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Pruritus in Cutaneous T-cell Lymphoma: A Review

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Abstract

Background—Pruritus can be a distressing and even debilitating symptom for patients with cutaneous T-cell lymphoma (CTCL). To date, few studies have evaluated the pathophysiology of this symptom. Due to this, therapy for pruritus in CTCL has mainly relied on those therapies that target and treat the lymphoma. For patients living with CTCL that relapses or becomes refractory to treatment, and who continue to experience severe itch, this lymphoma-targeted treatment may not be enough to combat their pruritus. Therefore, other itch-targeted therapies are needed for use in this disease

Objective—Evaluate the current evidence regarding the mechanism of action and treatments for pruritus associated with cutaneous T-cell lymphoma.

Methods—An explicit and thorough search was restricted to all peer-reviewed literature available through MEDLINE (1950 to September 2011) and pubmed.org. Search terms used were pruritus, cutaneous T-cell lymphoma (CTCL), mycosis fungoides (MF), and Sézary Syndrome (SS). All studies that involved pruritus in either CTCL, MF, or SS were evaluated by all three authors.

Results—The current literature helps to identify therapies and possible mechanisms for treating patients with CTCL associated pruritus. .

Limitation—Most studies were pre-clinical. Only studies involving mechanisms of action or treatment were included

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Conclusion—A guideline is necessary to assist in the treatment of pruritus in CTCL and additional studies are necessary to uncover the exact mechanism(s) of action.

Keywords

Pruritus; Cutaneous T-cell Lymphoma; Mycosis Fungoides; Sezary Syndrome; Pathophysiology; Therapy

Introduction

Pruritus, or an unpleasant sensation provoking the desire to scratch,(1) is often a dominant symptom seen in the dermatologic setting. The underlying cause can stem from a variety of different conditions, ranging from benign to life threatening. Cutaneous T-cell lymphoma (CTCL) is one of those potentially life-threatening causes of pruritus. Itch can be seen as an associated, or sometimes even presenting, symptom of CTCL.(2, 3) Cutaneous T-cell lymphoma includes a diverse group of neoplasms of skin-homing T-cells, with the most common presentations including mycosis fungoides (MF) and Sézary Syndrome (SS).(4)

Itch in CTCL, if present, is often worse at the later stages of the disease and in certain variants. In a study by Winkelmann, 28 out of 28 patients with SS had itch, and severe itch was a common symptom.(5) In addition, patients with SS are more likely to report having continuous itching, more episodes of insomnia, and more fatigue symptoms resulting in poor health related quality of life scores.(6) Green, *et. al.* have shown that the presence of pruritus correlates negatively with survival but only in so much as the likelihood of pruritus correlates with advanced stage.(7) Therefore, although pruritus is a marker of worse survival, its presence or absence does not change the prognosis obtained from standard TNMB staging.(7) Folliculotropic MF is one of the variants, which often has severe itching; one treatment center demonstrated 68% of patients with this variant experiencing severe itch.(8) Even though pruritus can be quite a distressing symptom for these patients, the research surrounding the mechanism of pruritus in this disease is only just beginning. Correspondingly, therapy for relieving pruritus in CTCL has relied mostly on attempts to control the disease with relatively few targeted itch therapies available. Here we summarize the research published to date on the mechanism and therapy of pruritus in CTCL, much of which has focused on MF and SS.

A Specific Neuronal Pathway for Pruritus

Pruritogenic stimuli are detected in the skin by primary sensory neurons whose cell bodies lie in the dorsal root ganglia. Specifically, a sub-population of skin-residing unmyelinated c-fibers was identified as the itch sensing cutaneous nerves.(9) Historically, this small group of unmyelinated c-fibers was shown to respond preferentially to chemical stimuli (histamine) and not to other mechanical or thermal stimuli.(9) However, recently a histamine-independent subset of cutaneous c-fibers was identified, suggesting that there are histamine and non-histamine sensing peripheral itch-specialized nerves.(10) Regardless, after these itch specific neurons have received a stimulus, they travel to the spinal cord and synapse with second order sensory neurons in the dorsal horn. These second order neurons come together to form part of the spinothalamic tract, which then ascends up to the brain. (11)

With an independent itch pathway defined, interest has turned to identifying mediators that initiate the stimulus and contribute to its propagation at each subsequent synapse in the hopes of finding a way to intervene in the itch pathway. Histamine, as previously discussed, is already known to directly stimulate this pathway.(9) However, as is seen clinically, the

itch of CTCL patients often fails to or only partially responds to anti-histamine medications. The roles of other histamine-independent mediators, therefore, have to be sought for CTCL.

Mechanism of Pruritus in CTCL: Potential Mediators Involved

Peripheral Mediators

Interleukins—Elucidation of the cytokine expression pattern of the T-cell malignant clones has been attempted over the years. Isolated Sézary clones were found to produce mRNA for interleukin (IL) 5, 10, and 13, and IL-10 and IL-5 at the protein level; thus a Th2-type cytokine profile.(12) In addition, peripheral blood mononuclear cells (PBMCs) isolated from patients with SS have been shown to produce significantly higher levels of IL-4 than IL-2 or Interferon-gamma (IFN- γ) when stimulated.(13, 14) Increased IL-4 production has also been found by flow cytometry for erythrodermic MF and SS patients as compared to earlier stage MF patients (stage I or II).(15) It is interesting to note that the pruritus of CTCL is often much more severe in Sézary patients, at a point in the disease where a more dominant Th2 cytokine picture appears to prevail. One consequence of a Th2 cytokine predominance is recruitment of eosinophils. Eosinophilia in CTCL is more common in advanced stages and associated with a worse prognosis.(16) Moreover, eosinophils found in the skin in CTCL are activated.(17) Because eosinophils can drive skin inflammation, such as occurs in chronic atopic dermatitis, it is possible that eosinophils play a major role in the skin pruritus of CTCL. However, no correlation between tissue or blood eosinophilia and pruritus has been reported.

There has also been a case report on the use of cyclosporine-A in a refractory case of SS with associated pruritus.(18) In this case, pruritus in this patient ceased after two days of treatment with cyclosporine-A. Cyclosporine-A has been found to work by blocking the production of IL-2 and other cytokines.(19) Knowledge of the mechanism of action of this drug, along with the quick response seen in the patient, may indicate a role for interleukins in the potentiation of pruritus in SS.

The role of interleukins as histamine-independent itch mediators has been proposed previously. Increased interleukin-4 expression in a transgenic mouse line caused the mice to develop a pruritic inflammatory dermatitis spontaneously, which was similar to atopic dermatitis.(20) It would be interesting to see if this interleukin, or any other, plays a role in the pathogenesis of itch in CTCL. Moreover, as there are currently inhibitors of these interleukins, such as Pitrakinra, in clinical trials for the treatment of other diseases, medical therapies may soon be available for CTCL patients with pruritus.(21)

Most recently, the role of IL-31 in pruritus has been studied in atopic dermatitis. The production of IL-31 by Th2 T-cells has been described previously, as has its ability to induce dermatitis in mice.(22) The IL-31 receptor has been found on human monocytes, macrophages(23), and also on nerves of the dorsal root ganglia(24). It is possible that this cytokine could induce these cells to release additional mediators involved in itch, or that this cytokine directly stimulates itch-sensing nerves. Recently, the newest histamine receptor, histamine receptor 4 (H4R), has been found to be present on human CD4+ T-cells, and its stimulation was found to increase mRNA expression of IL-31.(25) The possibility of the presence of the H4R on the Th2 T-cell clones of CTCL, as well as a role for IL-31, is a potential avenue of study. A study of the use of an H4 antagonist in an atopic dermatitis mouse model showed that this antagonist significantly reduced the pruritus in these mice, thus pointing to a role for these H4 blockers in pruritic dermatoses that can lack response to H1 antagonists.(26)

Neuropeptides (Substance P)—Neuropeptides are released from the terminal ends of cutaneous sensory nerves in the skin. One neuropeptide that has been implicated in pruritus is substance P. This neuropeptide activates the neurokinin-1 (NK-1) receptor, which has been found on keratinocytes and on the dorsal horn neurons of rats, with thoughts that either the sensory nerves are activated directly by substance P or indirectly by mediators released from the activated keratinocytes.(27, 28) The association of neuropeptides with the itch of CTCL can be made as a result of two case series that demonstrate the use of aprepitant as an antipruritic agent in CTCL.(29, 30) Aprepitant works by blocking the NK-1 receptor, which is the receptor for substance P. In the first series, three patients with SS and severe pruritus (requiring hospitalization for symptom management) were treated with aprepitant.(30) The degree of pruritus in this study was evaluated using a visual-analog scale with 0 representing no pruritus and 10 indicating the worst pruritus imaginable.(30) The patient's scores began at 7, 8, and 9 and then dropped to 2, 3, and 2, respectively, after only one day of aprepitant therapy.(30) In a second article, three patients with SS and two patients with erythrodermic MF, who had pruritus as the main symptom, were treated with aprepitant.(29) The patients would receive aprepitant therapy every two weeks for three consecutive days, 125 mg on day 1 and 80 mg on days 2 and 3. The median duration of therapy was 15 weeks. The patients continued their previous anti-pruritic treatment and their current CTCL therapy. Four out of five patients responded to therapy. A visual analog scale, with the same scale as in the previous series, assessed the severity of pruritus. The mean score before therapy was 9.8 $\pm$ 0.4, while after therapy; the mean score was 4.3 $\pm$ 3.4.(29)

Substance P has typically been associated with histamine-induced itch in the past.(31) However, some studies have shown substance P to be able to induce itching in mast-cell deficient mice, suggesting a role for substance P independent from that of histamine.(32) The success of aprepitant in anti-histamine unresponsive dermatologic conditions also suggests this role for substance P.(29, 30, 33) Substance P could therefore have some role in the itch of CTCL.

Proteinases—Dermal mast cells were found to be significantly increased in two cases of tumor-stage MF with associated hyperpigmentation and itching.(34) In addition, stem cell factor (SCF), the growth factor for mast cells, was found to be significantly increased in the serum of these two MF patients when compared to normal controls, and immunohistochemical staining for SCF on malignant T-cells, mast cells, endothelial cells, and keratinocytes was positive.(34) Levels of IgE were also significantly elevated in these two patients as compared to controls.(34) This study may suggest some role for mast cells in the pathophysiology of pruritus in CTCL. Studies with a larger sample size and different variations of the disease which are associated with itch are necessary to confirm if mast cells are involved in the pathogenesis of itch. If mast cells, indeed, are involved in the pruritus of CTCL, then proteinases, which are produced from the mast cells, may prove to be important mediators of itch in CTCL. Certain kallikrein-related peptidases have been found to activate the proteinase-activated receptor-2 (PAR-2) receptor located on cutaneous sensory nerves.(35) In addition, the PAR-2 receptor has been found on keratinocytes, fibroblasts, endothelial cells, and numerous immune cells (including T-cells and mast cells).(36) Potentially, the kallikrein-related peptidases could be produced by mast cells in CTCL and may provide an itch-inducing stimulus either directly by exciting the cutaneous sensory nerves or indirectly by activating other cells in the skin. (See also Table 1 for a summary of these peripheral mediators.)

Central Mediators

Gastrin-Releasing Peptide—Recently, the gastrin-releasing peptide receptor (GRPR) has been shown to be located in lamina 1 of the spinal cord,(37) and this receptor and its

agonist gastrin-releasing peptide (GRP) may play a critical role in itch transmission in the central nervous system. When neurons expressing GRPR in the spinal cord of mice were selectively ablated using bombesin-sap, the mice showed significant reductions in scratching when confronted with both histamine and histamine-independent mediators of itch.⁽³⁸⁾ This appears to represent the neuron pathway specific for itch in the central nervous system. It is likely that GRPR-positive neurons in the spinal cord also transmit itch in CTCL patients once the signal reaches the spinal cord.

Opioids—Patients given systemic opioid medications commonly develop pruritus. For this reason, there has been interest in understanding opioids as mediators of itch. So far, evidence points to two effects of opioids that could contribute to itch. Opioids have been found to induce mast cell degranulation leading to the release of histamine and proteinases.⁽³⁹⁾ The second is that opioids stimulate mu-opioid receptors, which have been found to be present both peripherally and centrally.⁽³⁹⁾ Naloxone, a drug that blocks opioid receptors, has been used to treat pruritus associated with cholestasis, chronic urticaria, and atopic dermatitis; and has been found to be effective based on double-blind controlled trials.⁽⁴⁰⁾ In relation to CTCL, naloxone was found to suppress the pruritus that an MF patient was experiencing in a single case report.⁽⁴¹⁾ Interestingly, in this patient, subsequent treatment with naltrexone, a drug thought to work by antagonizing the same opioid receptors as naloxone, actually exacerbated the patient's itch.⁽⁴¹⁾ This seemingly antithetical response may be explained by an imbalance in mu and kappa opioid receptor activation as has been proposed in some cases of chronic itch.⁽⁴⁰⁾ Indeed butorphanol, a mu antagonist and kappa opioid agonist, has recently been shown to have benefit in intractable pruritus.⁽⁴²⁾ Nevertheless, another case series found that naltrexone did alleviate the itch of MF patients, but this study was an open-labeled, non-placebo controlled trial.⁽⁴⁰⁾ More studies to evaluate the effectiveness of opioids and opioid antagonists in mycosis fungoides itch are warranted. (See Table 1 for a summary of these potential central mediators of pruritus.)

Therapy to Alleviate Itch in CTCL

Targeting the Lymphoma—Currently, treatment to alleviate itch in CTCL, similar to many other dermatoses associated with pruritus, relies on trying to remove the cause of the itch from the skin. Therefore, the most effective way to manage itch in CTCL is by working for a remission of the lymphoma.

The current treatments for CTCL can be divided into skin-directed therapy and systemic therapy. Of the skin-directed therapies, topical corticosteroids are widely used in all stages of CTCL in the hopes that it will help control the disease and palliate any cutaneous symptoms of itch. Other topical therapies, such as carmustine, topical retinoids, and mechlorethamine, while effective in treating early stage MF, also carry the possibility of inducing skin irritation and pruritus.⁽⁴³⁾

Phototherapy, a second skin-directed therapy, has been used to treat CTCL for many years. Psoralen plus ultraviolet A (PUVA), broad-band ultraviolet B (UVB), and narrow-band UVB phototherapies have proven their effectiveness in inducing remissions in patients with early-stage MF.⁽⁴⁴⁻⁴⁶⁾ The therapeutic effects of PUVA and UVB in immune-mediated skin diseases have been attributed to the direct apoptosis of lymphocytes, modification of cell surface receptors, and alteration in production of certain mediators.⁽⁴⁷⁾ PUVA and UVB therapies have been shown to induce apoptosis in PBMCs in vitro^(48, 49), and UVB has been shown to cause apoptosis of T-cells in the lesions of patients with psoriasis.⁽⁴⁹⁾ Broad-band UVB therapy affects mostly epidermal keratinocytes and Langerhans cells, while PUVA and narrow-band UVB are better able to penetrate to the dermis and thus reach the residing cells, including the T-cell clone of CTCL.⁽⁴⁹⁾ Also, both PUVA and UVB have

been found to decrease expression of the intercellular adhesion molecule-1 (ICAM-1) receptor, which is thought to limit the migration of inflammatory cells into the skin.(50-52) In regards to mediators, PUVA has been found to modulate cytokine production by T-lymphocytes; transiently increasing IFN- γ and decreasing IL-4 in culture supernatants from PUVA treated lymphocytes.(53) UVB has been shown to cause keratinocytes to produce multiple cytokines, including TNF-alpha, IL-1alpha, IL-6, IL-8, and IL-10.(54-58)

Although not skin-directed, a related therapy is that of extracorporeal photopheresis (ECP), which is a leukapheresis based therapy that exposes PBMCs to both 8-methoxypsoralen and ultraviolet A light.(59) ECP has shown its effectiveness in all stages of CTCL, especially in SS.(60) By inducing remission, a decrease in pruritus is generally observed clinically. ECP has been postulated to be therapeutically beneficial to patients with CTCL by similar mechanisms as PUVA therapy: ECP has been shown to cause the direct apoptosis of T-lymphocytes(61), and cause a change in the cytokine response similar to that seen with PUVA therapy.(62, 63) In 8 patients with early stage CTCL, 12 months of ECP therapy decreased the IL-4 production and increased the IFN- γ production.(62) Also, in 3 patients with SS treated with ECP for 8-24 months, INF- γ production by PBMCs increased significantly in all three cases, while IL-4 production decreased in the one patient that was tested for this cytokine.(64) However, the cytokine response demonstrated in these two studies has not been consistently reported in the literature. For example, CD4+ T-cells stimulated with phorbol 12-myristate 13-acetate and ionomycin had a switch from predominately Th2 type cytokines to Th1 type cytokines.(64)

Additional mechanisms include enhanced T-lymphocyte immunogenicity by way of increased MHC class I expression on the malignant T-cell clone.(65, 66) The presentation of tumor antigens by MHC class I to cytotoxic T-cells results in a cell-mediated immune response against the malignant T-cell clone.(67) More recently it has been shown that ECP can enhance monocyte differentiation to dendritic cells, thereby possibly increasing an anti-tumor response in antigen presenting cells.(68) In regards to pruritus, reduction with phototherapy-based therapies could be a combination of the decrease in the T-cell clone and the change in the production of certain pro-itch mediators.

Some systemic therapies have also been evaluated in their effectiveness to reduce pruritus for CTCL patients. For example, vorinostat was found to alleviate itch in 32.3% of patients with stage IB to IVB MF/SS and a baseline pruritus score greater than or equal to 3 on the visual analog scale.(69) Alemtuzumab was shown to decrease pruritus to a mean of 2 from a starting mean of 8 after 12 weeks of treatment in patients with predominately stage III or IV disease.(70)

Targeting the Itch—The use of drugs which are solely used to control the itch in CTCL, show promise as reported in previously discussed respective case reports and case series. To summarize, aprepitant (an antagonist of the NK-1 receptor of substance P) and naloxone/naltrexone (antagonists of the mu-opioid receptor) have shown a beneficial effect in patients with severe itch, who have SS and MF. In one report, aprepitant was used at a dose of 80 mg daily⁽³⁰⁾, while in another, aprepitant was given for three consecutive days every two weeks at dosages of 125 mg on day 1 and 80 mg on days 2-3.^(29, 30) In one case report, naloxone was administered by subcutaneous injections at a dose of 0.2 mg at night and then every 3-4 hours as needed for itch.⁽⁴¹⁾ In the case series, naltrexone was administered in doses ranging from 50-100 mg/d PO for one month.^(40, 71)

In addition, mirtazapine and gabapentin have been reported to be beneficial in relieving itch in patients with advanced-stage MF and SS.(71) Gabapentin, an anticonvulsant, has been postulated to bind to the $\alpha 2\delta 1$ subunit of a voltage-dependent calcium channel on the cell

membrane of neurons, and then once bound is able to block calcium influx preventing the release of neurotransmitters.⁽⁷²⁾ By preventing the release of neurotransmitters, the propagation of the itch signal to the brain can be dampened or even stopped. In addition, this drug, by preventing excitation of the neurons, could prevent the reflex release of neuropeptides and the subsequent effects of the neuropeptide mediators in pruritus. Mirtazapine, an antidepressant, works by blocking adrenergic, serotonergic, and histaminergic receptors.⁽⁷³⁾ Specifically, mirtazapine blocks adrenergic α_2 -autoreceptors, adrenergic α_2 -heteroreceptors, serotonergic 5-HT₂ receptors, serotonergic 5-HT₃ receptors, and histaminergic H₁ receptors.⁽⁷²⁾ By blocking, the α_2 adrenergic autoreceptors receptors, the release of norepinephrine is enhanced. By blocking the α_2 -heteroreceptors, 5-HT₂ receptors, and 5-HT₃ receptors, serotonin transmission by the 5-HT_{1a} receptor pathway is selectively increased. Mirtazapine also blocks the H₁ receptor.⁽⁷²⁾ Whether it is one receptor blockade or a combination of a few that helps mirtazapine relieve pruritus is not known. Demierre et al. recommended starting with gabapentin at 300 mg at night and increasing the dose as needed but not exceeding 2400 mg per day.⁽⁷¹⁾ They found that doses between 900-2400 mg of gabapentin daily was needed to help control itching in these patients. Mirtazapine (7.5-15 mg) is generally used at night to help ensure sleep, which would correspond with its H₁-antagonist properties.⁽⁷¹⁾ Although mirtazapine was generally used in conjunction with gabapentin in this case report, other case reports exist of using just mirtazapine to relieve itch in other anti-histamine resistant pruritic dermatoses⁽⁷⁴⁾, suggesting a role for mirtazapine in itch relief beyond just its sedative effects at the H₁ receptor.

Also, one patient with MF has been reported to respond to thalidomide.⁽⁷⁵⁾ While improving the patient's disease, thalidomide also reduced the pruritus experienced by this patient from a 6/10 down to a 2/10.⁽⁷⁶⁾ Thalidomide has been shown to reduce the itch associated with uremic pruritus and Hodgkin's disease in the past, however the exact mechanism by which thalidomide accomplishes this is unknown.^(76, 77) Thalidomide's ability to decrease the itch in the CTCL patient could be a result of destruction of the lymphoma cells, decreased production of the itch mediators, or a combination of both. Thalidomide has been found to preferentially co-stimulate cytotoxic CD8⁺ T-cells in vitro⁽⁷⁸⁾, and it has also been found to increase the number and activity of natural killer cells.⁽⁷⁹⁾ These cell types can target and rid the body of unwanted cancer cells. Stimulation of these cells in a CTCL patient would help rid the body of the lymphoma cells, and in doing so, also alleviate itch. Thalidomide has also been found to inhibit the production of TNF- α , IL-1 β , IL-6, and GM-CSF.⁽⁸⁰⁾ So far no evidence exists for the implication of any of these mediators in the pruritus of CTCL. However, IL-6 levels have been found to be elevated in uremic pruritus⁽⁸¹⁾, and in addition, thalidomide has been found to be useful in pruritus relief in this disease.⁽⁷⁷⁾ In addition, some evidence points towards the ability of thalidomide to stimulate the production of Th-1 type cytokines, including IL-2 and INF- γ .^(82, 83) INF- γ is known to suppress Th2-cytokines. Current evidence points to a Th2 cytokine profile being produced by the T-cell clones in CTCL. If the production of the Th2 cytokines is suppressed in patients with CTCL by INF- γ , then this could be beneficial in reducing the pruritus, if these Th2 cytokines are implicated in the mechanism of the pruritus.

For patients with severe itch in CTCL which is resistant to the more traditional treatments, aprepitant, naloxone, naltrexone, butorphanol, mirtazapine, gabapentin, and thalidomide may represent alternative therapies to help improve the quality of life for these patients. (See Table 2 for a summary of the itch-targeted therapies in CTCL.)

Conclusion

Just as the visual clinical presentation of CTCL can be highly variable, so can the degree of pruritus in this disease. The amount of itching can range from none at all to severity that requires hospitalization. And, oddly, itching can even present before the development of skin lesions, as reported in a few cases.(2, 3) The mechanism of itch in CTCL certainly presents a challenge to those researching it, and to those clinicians treating it. To date, therapy to treat itch in CTCL has mainly revolved around topical and systemic therapies that also suppress the T-cell clone. As some patients continue to relapse or become refractory to therapy, while continuing to experience severe itch, non-traditional anti-itch drugs may be the only glimpse of hope for relief in these patients. Aprepitant, gabapentin, mirtazepine, and naloxone/naltrexone are starting to show some efficacy as second or third line therapies. The next step is to better elucidate the mechanism behind the itch in CTCL so that more directed therapies can be applied.

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Abbreviations

CTCL	cutaneous T-cell lymphoma
MF	mycosis fungoides
SS	Sezary Syndrome
IL	interleukin
INF-γ	interferon gamma
NK-1	neurokinin-1
SCF	stem cell factor
PAR-2	proteinase-activated receptor-2
GRPR	gastrin-releasing peptide receptor
GRP	gastrin-releasing peptide
PUVA	psoralen plus ultraviolet A
UVB	ultraviolet B
PBMCs	peripheral blood mononuclear cells

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Table 1

Potential Peripheral and Central Pruritus Mediators in CTCL and Their Mechanisms

Mediator	Mechanism	References
Gastrin-releasing peptide (GRP)	Binds to gastrin-releasing peptide receptor (GRPR) located on neurons in lamina I of the spinal cord	Sun YG, Zhao ZQ, Meng XL, et al. ³⁸
Opioids	Activation of opioid receptors centrally or peripherally located on nerves or mast cells. May induce mast cell degranulation.	Sun YG, Zhao ZQ, Meng XL, et al. ³⁸ ; Yosipovitch G, Dawn AG, Greaves MW, et al. ³⁹
Interleukins IL-5 IL-10 IL-4 IL-31	Mechanism not known Mechanism not known Mechanism not known IL-31 receptor found on sensory nerve cells. IL-31 receptor also found on human monocytes and macrophages, may induce release of mediators from these cells.	Kasraie S, Niebuhr M, Werfel T ²³ ; Bando T, Morikawa Y, Komori T, Senba E ²⁴
Substance P	Activates NK-1 receptor located on keratinocytes and potentially dorsal horn neurons	Carstens EE, Carstens MI, Simons CT, Jinks SL ²⁷ ; Chang SE, Han SS, Jung HJ, et al. ²⁸
Proteinases (kallikrein-related peptidases)	Activates PAR-2 receptor, which has been found on cutaneous nerves, keratinocytes, fibroblasts, endothelial cells, immune cells	Rattenholl A, Steinhoff M ³⁶

Table 2

Summary of Itch-targeted Therapies in CTCL

Drug	Dosage	Mechanism of Action in Itch Relief	Reference
Aprepitant	80 mg PO daily or 125 mg PO on day 1, 80 mg PO on days 2-3 given for 3 consecutive days every 2 weeks	Neurokinin-1-receptor antagonist	Booken N, Heck M, Nicolay JP, Klemke CD ²⁹ Duval A and Dubertret L ³⁰
Naloxone	0.2 mg SQ qHS then q3-4 hours as needed	Mu-opioid receptor antagonist	Sullivan JR and Watson A ⁴¹
Naltrexone	50-100 mg PO daily	Mu-opioid receptor antagonist	Phan NQ, Bernhard JD, Lugar TA et al. ⁴⁰
Butorphanol	1 mg intranasal daily	Mu-opioid receptor antagonist Kappa-opioid receptor agonist	Dawn AG, Yosipovitch G. ⁴²
Mirtazapine	7.5-15 mg PO qHS	Uncertain; Adrenergic (α 2-autoreceptor, α 2-heteroreceptor), serotonergic (5HT2, 5HT3), and histaminergic (H1) receptor blockade	Demierre MF and Taverna J ⁷¹ ; Anttila SA and Leinonen EV ⁷³
Gabapentin	Start 300 mg PO qHS (Increase as needed not to exceed 2400 mg per day)	Binds to voltage-dependent Ca2+ channel on nerves, blocks Ca2+ influx, and prevents release of neurotransmitters	Demierre MF and Taverna J ⁷¹ ; Field MJ, Cox PJ, Stott E, et al. ⁷²
Thalidomide	Can start between 50 and 100 mg PO per day and then can increase to 100 mg per day if patient is able to tolerate	Uncertain; Stimulates cytotoxic CD8+ T cells and NK cells; inhibits production of TNF α , IL-1B, IL-6, GM-CSF; stimulates production of IL-2, INF- γ	Brightman L and Demierre MF ⁷⁵ ; Haslett P, Corral L, Albert A, et al. ⁷⁸ ; Davies F, Raje N, Hideshima T, et al. ⁷⁹ ; Corral L, Haslett P, Muller G, et al. ⁸⁰ ; Verbon A, Jeffermans N, Speelman P, et al. ⁸³