A systematic review on the management of pruritus in patients with cutaneous T-cell lymphoma

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Introduction: Cutaneous T-cell lymphomas (CTCLs) represent a rare group of primary cutaneous lymphomas. Pruritus is common in patients with CTCL and is severe and intractable in the subtypes Sézary syndrome (SS) and folliculotropic mycosis fungoides (MF). Materials and methods: We conducted a systematic review on interventions demonstrating efficacy in reducing pruritus in patients with CTCL. The primary aim of our study was to identify disease-directed and itch-directed therapies effective in reducing CTCL-associated pruritus. Our secondary aim was to outline various tools used to quantify itch in clinical studies. Results: Our study identified multiple disease-directed therapies effective in reducing CTCL-associated pruritus. Most evidence supported the use of histone deacetylase inhibitors. For the agents romidepsin, vorinostat, and quisinostat, reduction in pruritus was achieved in both disease responders and nonresponders. Various therapies were effective in managing pruritus associated with SS and folliculotropic MF. Vorinostat is effective in reducing pruritus in patients with SS. Extracorporeal photophoresis, total skin electron beam therapy, and romidepsin are effective in reducing pruritus in patients with folliculotropic MF. The antiemetic aprepitant is an effective targeted treatment of CTCL-associated pruritus. Aprepitant demonstrated efficacy in reducing pruritus in patients with all stages of MF, including patients with SS. Lignocaine administered via continuous subcutaneous infusion is effective in reducing pruritus in patients with advanced-stage MF, including patients with SS. The most frequently used tools to quantify itch were the Visual Analogue Scale and Numerical Rating Scale. Definitions of a significant reduction in pruritus were extremely varied between studies. Discussion: To our knowledge, this is the first systematic review specifically addressing the management of itch in patients with CTCL. Patients with all stages of CTCL were represented across included studies, including patients with folliculotropic MF and SS. A wide range of treatment options were identified, including options appropriate for patients with end-stage disease. Keywords: Cutaneous T-cell lymphoma, Pruritus, Treatment

Introduction

Cutaneous T-cell lymphomas (CTCLs) represent a rare group of primary cutaneous lymphomas. Multiple subtypes of CTCL are recognized, of which mycosis fungoides (MF) and Sézary syndrome (SS) are the most common. In MF, neoplastic cells are derived from noncirculating skin resident effector memory T cells, whereas in SS, neoplastic T cells have a central memory T-cell phenotype. CTCL can range from an indolent to highly aggressive disease, and management should be tailored according to the disease stage[1]. Early-stage disease is usually managed with skin-directed therapy, such as topical corticosteroids, topical chemotherapy, topical retinoids, phototherapy, and radiotherapy. Advanced-stage or transformed disease warrants systemic treatment, which may include systemic retinoids, interferon, histone deacetylase (HiDAC) inhibitors, systemic chemotherapy, and denileukin difitox. Extracorporeal photophoresis and various investigational therapies also have a role in the treatment of advanced-stage disease[1].

Patients with CTCL have a considerable burden of physical symptoms that affect their physical, social, and emotional well-being. Pruritus is the most commonly reported physical symptom in patients with CTCL, affecting up to 88% of patients[2,3]. Itch has a major negative impact on quality of life, interfering with daily activities, sleep, and mood[4]. The severity of CTCL-associated itch generally increases with disease progression. Pruritus is also more common in certain subtypes of CTCL, namely SS and folliculotropic MF[4,5]. Pruritus is defined as an unpleasant sensation that provokes the desire to scratch. Pruritus is a multidimensional symptom, with effects on cognition and emotion. Pruritus is mediated by histamine-dependent and histamine-independent pathways[6]. Conventional antipruritic therapies such as antihistamines are largely ineffective in relieving CTCL-associated pruritus, suggesting unique pathophysiology[2]. Recent research has aimed to elucidate the
mechanism of CTCL-associated pruritus. Possible mediators of pruritus in CTCL include interleukin (IL)-4, IL-31, and substance P[5].

Treatments for relieving pruritus in CTCL have mainly focused on disease-directed therapies, aimed at controlling the underlying lymphoma. Improvement in pruritus has been included as a specific endpoint in recent clinical trials of disease-directed therapies for CTCL. As research on the pathophysiology of CTCL-associated pruritus is relatively recent, few studies on targeted itch-directed therapies are available[6].

There are a lack of standardized methods used to measure and report itch in clinical studies. This makes it challenging to compare results from studies. A wide range of tools are used to measure the quality of life in patients with dermatological conditions, however, there is no agreed gold standard[3].

We conducted a systematic review on interventions demonstrating efficacy in reducing pruritus in patients with CTCL. The primary aim of our study was to identify disease-directed and itch-directed therapies effective in reducing CTCL-associated pruritus. Our secondary aim was to outline the various tools used to quantify itch in clinical studies.

Materials and methods

A study protocol was finalized in April 2020 and submitted to the PROSPERO register of systematic reviews. (Prospero registration number CRD42020149210, published on April 28, 2020).

Eligibility criteria

We included all clinical studies published in a peer-reviewed journal that included itch as a specific study endpoint. Studies were included only if a tool was used to objectively quantify itch. We excluded nonhuman studies, conference abstracts, and studies published in a language other than English. Given the rarity of CTCL as a disease entity, we placed no restriction on study design.

Information sources and search strategy

A literature search was performed on the September 10, 2019 for the purpose of identifying relevant published articles. The search was run in Ovid Medline, Ovid Embase, and Ovid Emcare. The date of coverage was not restricted and results were limited to articles in English only.

In Medline, the search strategy consisted of subject headings (MESH) and various text words to identify the literature. Subject headings used in Ovid Medline included: “Lymphoma, T-Cell, Cutaneous,” “Pruritus,” and “Treatment outcome.”

Subject headings were combined with keywords (and their word variations) such as “mycosis fungoides,” “itch,” and “therapy” using the “OR” Boolean operator to cluster all similar indexed and free terms together. The “AND” Boolean operator was applied to link the different concepts.

Searches in Embase and Emcare followed a similar format to the Medline search with variations according to each database’s subject thesaurus.

Complete search strategies for each database are outlined in Appendix I.

Study selection

The clinical librarian (S.L.) performed the literature search, retrieved all abstracts, and deduplicated results. Titles and abstracts of identified studies were independently screened by the review team members (G.F., O.S.), according to the inclusion and exclusion criteria. Full-text articles were obtained for studies meeting the inclusion criteria, and their eligibility for inclusion was independently assessed by the review team (G.F., O.S.). The final agreement on study eligibility was resolved by consensus among the collaborators.

Data extraction

Data were independently extracted by the review team (G.F., O.S.) using a pilot-tested form. Data extracted included study design, number of study participants, subtype of CTCL in study patients, intervention, a tool used to quantify pruritus, improvement in itch due to treatment, and if other pruritus treatments were permitted.

Results

Study selection

A total of 1452 records were retrieved by the search strategy. After adjusting for duplicates, 1129 records remained. Of these, 1051 studies were discarded based on a review of titles and abstracts. The full texts of 78 articles were reviewed, of which 27 were eligible for inclusion in accordance with the selection criteria. A flow diagram detailing the inclusion and exclusion of studies from the systematic review is shown in Figure 1.

Study characteristics

Our review identified a total of 18 studies on disease-directed therapies, and 9 studies on itch-directed therapies. Studies were categorized into levels of evidence, according to the National Health and Medical Research Council’s framework[7].

Bias assessment

All subtypes of CTCL were represented in studies, ranging from early-stage to advanced-stage disease. Most studies were unblinded and lacked a placebo control arm. A single randomized controlled trial (RCT) on the use of aprepitant was included, however, the study was small and underpowered. Almost all studies utilized descriptive statistics. The use of confounding antitch medications was permitted in 16 of the studies, and not permitted in 3 studies. It was unclear if other confounding treatments were used in 8 of the included studies.

Further assessments

Studies were heterogeneous in terms of methods used to quantify itch. As a result, a meta-analysis could not be performed.

Disease-directed therapies

Eighteen studies were identified on various disease-directed therapies. Most studies investigated the use of HiDAC inhibitors (7 studies).

HiDAC inhibitors

Six open-label interventional trials and 1 case series were identified on the use of HiDAC inhibitors, including the drugs romidepsin, vorinostat, quisinostat, and belinostat. The HiDAC studies included larger patient numbers than other studies and included patients with the advanced, treatment-refractory disease.
A significant reduction in pruritus was achieved with HiDAC inhibitors for patients with moderate and severe pruritus at baseline. A reduction in pruritus was found in both disease responders and nonresponders for the agents romidepsin, vorinostat, and quisinostat.

Vorinostat was effective in reducing pruritus in patients with SS. Although patients with SS were included in other HiDAC inhibitors trials, there was no specific comment on improvement in this subset of patients for other agents. Romidepsin demonstrated benefit in pruritus in patients with folliculotropic MF, a variant typically associated with intractable pruritus.

Denileukin diftitox only significantly reduced pruritus in patients with an objective disease response.

Alemtuzumab

One open-label interventional trial was found on the use of alemtuzumab, a humanized monoclonal antibody against CD52. A small trial in patients with treatment-refractory, advanced-stage disease demonstrated a reduction in pruritus with alemtuzumab. Reduction in pruritus was achieved for both disease responders and nonresponders, however, the benefit in nonresponders was modest.

Extracorporeal photopheresis (ECP)

One case report demonstrated a long-term reduction in pruritus with ECP in a patient with generalized syringotrophic MF, a rare variant of folliculotropic MF.

Total skin electron beam therapy (TSEBT)

One case series reported on the use of low-dose TSEBT in patients with MF, including 1 patient with folliculotropic MF. The patient with folliculotropic MF experienced a modest improvement in pruritus as a result of treatment.

Thalidomide

One case report was identified on the use of thalidomide in a patient with early-stage, treatment-refractory MF. Pruritus relief was sustained long-term, even after cessation of thalidomide.

Retinoids

Two open-label interventional trials were identified on topical retinoids (tazarotene and bexarotene), including patients with early-stage disease. Topical retinoids demonstrated no benefit on pruritus in the studies identified.

Combination therapy

Three open-label interventional trials were identified that used combination treatment. A trial on the use of vorinostat with bexarotene demonstrated improvement in pruritus in both disease responders and nonresponders. Combination therapy with a HiDAC inhibitor and DNA methyltransferase inhibitor (valproate plus hydralazine) was investigated in one trial, with pruritus improving in all patients. A trial investigating the use of combination therapy with bexarotene and rosiglitazone showed no significant reduction in pruritus.

Itch-directed therapies

A total of 9 studies were identified on itch-directed therapies. Of these, 8 were on the use of the antiemetic aprepitant. One study was identified on the use of lignocaine administered via continuous subcutaneous infusion.
| Intervention          | Study Type                          | Patients | Level of Evidence[7] | CTCL Subtypes                          | Measure of Pruritus | Definition of Significant Baseline Pruritus | Definition of Significant Reduction in Pruritus | Other Pruritus Treatments Permitted | Results                                                                 |
|----------------------|-------------------------------------|----------|----------------------|----------------------------------------|---------------------|-------------------------------------------|----------------------------------------------|--------------------------------|------------------------------------------------------------------------|
| **Disease-directed** | **HIDAC inhibitors**                |          |                      |                                        |                     |                                           |                                               |                               |                                                                        |
| Romidepsin           | Subanalysis of open-label, single-arm interventional trial[12] | 30       | IV                   | Tumor-stage or folliculotropic MF       | 100-mm VAS          | Yes                                        | Significant reduction in pruritus: No definition | No                             | Tumor-stage MF: Moderate-severe pruritus at baseline: mean pruritus reduction − 43 mm (± 27) Severe at baseline: − 45 mm (± 29) Folliculotropic MF: Moderate-severe at baseline: mean pruritus reduction − 53 mm (± 35) Severe at baseline − 60 mm (± 42) |
| **Romidepsin**       | Open-label, single-arm interventional trial[9] | 96       | IV                   | Stage IB–IVA CTCL (most > stage IIB, heavily pretreated) Included patients with SS | 100-mm VAS          | Yes                                        | Significant reduction in pruritus: Decrease in VAS of ≥ 30 for ≥ 2 consecutive cycles in patients with pruritus ≥ 30 on 100-mm VAS at baseline | No                             | Significant reduction of pruritus in 43% of patients, including 31% of patients with moderate pruritus at baseline, and 53% of patients with severe pruritus at baseline Complete response in 7/36 patients with severe pruritus at baseline Benefit in both disease responders and nonresponders |
| **Vorinostat**       | Open-label, single-arm, interventional trial[9] | 74       | IV                   | Stage IB–IVA CTCL Included patients with SS | 10-point VAS        | Yes                                        | Significant reduction in pruritus: ≥ 3-point improvement in VAS in patients with a baseline pruritus score of ≥ 3 on 10-point VAS, or complete resolution of pruritus for ≥ 4 continuous weeks, without an increase in the use of antipruritic medications | Permitted at stable doses | 32% of patients had a significant reduction in pruritus (including both disease responders and nonresponders) In patients with severe pruritus, 43% had a significant reduction in pruritus Significant reduction in pruritus in patients with SS (5/16 patients with SS) |
| Treatment | Study Design | Dose | Stage | Pruritus Def. | Pruritus Grading | Response Def. | Response Grading | Patient Selection | Study Outcomes |
|-----------|-------------|------|-------|--------------|----------------|---------------|----------------|-----------------|---------------|
| Vorinostat | Open-label, non-randomized, non-placebo-controlled, dose-comparison interventional trial[^10] | IV | Treatment-refractory CTCL (most > stage IIB) | NRS (scale of 0–10) | Yes | Baseline pruritus: ≥ 3-point improvement in scale of 0–10, or complete resolution of pruritus for at least 4 wk | Grading of response: No definition | Included patients with SS | Significant reduction in pruritus: 45% of patients with baseline pruritus scores had a significant reduction in pruritus in patients with severe pruritus at baseline, 50% has a significant reduction in pruritus in patients not achieving disease response, including patients with SS |
| Vorinostat | Prospective case series[^26] | IV | CTCL, any stage (progressive) | NRS (scale of 0–10) | Yes | Baseline pruritus: No definition | Grading of response: No definition | Included patients with SS, folliculotropic MF | Significant reduction in pruritus: Not specified 10/14 patients had improvement in pruritus (no elaboration on mean improvement), with the addition of vorinostat added to existing therapy |
| Quisinostat | Open-label, single-arm interventional trial[^11] | IV | Stage IB–IVA | 10-point VAS | Yes | Baseline pruritus: ≥ 3 on 10-point VAS | Grading of pruritus: Severe: 7–10 on 10-point VAS | Included patients with SS | Significant reduction in pruritus: Not specified 40% achieved a significant reduction in pruritus, including both disease responders (67%) and nonresponders (32%) |
| Belinostat | Open-label, single-arm interventional trial[^27] | IV | CTCL, any stage (most stage IV, treatment-refractory) | NRS (scale of 0–10) | Yes | Baseline pruritus: ≥ 3 on a scale of 0–10 | Grading of pruritus: No definition | Included patients with SS | Significant reduction in pruritus: Not specified 40% achieved a significant reduction in pruritus in 7/15 patients who had baseline pruritus scores ≥ 3, including 3/6 patients with severe pruritus at baseline |
| Denileukin diftitox | Randomized, open-label, non-placebo-controlled, dose-comparison interventional trial[^13] | IV | Stage IB–IVA CTCL (heavily pretreated) | 100-mm VAS FACT-G (Functional Assessment in Cancer Therapy-General questionnaire) 7-point global skin severity scale | Yes | Baseline pruritus: No definition | Grading of pruritus: No definition | Yes (antihistamines, topical emollients, and bath additives only, systemic steroids not permitted) | Significant reduction in pruritus: Pruritus at baseline compared with end-of-treatment period using Wilcoxon signed-rank test, results considered statistically significant when $P < 0.05$ | Median pruritus at baseline, the median decrease in pruritus severity at study endpoint: Disease responders: 5.3, 50% reduction at study endpoint ($P < 0.05$) Nonresponders: 5.5, 6.3% reduction at study endpoint (not significant) |

[^10]: Farrah et al. Itch (2021) 6:e55 www.itchjournal.com
| Intervention | Study Type | Patients | Level of Evidence | CTCL Subtypes | Measure of Pruritus | Benefit? | Definition of Significant Baseline Pruritus | Definition of Significant Reduction in Pruritus | Other Pruritus Treatments Permitted | Results |
|--------------|------------|----------|------------------|----------------|---------------------|---------|--------------------------------------------|---------------------------------------------|---------------------------------|---------|
| Alemtuzumab  | Open-label, single-arm interventional trial[14] | 22 IV Stage II–IV CTCL (treatment-refractory) Included patients with SS | 10-point VAS | Yes | Baseline pruritus: No definition Grading of pruritus: No definition | Significant reduction in pruritus: No definition Grading of response: No definition | Stable dose of <10mg prednisolone permitted | All patients: median baseline VAS 8 (range: 1–10), end-of-treatment VAS 2 (range: 0–9) Disease responders (11/17): median baseline VAS 8 (range: 6–10), end-of-treatment VAS 1 (range: 0–6) Nonresponders (6/17): median baseline VAS 6 (range 1–9), end-of-treatment VAS 5 (0–10) | |
| ECP          | Case report[13] | 1 NA Generalized syringotropic MF | NRS (scale of 0–10) | Yes | Baseline pruritus: No definition Grading of pruritus: No definition | Significant reduction in pruritus: No definition Grading of response: No definition | Topical corticosteroids permitted | Baseline pruritus 10/10 After cycle 3, pruritus reduced to 7/10 After cycle 6, pruritus reduced to 1/10 Remained stable on monthly ECP for 15 mo (then pruritus progressed, added oral bexarotene) | |
| Low-dose TSEBT | Retrospective case series[16] | 8 IV MF (including folliculotropic) | NRS (scale of 0–10) Dermatology Life Quality Index | Yes | Baseline pruritus: No definition Grading of pruritus: No definition | Significant reduction in pruritus: No definition Grading of response: No definition | Not specified | Mean scores for pruritus Before TSEBT: 3.43 After TSEBT: 1.88 | |
| Thalidomide | Case report[17] | 1 NA Stage IB MF (treatment-refractory) | NRS (scale of 0–10) | Yes | Baseline pruritus: No definition Grading of pruritus: No definition | Significant reduction in pruritus: No definition Grading of response: No definition | Not specified | Baseline pruritus score of 6, reduced to 2/10 at 8 wk of treatment Ceased treatment at week 18, with sustained relief of pruritus (no pruritus at 7 mo) | |
| Oral retinoids | Bexarotene | 94 IV Stage IIB–IVB CTCL (treatment-refractory) Included patients with SS | Scale of 0–8 using index lesions Spitzer quality of life questionnaire Nonvalidated CTCL-specific questionnaire | Yes | Baseline pruritus: No definition Grading of pruritus: No definition Moderate: 4–5 on a scale of 0–8 Severe: 6–8 on a scale of 0–8 | Significant reduction in pruritus: No definition Grading of response: No definition | Yes | Mean grade of pruritus decreased from 3.9/8 at baseline, to 3.2/8 at week 16 (does not separate disease responders and nonresponders) Improvement in nonvalidated CTCL-specific questionnaire, not Spitzer | |
| Treatment | Type | Patients | Follow-up | Baseline | Pruritus Grading | Significant Reduction in Pruritus | Response Grading | Improvement | Notes |
|-----------|------|----------|-----------|----------|-----------------|---------------------------------|-----------------|------------|-------|
| Topical retinoids | | | | | | | | | |
| Topical tazarotene gel | Open-label, non-vehicle-controlled, single-arm interventional trial | 20 | IV | Early patch or plaque-stage MF <20% BSA | Scale of 0–5 | No Baseline pruritus: No definition Grading of pruritus: Moderate: 3–4 on a scale of 0–5 Severe: 5 on a scale of 0–5 | Significant reduction in pruritus: Mean change in pruritus from baseline evaluated using the Wilcoxon signed-rank test (assuming $P < 0.05$) Grading of response: No definition | Yes | Mean difference in pruritus from baseline ~0.12 ($P = 0.55$) No significant change in pruritus |
| Topical bexarotene gel | Open-label, non-vehicle-controlled, single-arm interventional trial | 50 | IV | Stage IA-IIA CTCL (treatment-refractory) | Scale of 0–8 using index lesions Spitzer quality of life questionnaire Nonvalidated CTCL-specific questionnaire | No Baseline pruritus: No definition Grading of pruritus: Moderate: 4–5 on a scale of 0–8 Severe: 6–8 on a scale of 0–8 | Significant reduction in pruritus: No definition Grading of response: No definition | Yes | Mean grade of pruritus decreased from ~2 at baseline, to ~1 at week 16 (does not separate disease responders and nonresponders) Improvement in nonvalidated CTCL-specific questionnaire, not Spitzer |
| Combination therapies | | | | | | | | | |
| Vorinostat + bexarotene | Open-label, single-arm, dose-escalation interventional trial | 23 | IV | Stage IB–IVB Included patients with SS | 10-point VAS Functional Assessment of Cancer Therapy-General Skinex-16 | Yes Baseline pruritus: No definition Grading of pruritus: No definition | Significant reduction in pruritus: ≥3-point reduction in pruritus score on 10-point VAS, or complete resolution Grading of response: No definition | Not specified | 7 patients experienced a significant reduction in pruritus Improvement in both disease responders and nonresponders |
| Bexarotene + rosiglitazone | Open-label, single-arm interventional trial | 4 | IV | Stage IA–IVA CTCL Included patients with SS | 100-mm VAS Functional Assessment of Cancer Therapy-General | No Baseline pruritus: No definition Grading of pruritus: No definition | Significant reduction in pruritus: Reduction in pruritus score on 100-mm VAS, with an improvement in quality of life measure (FACT-G) Grading of response: No definition | Not specified | 3 of 4 patients had improvements in pruritus scores, however, quality of life (as assessed by FACT-G) remained relatively unchanged for all 4 patients Concluded no meaningful improvement in itch |
| Hydralazine + valproate | Open-label, single-arm interventional trial | 14 | IV | MF, LyP | 10-point VAS | Yes Baseline pruritus: >3 on 10-point VAS Grading of pruritus: Moderate: 4–6 on 10-point VAS Severe: 7–10 on 10-point VAS | Significant reduction in pruritus: ≥3-point reduction in patients with baseline pruritus >3 on 10-point VAS Grading of response: Partial response: ≥3-point reduction in patients with baseline pruritus >3 on 10-point VAS Complete response: no pruritus for ≥4 continuous weeks, without an increase in the use of antipruritic medications | Permitted at stable doses | All patients had moderate or severe pruritus at baseline All patients had improvement in pruritus, with complete response in 13 patients, and partial response in 1 patient |
| Intervention | Study Type | Patients | Level of Evidence\(^2\) | CTCL Subtypes | Measure of Pruritus | Definition of Significant Baseline Pruritus | Definition of Significant Reduction in Pruritus | Other Pruritus Treatments Permitted | Results |
|-------------|------------|----------|-------------------------|----------------|---------------------|---------------------------------------------|-----------------------------------------------|--------------------------------|---------|
| Itch-directed Aprepitant | Randomized, double-blind, placebo-controlled cross-over trial\(^2\) | 5 | Unable to grade | SS | 100-mm VAS Dermatology Life Quality Index | Baseline pruritus: >40 mm on 100-mm VAS Grading of pruritus: No definition | Significant reduction in pruritus: Paired comparisons between time points were made using a Wilcoxon signed-rank test Hypotheses were tested at the level of \(\alpha = 0.05\) Grading of response: No definition | Yes, at stable doses | Pruritus did not change over 7 d of treatment in the placebo arm, however, increased significantly during the aprepitant treatment However, study inadequately powered (according to full study protocol) |
| Aprepitant | Retrospective case series\(^3\) | 17 | IV Stage IB–IV CTCL | NRS (scale of 0–10) Qualitative Patient’s Global Assessment (PtGA) | Yes | Significant reduction in pruritus: Compared mean pruritus at various time intervals, calculating confidence intervals and P-values (\(P < 0.05\)) Grading of response: No definition | Yes, at stable doses | Mean baseline pruritus score 10/10, mean pruritus score after 1 mo 7/10 (95% CI: 5–8, \(P < 0.001\)) Maximum benefit during first week of treatment, mean pruritus score 5/10 (95% CI: 3–7, \(P < 0.001\)) |
| Aprepitant | Retrospective case series\(^3\) | 4 | IV MF, LyP, cutaneous anaplastic lymphoma | NRS (scale of 0–10) | Yes | Significant reduction in pruritus: No definition Grading of response: No definition | Yes | Partial in all patients Beneficial for up to 12 mo |
| Aprepitant | Case series\(^3\) | 2 | IV SS | 10-point VAS Dermatology Life Quality Index | Yes | Significant reduction in pruritus: No definition Grading of response: No definition | Not specified | Patient 1: Baseline VAS = 8, at day 5 VAS = 2 Patient 2: Baseline VAS = 9, at day 5 VAS = 3 Pruritus increased when aprepitant ceased Overall response rate 80% Baseline mean VAS 9.8 (± SD 0.4) Mean VAS after intervention 4.3 (± SD 3.4) (\(P = 0.125\)) Reduction in VAS noted after 1 cycle of aprepitant, with further decreases at follow-up (24 wk) |
| Aprepitant | Open-label, single-arm interventional trial\(^3\) | 5 | IV Erythrodermic MF/SS Included patients with SS | 10-point VAS Dermatology Life Quality Index | Yes | Significant reduction in pruritus: >50% reduction in 10-point VAS compared with baseline Grading of response: Partial response: 25%–50% reduction in 10-point VAS compared with baseline | Yes, at stable doses | Not specified | Not specified |
### Aprepitant

| Study Type | Case Series/Case Report | Number | Stage | SS | VAS Scale | VAS Baseline | Significant Reduction in Pruritus | VAS Improvement |
|------------|-------------------------|--------|-------|----|-----------|--------------|----------------------------------|-----------------|
| Case Series | 3 IV SS 10-point VAS    | Yes    | Baseline pruritus: No definition | Grading of response: No definition | No            | VAS at baseline to > day 2 to > day 7 |
| Case Report | 1 NA Tumor-stage MF  NRS (verbal scale of 0–10) | Yes | Baseline pruritus: No definition | Grading of response: No definition | Yes | Baseline VAS 10/10 |
| Case Report | 1 NA Stage IB MF 10-point VAS | Yes | Baseline pruritus: No definition | Grading of response: No definition | Yes | Baseline VAS 10/10 |

### Lignocaine (via continuous subcut infusion)

| Study Type | Retrospective Case Series | Number | Stage | SS | VAS Scale | VAS Baseline | Significant Reduction in Pruritus | VAS Improvement |
|------------|--------------------------|--------|-------|----|-----------|--------------|----------------------------------|-----------------|
| Retrospective Case Series | 19 IV Advanced CTCL Included patients with SS 10-point VAS (scratching behavior used if VAS not recorded) | Yes | Baseline pruritus: No definition | Grading of response: No definition | Yes | Complete response in a mean of 26.7% treatment days |

**Notes:**
- CI indicates confidence interval; BSA, body surface area; CTCL, cutaneous T-cell lymphoma; ECP, extracorporeal photophoresis; HDac, histone deacetylase; LyP, lymphomatoid papulosis; MF, mycosis fungoides; NA, not available; NRS, Numerical Rating Scale; SS, Sézary syndrome; TSEBT, total skin electron beam therapy; subcut, subcutaneous; VAS, Visual Analogue Scale.
Aprepitant

Eight studies were identified on the use of aprepitant, including 1 RCT, 1 open-label interventional trial, 4 case series, and 2 case reports. Studies included patients with all stages of MF, including patients with SS. Aprepitant was effective in reducing pruritus, with a rapid time of onset (within hours to days). Reduction in pruritus could be sustained long term, for up to 13 months (until the patient passed away from disease) in 1 case report[24].

One RCT concluded that aprepitant was not beneficial in patients with SS. However, the study included only 5 patients, was underpowered, and only followed patients for 21 days[23].

Lignocaine via continuous subcutaneous infusion

A retrospective case series was identified on the use of lignocaine via continuous subcutaneous infusion. This study included patients with advanced CTCL, including patients hospitalized for end-of-life care. Lignocaine via continuous subcutaneous infusion was effective in reducing pruritus in patients with the advanced-stage disease[6].

Tools used to quantify pruritus in studies

A variety of tools were used in clinical studies to quantify itch. All studies used some form of numerical scale. The most commonly used tools were the 10-point Visual Analogue Scale (VAS) (n = 10), 100-mm VAS (n = 5), and a Numerical Rating Scale (NRS) from 0 to 10 (scale from 0 to 10 [n = 8]), verbal scale from 0 to 10 [n = 1]). Other measures included a scale of 0–8 using index lesions (n = 2), and a scale of 0–5 (n = 1).

A significant baseline level of pruritus was defined in only 7 studies. Significant baseline pruritus was defined as ≥ 30 mm on 100-mm VAS (n = 1), ≥ 3 on 10-point VAS (n = 2), ≥ 3 on a scale of 0–10 (n = 1), > 3 on 10-point VAS (n = 1), > 40 mm on a 100-mm VAS (n = 1), and “persistent itching despite at least 1 previous antipruritic at full dose” (n = 1).

Several studies included definitions of “moderate” and “severe” baseline pruritus. Definitions for moderate baseline pruritus included 30–69 mm on 100-mm VAS (n = 2), 4–6 on 10-point VAS (n = 1), 3–4 on scale of 0–5 (n = 1), and 4–5 on scale of 0–8 (n = 2). Definitions for severe baseline pruritus included 70–100 mm on 100-mm VAS (n = 2), 7–10 on 10-point VAS (n = 3), 7–10 on a scale of 0–10 (n = 2), 5 on scale of 0–5 (n = 1) and 6–8 on scale of 0–8 (n = 2).

Definitions of a significant reduction in pruritus were extremely varied between studies, and are shown in Table 1. Some studies graded improvement in pruritus as “partial” or “complete,” again using varied definitions. Definitions of a partial response included a ≥ 3-point reduction in patients with baseline pruritus > 3 on 10-point VAS (n = 1), a 25%–50% reduction in 10-point VAS compared with baseline (n = 1), and a VAS 3–6 on 10-point VAS on a treatment day (n = 1). Definitions of a complete response included VAS of 0 on 100-mm VAS for at least 2 treatment cycles (n = 1), the disappearance of pruritus for ≥ 4 continuous weeks without an increase in the use of antipruritic medications (n = 1), and VAS 0–2 on 10-point VAS on a treatment day (n = 1).

In addition to quantitative tools, several studies utilized qualitative tools to measure the quality of life. Qualitative tools included the Functional Assessment in Cancer Therapy-General questionnaire (n = 3), patient-rated 7-point global skin severity scale (n = 1), Dermatology Life Quality Index (n = 6), Spitzer quality of life questionnaire (n = 2), a nonvalidated CTCL-specific questionnaire (n = 2), Skindex-16 (n = 1) and Qualitative Patient’s Global Assessment (n = 1).

Discussion

Pruritus is a common symptom of CTCL and has a major impact on the quality of life for both patients and their caregivers. A variety of disease-directed and itch-directed therapies demonstrated efficacy in relieving pruritus associated with CTCL. Pruritus relief can be achieved in patients with advanced-stage and treatment-refractory disease, including patients with folliculotropic MF and SS.

Our systematic review identified multiple disease-directed therapies effective in reducing CTCL-associated pruritus. Most evidence supported the use of HiDAC inhibitors. Other effective treatments include denileukin diftitox, alemtuzumab, ECP, TSEBT, thalidomide, bexarotene, combination therapy with vorinostat, and bexarotene, and combination therapy with valproate and hydralazine (HiDAC inhibitor and DNA methyltransferase inhibitor).

In some studies, pruritus was reduced in both patients achieving an objective disease response, and nonresponders. Pruritus relief was achieved for both disease responders and nonresponders with the agents romidepsin, vorinostat, quinostat, alemtuzumab, and combination therapy with vorinostat and bexarotene. These results suggest that the clinical benefit of agents may extend beyond objective disease responses, and should be taken into consideration when assessing a patient’s response to treatment.

SS and folliculotropic MF are subtypes of CTCL associated with severe pruritus. Vorinostat was effective in reducing pruritus in patients with SS[9,10]. Folliculotropic MF involves deeper periannexal structures and is generally considered resistant to skin-directed therapies. Our results demonstrate that the skin-directed therapies ECP and TSEBT are effective in reducing pruritus in patients with folliculotropic MF. The systemic therapy romidepsin also demonstrated efficacy in reducing pruritus in patients with folliculotropic MF.

A significant proportion of patients with CTCL develop the treatment-refractory disease, with severely debilitating pruritus. There is a need for targeted symptomatic approaches for those patients who do not respond to disease-directed therapies, or for when disease-directed therapies are not appropriate.

Our results support the use of the antiemetic aprepitant as a targeted treatment of CTCL-associated pruritus. Substance P is a neuropeptide released from sensory nerve endings in the skin. Substance P activates neurokinin-1 receptors present on keratinocytes, and on neurons in the dorsal root ganglia. High levels of Substance P in keratinocytes are associated with pruritus. Aprepitant is a neurokinin-1 antagonist, inhibiting the effect of substance P[2,5]. Aprepitant demonstrated efficacy in reducing pruritus in patients with all stages of MF, including patients with SS. The effect is rapid in onset, and reduction in pruritus was sustained in some studies. These findings add to the body of evidence suggesting that Substance P is an important mediator of pruritus in CTCL.

Lignocaine administered via continuous subcutaneous infusion is effective in reducing pruritus in patients with advanced-stage MF, including patients with SS. Lignocaine blocks sodium channels in neuronal cell membranes, and antagonizes kappa-opioid antagonist-induced scratching in mouse models[14]. Lignocaine administered by subcutaneous infusion should be considered in patients with intractable pruritus. This intervention also provides an important treatment option for symptom control in patients receiving end-of-life care.

Our systematic review highlights the variety of tools used to quantify itch in clinical studies and the subsequent difficulties in comparing results across studies. An ideal tool to quantify a
symptom must be well-validated, appropriate for progressive conditions, simple to complete, and multidimensional[3].

Our study identified the VAS as the most commonly used tool for measuring pruritus, using either a 100-mm VAS or 10-point VAS. The VAS was originally developed to assess the intensity of pain and has been adapted for use in the measurement of itch. The VAS is a 100-mm long line, on which patients indicate the severity of pruritus by crossing the line at the point that corresponds to their pruritus intensity. The VAS is a simple and reproducible tool and is one of the most commonly used methods of assessing pruritus severity. Studies have demonstrated that the VAS is a reliable method of pruritus assessment. The VAS is quick to perform and suitable for repeat assessments in clinical settings. The VAS demonstrates good test-retest reproducibility in patients with pruritic skin conditions. However, the VAS is a unidimensional tool, and only measures itch intensity. The tool is unsuitable for patients with motor deficits or cognitive issues, which may exclude the elderly or patients receiving end-of-life care[35].

The next most frequently used measure of pruritus identified by our study was the NRS. The NRS is a similar method of pruritus measurement to the VAS. Patients rate pruritus intensity on a scale from 0 to 10 (no pruritus to worst imaginable pruritus) measured to the VAS. Patients rate pruritus intensity on a scale from 0 to 10 (no pruritus to worst imaginable pruritus measurement to the VAS). The NRS has been validated as a tool for assessing pain severity. In the study of itch, high concurrent validity in pruritus intensity assessment has been shown with both the VAS and NRS. However, discrimination of pruritus intensity using the VAS may be more sensitive than with the NRS[35].

Studies included in our systematic review varied greatly in the definition of significant pruritus at baseline, and what constitutes a clinically meaningful reduction in pruritus. More recent trials on the use of HiDAC inhibitors defined a clinically meaningful reduction in pruritus as a ≥30 mm (or ≥3 points) improvement in VAS in patients with a baseline pruritus score of ≥30 mm (or ≥3 points), without an increase in the use of antipruritus medications, over a defined time period. This varied between 2 consecutive treatment cycles, 3 continuous weeks, and 4 continuous weeks[6-11,22]. In these studies, a ≥30 mm reduction in pruritus was prospectively selected as a clinically significant reduction in pruritus based on expert opinion, and previous use in other clinical trials[36]. A clinically significant reduction in pruritus should be defined more vigorously, ideally by incorporating the patient’s perception of pruritus relief.

The need for breakthrough medication can be considered a surrogate marker of a patient experiencing inadequate symptom relief. In the acute pain setting, the action of a patient not requesting breakthrough analgesia can be considered a marker that the patient perceives the therapy as effective. This marker has been used in previous studies to determine thresholds in pain scales that are considered clinically significant. This method places a stronger focus on the patient’s experience of pain, rather than arbitrarily assigning a numerical value as significant. This approach could be translated to research on pruritus. This information is simple to capture in the setting of a trial, and clinically appropriate. Although the choice of scales and analyses for the study of itch would differ, the same marker could be used to calculate a patient-determined clinically significant reduction in pruritus[38-40].

To our knowledge, this is the first systematic review specifically addressing the management of itch in patients with CTCL. Patients with all stages of CTCL were represented across included studies, including patients with folliculotropic MF and SS, specific subtypes associated with severe and intractable pruritus. A wide range of treatment options were identified, including options appropriate for patients with end-stage disease.

Our systematic review has limitations. We limited results to articles published in English, excluded conference abstracts, and did not contact authors for further information regarding studies. Our systematic review retrieved no studies on certain treatments that are commonly used for the management of pruritus in clinical practice, including wet wraps, emollients, narrow-band UVB, topical and oral corticosteroids, naloxone, naltrexone, butorphanol, mirtazapine, and gabapentin[5]. We also found no studies on the disease-directed therapy mogamulizumab. This may be a reflection of our inclusion criteria.

The HiDAC inhibitors may be overrepresented in our results. As recent studies on the use of HiDAC inhibitors for CTCL included a reduction in pruritus as a study outcome, more of these studies met our inclusion criteria. This does not necessarily imply that the HiDAC inhibitors are the most effective treatment for CTCL-associated pruritus.

We acknowledge that most included studies fall into low levels of evidence, particularly for itch-directed studies. Evidence supporting some agents was based only on case reports, and we acknowledge the risk of publication bias associated with case reports. However, given the rarity of CTCL as a disease entity, well-designed RCTs for this patient population are impracticable.

CTCL-associated pruritus is a debilitating symptom and requires a systematic treatment approach. We have identified multiple disease-directed and itch-directed therapies demonstrating efficacy in reducing pruritus in patients with CTCL.

Translating a subjective experience into an objective measure used for research and treatment evaluation is challenging. Our study identified the VAS and NRS as the most commonly used measures of pruritus in patients with CTCL. However, a unidimensional numerical scale alone does not adequately capture the patient’s experience of pruritus.

By drawing on the pain literature, various research techniques could be translated to the study of itch. The VAS or NRS should be validated to define a patient-determined clinically significant reduction in pruritus. For example, a patient not requiring breakthrough medication could be considered a surrogate marker of a patient experiencing adequate symptom relief. Validating the VAS or NRS for use in the study of itch would allow comparison of results between studies, as well as pooling of results across studies. This would assist in adding to the body of research on this rare and debilitating disease.

**Assistance with the study**
None.

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None.

**Presentation**
Preliminary data displayed as a poster presentation at the 10th World Congress on Itch 2019, Sydney, NSW, Australia.

**Conflict of interest statement**
The authors declare that they have no financial conflict of interest with regard to the content of this report.
Appendix

Appendix I

Search strategies for databases Ovid Medline, Ovid Embase, and Ovid Emcare.

Database: Ovid MEDLINE(R) ALL
<1946 to September 06, 2019>
Search Strategy:
1 exp Lymphoma, T-Cell, Cutaneous/ (9438)
2 (ctcl or cutaneous t-cell lymphoma* or mycosis fungoides or sezary or alibert-bazin or skin lymphoma*).mp. (19363)
3 1 or 2 (13724)
4 exp Puritus/ (13306)
5 (puritus or itch*).mp. (31126)
6 4 or 5 (32451)
7 (treatment* or therap* or manag* or intervention* or control or alleviate or remedi*) or cure or phototherapy or antipruritic*).mp. (11202939)
8 exp treatment outcome/ (995200)
9 (“therapeutic use” or therapy).fs. (3585811)
10 7 or 8 or 9 (11213178)
11 3 and 6 and 10 (223)
12 limit 11 to english language (193)

Database: Embase <1974 to 2019 September 06>
Search Strategy:
1 exp cutaneous T cell lymphoma/ (13724)
2 (ctcl or cutaneous t-cell lymphoma* or mycosis fungoides or sezary or alibert-bazin or skin lymphoma*).mp. (19363)
3 1 or 2 (19363)
4 exp Puritus/ (881103)
5 (puritus or itch*).mp. (97857)
6 4 or 5 (101761)
7 (treatment* or therap* or manag* or intervention* or control or alleviate or remedi*) or cure or phototherapy or antipruritic*).mp. (14818207)
8 exp treatment outcome/ (1556096)
9 (“therapeutic use” or therapy).fs. (1453047)
10 7 or 8 or 9 (1482022)
11 3 and 6 and 10 (1194)
12 limit 11 to english language (1106)

Database: Ovid Emcare <1995 to 2019 week 36>
Search Strategy:
1 exp cutaneous T cell lymphoma/ (13131)
2 (ctcl or cutaneous t-cell lymphoma* or mycosis fungoides or sezary or alibert-bazin or skin lymphoma*).mp. (1676)
3 1 or 2 (1676)
4 exp Puritus/ (200606)
5 (puritus or itch*).mp. (21026)
6 4 or 5 (21975)
7 (treatment* or therap* or manag* or intervention* or control or alleviate or remedi*) or cure or phototherapy or antipruritic*).mp. (2743252)
8 exp treatment outcome/ (4730864)
9 (“therapeutic use” or therapy).fs. ) (6)
10 7 or 8 or 9 (2819668)
11 3 and 6 and 10 (158)
12 limit 11 to english language (153)

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