Title/short title:

Systematic Review of Efficacies and Adverse Effects of Treatments for Pityriasis Lichenoides

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Statements:

What's already known about this topic?

- Pityriasis lichenoides (PL) is a spectrum of dermatoses characterized by papulosquamous lesions.
- There is no current consensus on the treatment of PL and no previous systematic reviews have assessed this.

What does this study add?

- Most studies for treatment of PL are hospital-based and few randomized controlled studies exist.
- We highlight the importance of distinguishing between PLC and PLEVA patients in assessing treatment outcomes, extending the length of follow-up for PLC patients in remission, and propose a standardized definition of PL complete and partial remission.

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Abstract

Introduction: Pityriasis lichenoides (PL) is a papulosquamous dermatosis affecting both children and adults for which no standard treatment currently exists. The aims of our systematic review were to characterize different treatment options and develop an evidence-based treatment algorithm for PL.

Methods: A systematic search of published literature on PL treatments was performed on December 23rd, 2017 via the Medline, Embase, CINAHL, CENTRAL, ClinicalTrials.gov, and the EU Clinical Trials Register databases.

Results: Of 1090 abstracts retrieved, 27 full-text articles with 502 participants were included for analysis. 17 of the full-text articles were retrospective cohorts and 2 were randomized control studies. Treatment modalities included in these articles were phototherapy, antibiotics, methotrexate, pyrimethamine and trisulfapyrimidine, corticosteroids (CTS) and conservative treatment. Of these treatments, phototherapy led to complete remission in the highest proportion of patients and topical CTS was found to have been trialed in the highest number of patients.

Conclusions: The current literature consists almost entirely of uncontrolled studies and none provide compelling data to support an evidence-based approach to PL treatment. PLC and PLEVA should be distinguished in response to treatment and definitions of response to treatment must be standardized. Additional randomized control studies with longer follow-ups will help better differentiate between treatment efficacies and adverse effects.

Introduction

Pityriasis lichenoides (PL) is a papulosquamous dermatosis of unknown etiology affecting both children and adults[1]. It is thought to encompass a spectrum including both acute and chronic forms, pityriasis lichenoides et varioliformis acuta (PLEVA), and pityriasis lichenoides chronica (PLC)[2,3]. PLEVA, also known by its eponym Mucha-Haberman disease (MHD), is the self-limited acute form typified by generalized papules that undergo necrosis and varioliform scarring[4]. The chronic form, PLC, is characterized by red scaly macules that periodically relapse and undergo remission over several years[3,5]. PLC and PLEVA lesions tend to show predilection for the anterior trunk, flexural surfaces, and proximal extremities, and the two may co-exist in the same patient[5]. While the disease is often benign, systemic symptoms such as fever and lymphadenopathy have been known to occur, especially in the acute presentation[4,6].

PL is not uncommon with an incidence estimated at 0.05%[1]. It appears to have no racial or geographic predisposition, although it is seen slightly more in males in late childhood or young adulthood[2,7,8]. Diagnosis of this disease is made through clinical presentation and skin biopsy. Histopathologically, PL often demonstrates parakeratosis, spongiosis and extravasation of lymphocytes with epidermal invasion[3,9].

Cosmetic and symptomatic concerns of PL patients have led to the development of treatment options despite its benign course. Ultraviolet therapy, anti-bacterials such as erythromycin and tetracycline, and immunosuppressants such as methotrexate are among the major therapies that have been explored[8,10–15]. However, with each having different success rates and adverse effect profiles, no standard treatment modality currently exists for PL. The aims of the analysis were to characterize different treatment options and develop an evidence-based treatment algorithm for PL.

Methods

The protocol for this review was defined a priori and registered online in the PROSPERO international prospective register of systematic reviews on January 12, 2018

(CRD42018084192).

Search methods

A literature search was performed of the following databases for studies up to December 23rd, 2017: MEDLINE via Ovid; EMBASE via Embase.com; the Cochrane Skin Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library; the Cumulative Index to Nursing and Allied Health Literature (CINAHL); ClinicalTrials.gov; and the European Union (EU) Clinical Trials Register. The search was limited to published English-language papers and human subjects. Search strings were developed for each database, including keywords and subject headings for PL (Appendix S1). All abstracts were reviewed by two authors, with conflicts resolved by a third, to select relevant articles. Data extraction was performed by two authors with 20% overlap and no significant discrepancies were identified.

Types of studies

Inclusion criteria were cohort, case-control, randomized-control, cross-sectional and case series studies. Exclusion criteria were reviews, ongoing studies, conference proceedings and abstracts and case series where n<5.

Types of participants

Inclusion criteria were participants of any age, ethnicity or genders with PLC or PLEVA. To maximize cases identified, there were no exclusion criteria.

Primary outcome measures

Primary outcome measures were characteristics of treatment regimens for PLC and PLEVA, characterized by their doses, durations and patient selection descriptors. In addition, we studied the clinical effects of those treatment regimens, characterized by their rates of success in eliciting partial and complete remission and their association with any adverse effects.

Secondary outcome measures

Secondary outcomes measures included the time frame for response of each treatment for PLC and PLEVA, and any data on recurrence.

Risk of bias

Risk of bias assessments were completed by two independent reviewers (F.J., C.S, Appendix S2). The Newcastle-Ottawa Scale was used to assess risk of bias for cohort studies[16]. The Cochrane Risk of Bias Assessment Tool was used to assess randomized control trials[17]. Disagreements were resolved by consensus and discussion.

Results

The search strategy results are summarized in Figure 1. Of 1090 abstracts retrieved, 929 studies were excluded in title and abstract screening. Of the 159 studies included in the full-text screening, 27 full-text articles with a combined total of 502 patients were included for analysis: 16 retrospective cohort studies, 7 prospective cohort studies, 2 randomized control studies, and 2 case series. One article was excluded after two independent raters failed to retrieve it despite best efforts; based on the title which describes assessing phototherapy for all pediatric patients, it is unlikely to have included many PL patients.

Between the two controlled trials published to date, both had a limited sample and one compared UVB only against PUVA[22,31]. Of the 17 studies that reported the population source of their subjects, 13 studies reported on patients treated at an institution or hospital; the remaining studies included patients treated either by an individual practitioner or a regional community clinic. Table 1 includes the patient demographics, interventions and treatment responses reported by individual studies. Definitions of complete and partial remission used by each study, where available, have also been reported in Table 1.

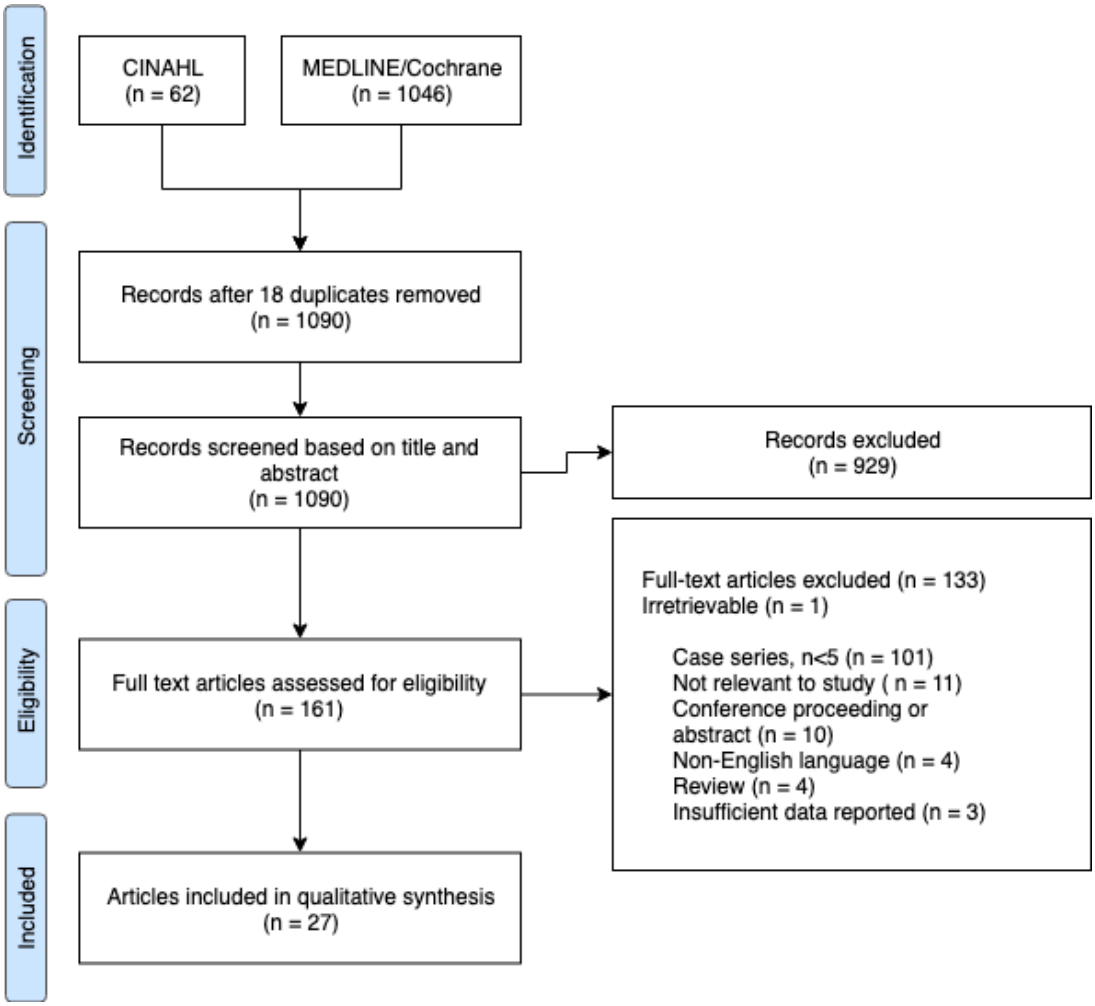

Figure 1. Article selection

Individual treatments

Phototherapy

Phototherapy (including BB-UVB, NB-UVB and UVA) was given to 309 subjects[14,15,26–35,18–25]. One study (n=15) utilized heliotherapy[27]. BB-UVB, NB-UVB and UVA modalities were either used in isolation, in combination with one another, or in combination with other topical or systemic interventions. The most common frequency of treatment for UV therapy was 3 times weekly. In 7 subjects, phototherapy or combinatory phototherapy was listed as a previous treatment with partial or poor effect[18,36,37]. One study not included in this sum reported that 6 of their subjects were previously treated with NB-UVB, antibiotics and/or systemic steroids[36].

Complete response using UVB, BB-UVB, NB-UVB, and PUVA in isolation with or without topical emollients was reported in 53.2% (n=25/47), 90.9% (n=20/22), 75.0% (n=102/136) and 69.4% (n=25/36) subjects, respectively. Partial response was reported in 31.9% (n=15/47), 0% (n=0/22), 20.6% (n=28/136) and 22.2% (n=8/36) subjects, respectively. In one of these studies, 2 subjects experienced complete remission (CR) and 1 subject experienced partial remission (PR) after being treated with NB-UVB following an unsuccessful intervention with antibiotics[32].

Of the studies which assessed or reported relapse rates after phototherapy in isolation or with other therapies, 66 subjects experienced relapse of either PLC or PLEVA[18,21–24,28–30,33,37].

Reported side effects for phototherapy include erythema (n=32), pruritus (n=5, burning (n=1), tingling (n=1), folliculitis (n=1), headaches (n=1) and dryness (n=8)[15,18,19,21,25,28,29,31,33,37]. The most common adverse effect, erythema, ranged from “mild” to “severe”; in one study, it was reported to be severe enough in 5 subjects to warrant discontinuation of phototherapy[15].

For the 15 subjects treated annually with heliotherapy at a frequency of 10 days per year, 60% had all or almost all lesions cleared for at least two years after treatment and 27% had at least 50% of lesions cleared for at least two years after treatment[27]. No adverse effects were described.

Antibiotics

One hundred and twenty-four subjects were treated with erythromycin, tetracycline, doxycycline or another antibiotic[30–35,38–40]. In 40 subjects, antibiotics were listed as a previous treatment but the effect and the name of the antibiotic was rarely documented[14,15,18,21,22,24,29,30,32,36]. In one study, 4 of 7 subjects who received antibiotic treatment exhibited no response; these 4 subjects were then treated with NB-UVB, and 3 responded at least partially[32]. In two of the studies not included in this sum, one reported that 6 of their subjects were previously treated with NB-UVB, antibiotics and/or systemic steroids while the other reported "most" of their 11 subjects were previously treated with topical corticosteroids (CTS) and systemic tetracycline[15,36].

Complete response using erythromycin or tetracycline in isolation was reported in 66.0% (n=31/47) and 52.9% (n=9/17) subjects, respectively. Partial response was reported in 8.5% (n=4/47) and 35.3% (n=6/17) subjects, respectively. Of the studies which reported a rate, 16 subjects experienced relapse of either PLC or PLEVA after treatment antibiotics in isolation or in combination with another intervention[30,33,38–40].

Adverse effects were only reported by one study where subjects were treated with 20-50mg/kg of erythromycin daily in 2-4 divided doses over four months[38]; pruritus and arthralgia was reported in 79% and 4%, respectively, of the 24 subjects who participated in the study.

Methotrexate

Methotrexate was used to treat 6 MHD subjects of 1 case series at individualized doses and frequencies for each of the subjects; the method used to calculate these dosing patterns were not described[12]. The study did not provide a definition for CR, but reported CR was observed in all 6 subjects. All 6 subjects experienced remission after an undefined period of monitoring. No adverse effects were reported. In 4 subjects, methotrexate was listed as a previous and unsuccessful treatment[18].

Bromelain

Bromelain, a proteolytic enzyme derived from the stem of a pineapple plant, was used to treat subjects with PLC in 1 prospective cohort study (n=8)[36]. CR was defined by the study as 100% of lesions cleared and CR was reported in all 8 subjects. Relapse was observed in 25% of subjects (n=2) within 1 year. No adverse effects were described.

Pyrimethamine and trisulfapyrimidine

Among the different hypotheses proposed for the etiology of PLC, infectious agents have been postulated. One study used a treatment regimen of two antiparasitic drugs, pyrimethamine and trisulfapyrimidine to assess if the common parasite toxoplasma gondii has a role in PLC[41]. Eight of the 22 subjects in this study were found to be *Toxoplasma* seropositive and all five patients who experienced complete subsidence of skin lesions were *Toxoplasma* seropositive. No relapse rates or adverse effects were reported in these five patients. The remaining 17 subjects exhibited no response to pyrimethamine and trisulfapyrimidine.

Corticosteroids

One hundred and one subjects were treated with CTS in isolation or in combination with another therapy[14,30–33,35]. Complete response using CTS in isolation was reported in 4.4% (n=2/45)[31]. Partial response was reported in 80.0% (n=20/25) subjects[30,31]. CTS were the most commonly reported treatment previously used among all of the subjects assessed in this review. 63 reported subjects, and substantially more unreported subjects, received either topical or oral steroids as a previous treatment[12,14,35,40,15,18,21,22,24,25,29,30]. CTS effect was often unreported or reported to be unsuccessful; one study stated that it was “effective” for only 2 out of “most” of their 157 subjects who had received CTS treatment[30].

No study reported adverse effects of CTS. No relapse rates were reported in studies where CTS were used in isolation as an intervention, and the isolated effects of CTS are difficult to determine in the setting of studies which utilized combinatory therapies.

Conservative treatment

Two subjects received no active treatment and were observed only[32,35]. Further data is only available for one of the two subjects who experienced complete resolution of lesions[32]. No relapse rates were reported.

Other treatments

Topical emollients and anti-histamines have also been utilized in combination with other therapies, however their isolated effect on lesions, relapse rates and adverse effects, if any, are difficult to determine[15,33].

Risk of bias

An assessment of risk of bias is included in Appendix A2. Both RCTs had low rates of incomplete data but high rates of bias (Appendix A2). Only two of 23 cohort studies had a comparable control population or a population controlled for age. Otherwise, the cohort studies each had a moderate level of risk of bias.

Discussion

This systematic review aimed to provide an updated review of the spectrum and efficacy of treatments in PLC and PLEVA. We build upon recent work by Bellinato *et al.* on PL treatments by summarizing the adverse effects and rates of relapse reported for individual treatments, in addition to identifying opportunities to improve gaps in current PL literature[42]. Our overall findings reveal underwhelming quality and quantity of evidence for PL treatments. The majority of studies retrieved had a small sample size (n≤15) and were hospital-based, limiting their generalizability, and none had robust evidence to support a specific treatment option for PL.

Summary of current evidence available for the treatment of PL

While no study provided any robust evidence, of the treatment options and combinations described for PL, phototherapy, antibiotics and corticosteroids has been studied the most; with CR being achieved in 53.2-90.9%, 52.9-66.0% and 4.4% of subjects treated by the respective

interventions, and PR being achieved in 0-22.2%, 8.5-35.3% and 80.0%. Of these treatments, BB-UVB demonstrated the highest rate of success in achieving CR with a rate of 90.9%; however, only 22 subjects thus far have been trialed on BB-UVB, and further studies of its efficacy and side effects are necessary to elucidate its potential as an option for PL therapy. Of the adverse effects currently known to have been associated with phototherapy, the most common is erythema, which led to discontinuation of treatment in 46% of subjects (n=5) in 1 study[15]. Using the minimal erythema dose (MED) to calculate the initial dose may help minimize the risk of this side effect[43].

Only two randomized control trials were found[22,31]. In one study (n=30), PUVA had the highest rate of remission as compared to topical CTS or topical CTS with tetracycline[31]. Respectively, 62.5% (n=5/8), 25% (n=2/8) and 7% (n=1/14) patients treated with these interventions experienced CR and 25% (n=2/8), 25% (n=2/8), and 79% (n=11/14) experienced PR. Significant therapeutic results were only observed with PUVA compared to tetracycline and/or CTS, and the researchers concluded that PUVA is more effective than the other tested modes of treatment for PL[31]. However, it should be noted that the clinical setting and geographical location from which subjects were recruited for this study is unknown, making these conclusions challenging to contextualize. In the other study, PUVA was compared with NB-UVB, but no significant difference was found between the two modalities[22].

Identified gaps and problems with current literature on PL treatments

PLC and PLEVA patients should be distinguished in their response to treatment

As PLC and PLEVA are both uncommon diseases but are both considered on the spectrum of PL, many studies to date have not distinguished between the two when reporting response to treatment, rates of remission, and rates of adverse effects. However, PLC and PLEVA are dissimilar in histopathology, morphology, and pattern of recurrence as described elsewhere[2]. It is highly likely that neglecting to distinguish between the two in the assessment of their response to treatments is inappropriate and may have implications to clinical safety. Studies which distinguish between PLC and PLEVA are highly recommended to improve the body of

literature available for these distinct subsets of PL, and those that do not distinguish between the two are discouraged.

Follow-up on rates of relapse following PL remission should extend 12 months

The majority of studies to date either did not report any follow-up data or followed patients for less than one year. While this likely has less significant implications for the study of patients with PLEVA, PLC is a subset of PL which is chronic, and is a disease characterized by its potential to undergo remission for years before the patient relapses[3,5]. Although loss to follow-up in clinical trials is often a challenge, for studies assessing PLC patients, we recommend that completion of the trial is essential to assess true response to treatment. We recommend the length of follow-up for PLC patients following remission be extended to 12 months, as spontaneous regression of PL is reported to be seen on average between 3 to 12 months[10].

Heterogeneity in outcome definitions and outcome measures limit analysis

A limitation of our analysis was the variation in outcome definitions between studies, with several studies defining CR as at least 90% of lesions cleared and PR as 50-90% of lesions cleared[18,22,23], while another study defined CR as at least 75% of lesions cleared and PR as 50-75% of lesions cleared[44]. Similarly, the heterogeneity in outcome measures assessed between studies made pooling of results impossible, and contributed to lack of sufficient data on duration of follow-up, quality of life, relapse rates and adverse effects for all treatments. Overall, adverse effects, quality of life, and relapse rates of PL treatments have been underreported, with more than half of the studies not including this information.

Impact of gaps in literature on clinical practice

During the course of this review, we found that these gaps ultimately limited our capacity to address the primary aim of this study. The current literature on the efficacy, benefits, and risk of PL treatments is not conducive to a rigorous pooled comparison. The potential of ongoing PL research is impeded by this lack of a standard definition and methodology, and it propagates

the problem for practitioners seeking an evidence-based algorithm to address the concerns of their PL patients.

We advocate for changes which support the potential for such an evidence-based treatment algorithm for PL, and propose standardized definitions and standardized reporting of specific treatment outcomes. Based on the definitions used most frequently by studies to date, we recommend “complete remission” for future PL studies to be defined as no less than 90% of lesions cleared, and “partial remission” to be defined as no less than 50% of lesions cleared. We also recommend the following outcome measures be reported by each study: patient’s PL subtype, mean duration with PL, history of previous treatments, dose of treatment, response to treatment (complete, partial, or no response), time for response to treatment, length of follow-up, rate of relapse, and adverse effects.

Conclusions

There is currently insufficient evidence to recommend an algorithmic approach for the treatment of PLC or PLEVA and a lack of understanding regarding the potential adverse effects of treatment to patients. While there is more evidence for phototherapy compared to other treatments, overall, more randomized control studies with standardized outcomes and longer follow-ups are required to truly understand the impact of medical intervention. Our recommendations for future studies are to distinguish between PLC and PLEVA patients in assessing treatment outcomes, to extend the length of follow-up of at least PLC patients, and to report based on the proposed definitions of complete and partial remission and outcome measures to support the potential for an evidence-based algorithm for PL treatment in the future.

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