has been known for decades to be the most common symptom of Hodgkin's disease.^{10,22-23} Itch could precede the development of Hodgkin's disease.¹² In several cases, itch can present with ichthyosiform skin changes on the extremities (Yosipovitch G, unpublished data) or as a new onset eczema lesions with Hodgkin's disease.¹²

Pathophysiological mechanisms

The pathophysiological mechanisms of pruritus associated with these systemic diseases remain poorly understood. Recently major advancements have been achieved in understanding the neurobiology of itch both peripherally and centrally. In the following section we will review itch neural pathway and mediators that could possibly be associated with chronic itch of different origins, and then list potential mediators and relative receptors uniquely related to the systemic diseases we address in this review.

Itch-specific neural pathway

More than 10 years ago, Schmelz et al. were the first to identify specific slow conducting histamine-sensitive but mechano-insensitive C nerve fibers that transmit itch in humans.²⁴ Selectively histamine-responded neurons were also identified in lamina 1 neuron cells in the spinal cord of the cat.²⁵ This was regarded as a breakthrough discovery of itch specific pathway. However, this histamine-sensitive pathway does not seem to play a major role in the modulation of chronic itch, due to the fact that patients with systemic diseases-associated itch generally lack response to oral antihistamines, even with high dose inhibiting histamine response. Moreover, the function of these fibers cannot explain the itch induced by exposure to mechanical stimuli such as wearing clothing containing wool.

It has been for long time suggested that nonhistaminergic pathway likely plays a role in the transmission of chronic itch. In the last two years, several groups were able to identify another distinct group of nerve fibers that also transmit itch in the spinal cord of monkeys, as well as in humans. These fibers were found to respond to *Mucuna pruriens*, a plant containing a protease named mucunanin, plant reported by Shelley decades ago to induce itch without flare.²⁶ Mucunanin induces itch by activation of C nerve fibers that do not respond to histamine but respond to mechanical stimuli.^{27,28,29} The role of this newly identified itch pathway in chronic itch and systemic diseases remains to be elucidated. The demonstration of dual, independent itch-transmitting pathways suggests the possible existence of other types of itch pathways including those that more closely mirror systemic disease-associated itch.

Nerve sensitization in chronic itch

Patients with chronic itch seem to have hypersensitive nerve fibers that could be activated by noxious stimuli, whereas noxious stimuli such as heat stimuli or scratching can inhibit itch in healthy subjects.³⁰⁻³¹ Studies on patients with chronic itch demonstrated that both mechanical and noxious heat stimuli could be perceived as itch and aggravate itch in skin lesions of patients with atopic dermatitis (AD).³²⁻³³ Both central and peripheral sensitizations are suggested to contribute to this abnormal modulation in patients with chronic itch. Nerve growth factor (NGF) released by keratinocytes was suggested to be crucial in the sensitization and increased number of nerve fibers in patients with AD.³⁴⁻³⁵ Using AD mouse model researchers recently showed that excessive production and secretion of neurotrophic factors including glial cell line-derived neurotrophic factor (GDNF) and NGF were closely associated with skin hypersensitivity to itching.³⁶ GDNF and NGF belong to a family of neurotrophin that are involved in the development of central and peripheral nerve systems. Central sensitization of itch signaling, at spinal cord and brain levels, may also contribute to abnormal modulation of chronic itch, similar to that observed in chronic pain. Our group recently demonstrated that brain areas involved in the central sensitization of itch such as anterior cingulate cortex (ACC) were highly activated in acute itch in AD patients, compared to healthy controls.³⁷ Currently, there are no studies examining nerve sensitization in itch associated with ESRD, chronic liver disease and lymphoma.

Peripheral and central itch mediators

Histamine receptors—In addition to classic histamine 1 receptor (H1R), histamine 4 receptor that is localized on various immune and inflammatory cells have been shown to play a role in the modulation of itch³⁸; H4R antagonists were proved to inhibit experimentally-induced itch.³⁹⁻⁴⁰⁻⁴¹ H3R, which has been found in the central and peripheral nerve systems, also seemed to be involved in the modulation of itch in animal models.⁴²⁻⁴³ However, the roles of these two histamine receptors in modulation of chronic itch in humans have not been studied yet.

Proteinases—Proteinase-activated receptor-2 (PAR-2), a G protein-coupled receptor subfamily localized on C fiber terminals, may play an important role in the modulation of itch. Using dermal microdialysis researchers have shown the levels of tryptase and its receptor PAR-2 to be elevated four-fold in atopic dermatitis patients.⁴⁴ Cowhage containing mucunain (a novel cysteine protease) has recently been shown to elicit nonhistaminergic itch via activation of PAR2 and PAR4.⁴⁵ The role of PAR-2 in chronic itch associated with systemic diseases worth further investigation.

TRPV receptors—Transient receptor potential vanilloid subtype 1 (TRPV1), a capsaicin receptor, is not only expressed on primary afferent nociceptive neurons and their terminals but also on a variety of cutaneous components including keratinocytes, dendritic cells and dermal mast cells.⁴⁶⁻⁴⁷ TRPV1 was recently discovered as a new player in the pathogenesis and treatment of itch via the activation of phospholipase A2 and 12-lipoxygenase.⁴⁸⁻⁴⁹ Transient receptor potential vanilloid subtype 3 (TRPV3), which has been recently associated with the development of pruritus in mice,⁵⁰ could be another potential TRP channel involved in the modulation of chronic itch. The roles of TRPV1 and TRPV3 in the modulation of itch in the systemic diseases in humans have not been studied yet.

Gastrin-Releasing peptide—Sun and Chen⁵¹ have demonstrated the important role of gastrin-releasing peptide (GRP) and its receptor (GRPR) within the spinal cord of mice in mediating pruritic stimuli of different origins. GRP is one of mammalian bombesin-related

peptides. The role of GRPR in the pathogenesis of chronic itch in humans remains to be determined.

Endogenous opioids—Intense, generalized itch is known to be one of the most common side effects of analgesic therapy with exogenous mu-opioid. Endogenous opioids are important players in the pathogenesis of itch per se, as well as itch related to systemic disease. Opioid peptides induce itch by degranulation of cutaneous mast cells,⁵² or through a direct central and peripheral pruritogenic effect by activating mu receptors.^{52·53·54·55} Mu- and kappa-opioid receptors agonists may act inversely in terms of their pruritic properties. The role of endogenous opioids in pathogenesis of cholestatic pruritus was first reported in 1979, and mu-receptor antagonist naltrexone dramatically improved intractable pruritus in a patient with PBC.⁵⁵ Moreover, the plasma of both cholestatic patients and cholestatic animal models showed elevated serum levels of opioids,^{56·57·58·59} although a correlation between opioid levels and the severity of itch has not been shown.⁵⁷ Hepatocytes and cholangiocytes have been proposed to be the source of elevated opioids in cholestasis.^{60·61}

An increased ratio of serum beta-endorphin to dynorphin A was reported in HD patients compared with healthy controls, and the ratio increased with the increased intensity of itch.⁶² Dynorphin A is a kappa-receptor agonist while beta-endorphin is a mu-receptor agonist, suggesting that an imbalance with overactivity of mu-opioid system is involved in ESRD-associated itch. Moreover, kappa-receptor agonist nalfurafine was shown to significantly decrease itch intensity and excoriations in HD patients.⁶³

The role of endogenous opioid system in the pathogenesis of pruritus in lymphoma has not been studied yet. However, the efficacy of butorphanol (a kappa-opioid agonist and mu-opioid antagonist) in the treatment of pruritus in a non-Hodgkin lymphoma patient indicated the possible involvement of opioids in the modulation of this type of pruritus.⁶⁴

Interleukins—Interleukins (IL) such as IL-2 have a role in eliciting itch in atopic dermatitis and other inflammatory skin diseases,⁶⁵ however their roles in itch associated with systemic diseases remain incompletely understood. The recent discoveries of IL-31 (a TH2 cell-derived cytokine) capable of eliciting itch, and increased IL-31 level in atopic dermatitis and prurigo nodularis, indicated a potential role of this cytokine in the modulation of chronic itch.⁶⁶ IL-31 antibody could effectively reduce scratching behavior in an atopic dermatitis-like murine model during the onset of clinical skin manifestations, suggesting the potential therapeutic role of IL-31 antibody in treatment of chronic itch.^{66·67} Other cytokines with possible roles in the modulation of itch are IL-6⁶⁸ and Tumor Necrosis Factor (TNF-alpha). Although the new TNF inhibitors do not seem to have a direct antipruritic effect, the old non-specific TNF inhibitor thalidomide has been shown to have antipruritic effect.⁶⁹

Other factors that may contribute to the pathophysiology of itch include endocannabinoid system,^{70·71} Gamma-aminobutyric acid (GABA) and its responsive receptor.^{72·73} Their roles in the modulation of chronic itch in systemic diseases have not been studied yet.

Pathophysiology of itch in ESRD

The pathophysiologic mechanism of ESRD still remains poorly understood and the pruritogens involved have not been identified completely. It has been postulated that ESRD itch is associated with a proinflammatory state and an imbalance of the Th1 cytokines. ESRD patients with itch had higher serum C reactive protein.⁷⁴ Kimmel et al. found that HD patients with pruritus had significantly enhanced Th1 cytokines and IL-6 levels.⁶⁸ In line with this theory, ultraviolet B (UVB) light,⁷⁵ tacrolimus,^{76·77} and thalidomide⁷⁸

alleviate pruritus in patients with ESRD. UVB attenuates Th1 cell differentiation and decreases IL-2 production. Thalidomide inhibits T-helper cell type 1 activation by decreasing tumor necrosis factor alpha levels whereas tacrolimus suppresses T-lymphocyte activation by inhibiting activity of the phosphorylase enzyme calcineurin.¹³ In addition, patients on statin therapy which is capable of decreasing serum proinflammatory cytokine and C-reactive protein levels were less prone to itch.⁵ However, a recent study did not find a correlation between itch and C-reactive protein or other inflammatory serum proteins in patients with chronic renal disease.⁷⁹

Peripheral neuropathy is a common manifestation of ESRD. It was postulated that ESRD itch could be related to neuropathy. Neuron-specific enolase immunoreactive nerve fibers were found to sprout throughout the epidermis in HD patients but not in healthy controls,⁸⁰ however, other study presented contradictory findings.⁸¹ A neurophysiologic study using quantitative sensory testing did not find an association between abnormal C nerve fiber function in ESRD and itch.⁸²

Many other factors have been considered in the pathophysiology of ESRD pruritus.¹³ Of note several studies found increased serum levels of calcium and phosphate levels with ESRD pruritus.^{5,6} A recent study suggested that increased levels of calcium in the deeper layers of the epidermis were involved in ESRD itch.⁸³ Skin dryness is the most common skin manifestation of ESRD^{84,85} and has been shown to be related with presence of itch in several studies,⁵ while other studies did not find an correlation.^{86,87} Several studies reported conflicting results regarding an association between skin barrier damage and ESRD itch. We recently assessed for the first time the skin barrier function and lipid content and its relation to itch in ESRD. Although we have found significant abnormal barrier function which was correlated with low levels of glycerol, our findings did not support any association between skin barrier function and ESRD itch.⁸⁸ Inadequate removal of medium molecular weight uremic toxins has been suggested as another possible cause for ESRD itch.¹³ We have recently found that higher efficacy of removal of small molecular toxin by standard assessment of Kt/V was associated with ESRD pruritus,⁵ while previous study did not find such an association.⁸⁹

Pathophysiology of cholestatic pruritus

Multiple factors participate in the pathophysiology of cholestatic pruritus. Bile salts, bile acids, bilirubin and other cholephiles accumulating in circulation and tissues have been historically considered as major causes for cholestatic pruritus. In patients with longstanding intractable cholestatic pruritus, dilating major bile duct stenosis or nasobiliary drainage of bile was reported to remarkably ameliorate pruritus within hours.^{90,91} However, it is clear that in many cholestasis patients bile acids resins do not improve itch. Moreover not every patient with cholestasis and elevated plasma bile salts experiences itching.⁹² In some patients pruritus improved spontaneously despite persistently elevated levels of bile salts.⁹² Moreover, kinetics and concentration of bile salts seem unrelated to itch intensity in cholestatic patients.^{91,93} Bile salts still possibly play a complex role in the modulation of cholestatic pruritus directly or indirectly, via interaction with other pruritic systems. The frequency and intensity of cholestatic pruritus do not correlate with the severity of cholestasis.⁹⁴ The role of elevated endogenous opioids in the pathogenesis of cholestatic pruritus (as mentioned above) is beyond any doubt.

Pathophysiology of itch in lymphoma

To our knowledge, there is no study that focuses on the specific mediators of itch associated with lymphoma. Cytokines such as IL-6 and IL-8, which have been reported to increase in ESRD-associated itch and atopic dermatitis respectively,^{68,95} are closely related to

pathophysiology of lymphoma.⁹⁶⁻⁹⁷ Their roles in pathogenesis of itch in this systemic disease are worthy of further investigation.

Treatment options

Unfortunately, to date there are no specific antipruritic treatments. The focuses of current strategies are to reduce the intensity of itch and to block afferent transmission via peripheral and central neural mechanisms. There are a limited number of studies examining the efficacy of these agents for treatment of itch in systemic diseases and most of data presented is based on case series or small-scale studies. The purpose of this section is to review the rationale systemic therapeutic ladders for pruritus associated with ESRD, chronic liver disease and lymphoma (*see* figure 1, figure 2, figure 3).

Antidepressants for itch

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs such as sertraline and paroxetine, act by selective inhibition of serotonin reuptake. Their beneficial effect is presumably via alteration of neurotransmitters' concentrations within the central nervous system. Several recent reports have shown paroxetine to be effective in the treatment of systemic itch of different types. The antipruritic effect takes 2–3 weeks from commencement of treatment to become effective. A recent open-labeled study showed paroxetine and fluvoxamine to be efficient in the treatment of different types of chronic itch including systemic lymphoma and solid carcinoma.⁹⁸

Selective Neuroepinephrine Re-Uptake Inhibitors (SNRI)

SNRIs relieve itch possibly by reducing central sensitization to itch due to their effects on both serotonin and noradrenergic α_2 receptors, as they do in treatment of neuropathic pain.⁹⁹⁻¹⁰⁰ We found mirtazapine to be particularly effective in treatment of nocturnal pruritus.¹⁰¹ Mirtazapine has been reported to be effective in the treatment of itch associated with PBC, ESRD and lymphoma.¹⁰² The new SNRIs such as venlafaxine and duloxetine do not seem to have significant antipruritic effects in our experience.

Neuroleptics

Gabapentin and pregabalin are structural analogues of the neurotransmitter gamma-aminobutyric acid (GABA). The exact mechanisms of their antipruritic effects are not clear. They probably inhibit central itch pathways, as they do in neuropathic pain.¹⁰³

Sedating antihistamines

Sedating antihistamines still have a role in treating itch, especially nocturnal itch.¹⁰⁴ Sedating antihistamines such as hydroxyzine at high dose commonly are used to treat pruritus in patients with chronic renal disease and PBC probably by exerting a beneficial effect through their soporific properties. Doxepin, a tricyclic antidepressant, has a similar effect as SSRI and is also used to treat nocturnal itch, probably amid its potent antihistamine H1 receptor property.

Opioids antagonists and agonists

Mu-opioid antagonists, such as naltrexone and naloxone, have been proven to be efficient in the treatment of cholestatic pruritus¹⁵⁻¹⁰⁵ but showed conflicting results in ESRD itch.¹⁰⁶⁻¹⁰⁷ One of the major caveats of using these drugs in chronic liver disease is that they can cause pain by antagonizing mu-receptor. Pain causes significant suffering in this population.

Recently nalfurafine (TRK-820), a kappa-receptor agonist, showed a antipruritic effect in the treatment of severe ESRD-associated pruritus.¹⁰⁸ It has also been shown to successfully relieve pruritus in an animal model with cholestasis.¹⁰⁹ However, TRK-820 is not available commercially yet. Butorphanol is a commercially available analgesic with activity of antagonizing mu-receptor and agonizing kappa-receptor, which was showed to be efficient in the treatment of intractable pruritus associated with lymphoma or PBC and other systemic diseases.⁶⁴

Ultraviolet (UV) therapy

UVB is well known to relieve pruritus in systemic diseases particularly in chronic renal disease.¹³ It was also reported to treat itch associated with chronic liver, however its efficacy is limited. The possible mechanism is via the chemical modification of pruritogens in the skin or an alteration of skin sensitivity to pruritogens. The role of UV therapy including both narrow band UV-B and Psoralen plus ultraviolet (UV) A (PUVA) is well established for cutaneous T cell lymphoma¹¹⁰ but has not been reported to our knowledge for itch associated with systemic lymphoma.

Behavioral therapy targeting the central nervous system

Several reports have shown that techniques of relaxation and behavioral therapies as an adjunctive therapy can attenuate itch and scratching.⁹⁹

Treatment of pruritus in ESRD (see figure 1)

A placebo controlled double blind study in 25 patients with ESRD-associated pruritus found that 300 mg of oral gabapentin administrated after each hemodialysis session was an effective and safe regimen for ESRD pruritus.¹¹¹ A similar observation suggested a lower dose of gabapentin (100 mg after a hemodialysis session) with slow upward titration to decrease the risk of gabapentin-induced neurotoxicity and/or coma in ESRD patients.¹¹² A large-scale, placebo-controlled, double blind clinical trial showed that nalfurafine, a kappa-receptor agonist significantly improved itch and sleep disturbance in patients with chronic renal disease-associated pruritus.¹⁰⁸ Phototherapy with UV-B has been used for more than a decade for ESRD-associated itch and is still considered a treatment of choice in many centers. It is important to inform the patient that in the first 2 weeks that the itch may worsen and the antipruritic effect is noticed only after 1–2 months of treatment. The possible antipruritic mechanism of UV-B is decrease in proinflammatory cytokines. The initial case series of 0.03% topical tacrolimus exerting antipruritic effect on ESRD-associated itch¹¹³ led us to perform a double blind randomized controlled study with 0.1% tacrolimus ointment. The results of this study did not show that topical tacrolimus was more effective than the vehicle in relieving itch.¹¹⁴ Topical therapies with emollients have shown a moderate beneficial effect in reducing itch intensity in ESRD patients.⁸⁴ A recent randomized double-blind trial showed that high-permeability hemodialysis was significantly more effective in relieving pruritus in ESRD patients than conventional haemodialysis,¹¹⁵ in contrast to the traditional concept that ESRD-related itch is not affected by types of dialysis. A topical emollient containing structured lipids with endocannabinoids was shown to improve itch and xerosis in ESRD patients.¹¹⁶ In a double-blind, placebo-controlled study, 0.025% capsaicin cream significantly alleviated pruritus in HD Patients.¹¹⁷ We use topical capsaicin only to treat localized itch. A pramoxine 1% based lotion was recently shown to be efficient in treatment of itch associated with ESRD in a double-blind, placebo-controlled study.¹¹⁸

Treatment of pruritus in chronic liver disease (see figure 2)

Cholestyramine is a non-absorbable anion exchange resin that binds bile salts and has been used for more than a decade for cholestatic itch. A recommended starting dose is 4 gram once to twice a day and it can be extended up to 4 grams four times a day. It should be taken 1 hour before and after breakfast and at least 4 hours prior to any other medication.¹⁵

Ursodeoxycholic acid, a secondary bile acid that reduces the rate at which the intestine absorbs cholesterol molecules and constitutes up to 3% of human bile acid pool and up to 50% upon oral administration, could render the bile acid pool more hydrophilic; it is the only approved medical treatment of PBC, and has been proved to be antipruritic in small trials.¹¹⁹ However, ursodeoxycholic acid has not been convincingly shown to improve cholestatic pruritus in randomized, placebo-controlled trials.¹²⁰ Rifampicin is a P450 cytochrome enzyme inducer but its exact antipruritic mechanism is not clear. Its dose at 300–600 mg/day or 10 mg/kg/day was showed to alleviate cholestatic pruritus.¹⁵ It may accelerate the metabolism or secretion of the pruritogens and can be used as an effective short-term treatment of cholestatic pruritus.¹²¹ Because of potential hepatotoxicity caused by rifampicin, liver transaminases should be frequently tested. Sertraline has been shown in a small randomized double-blind study at a dose of 75–100 mg/day to be an effective choice for cholestatic itch.¹²² A molecular adsorbent recirculating system (MARS) (albumin liver dialysis) used in patients with acute and chronic liver failure was reported to abate cholestatic itch.¹²³ Gabapentin, which has been proved efficient in treatment of ESRD-associated itch,¹²⁴ did not show efficacy in treatment of cholestatic pruritus in a double-blind, placebo-controlled trial.¹²⁵

Treatment of pruritus in lymphoma (see figure 3)

A recent case series reported that combination of low dose of mirtazapine (7.5 to 15 mg at evening) and gabapentin (300 mg at night up to 900–2400 mg per day) was effective in treatment of cutaneous T-cell lymphoma.¹²⁶ Butorphanol has been used to treat intractable itch in lymphoma with dose of 3–4 mg/day.⁶⁴ Another option that we found helpful to alleviate intractable lymphoma itch is oral prednisone 40 mg tapering down gradually in 3 weeks.

Conclusion

Chronic itch associated with ESRD, chronic liver disease and lymphoma has a profound impact on the quality of life of the affected patients. The underlying mechanisms responsible for these types of itch are still largely unclear. The recent advances in understanding of specific itch pathways and mediators will hopefully lead to novel therapies. The ideal antipruritic therapies are years away. Combinative therapies reducing itch sensitization and transmission are of prime importance. Future studies and particularly carefully-designed controlled treatment trials will enable us to provide a better treatment for this chronic itch.

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Figure 1.
Therapeutic ladder of the treatment of pruritus in ESRD

Figure 2.
Therapeutic ladder of the treatment of pruritus in chronic liver disease

Figure 3.
Therapeutic ladder of the treatment of pruritus in lymphoma

Table 1

Recommended systemic treatment for systemic diseases-associated pruritus

Drug names	Antipruritic mechanisms	Suggested doses
Hydroxyzine	H1-antihistamine and sedating	50–100 mg/day
Doxepin	H1-antihistamine and tricyclic antidepressant	25–75 mg/day
Naltrexone	Mu-opioid antagonist	25–50 mg/day
Butorphanol	Mu-antagonist and kappa-agonist	1–4 mg/day intranasally
Gabapentin	Central and peripheral itch pathway inhibitor	300 mg up to 3200 mg/day
Pregabalin	Central and peripheral itch pathway inhibitor	150 mg/day to 300 mg/day
Mirtazapine	α_2 adrenergic receptor antagonist	15 mg at night