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DERMATOLOGY | REVIEW ARTICLE

Treatment of cutaneous lichen planus (Part 1): A review of topical therapies and phototherapy

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Abstract: *Background:* Lichen planus is a chronic inflammatory immune-mediated disease that more frequently affects the skin and oral mucosa. Various treatment modalities are available for the condition. The aim of this review is to provide clinicians with consolidated evidence of the various treatments of cutaneous lichen planus (CLP). This first part focuses on topical therapies and phototherapy. *Methods:* Various Databases were searched for all studies up until January 2018, which reported on topical therapies and phototherapy for CLP. There were no exclusions based on study design. *Results:* We identified four systemic reviews and four reviews. We found additional single studies that contributed to this review. Evidence supporting the use of topical corticosteroids, as a first-line therapy, is absent. *Conclusion:* Narrowband UVB is the preferred phototherapeutic treatment option for cutaneous lichen planus and should be considered before commencing systemic treatment. Topical calcineurin inhibitors show promising results despite evidence only available from case reports. Vitamin D₃ is not recommended for the treatment of cutaneous lichen planus due to poor patient outcomes. The second part of this

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PUBLIC INTEREST STATEMENT

Lichen planus is a skin condition which has been named as it resembles the "lichens" in the plant world. It is an itchy, chronic problem which can go on for years as it can be difficult to control and the itching can be distressing for those affected. In some patients, it can cause significant scarring. Although various treatment options have been used in the treatment of lichen planus, it is still challenging to choose the most effective one. In this investigation, all topical treatments used were evaluated so that both doctors and patients could be better informed about their choices. It was found that topical steroids, the first line of treatment for lichen planus, have not been investigated enough to prove that they work. Light therapy in the form of ultraviolet light has been shown to be effective and should be used before embarking on oral treatments for lichen planus.

review will investigate the efficacy of systemic treatments for cutaneous lichen planus in the current literature.

Subjects: Pharmaceutical Medicine; Dermatology; Pharmacy & Dispensing

Keywords: cutaneous lichen planus; topical treatments; phototherapy; review

1. Introduction

Lichen Planus (LP) is a chronic inflammatory immune-mediated disease that more frequently affects the skin and oral mucosa (Le Cleach and Chosidow, 2012; Gorouhi, Davari, & Fazel, 2014). Other areas that may be affected include the scalp, hair, nails and mucous membranes of the genitalia, oesophagus and conjunctiva (Le Cleach and Chosidow, 2012). The global prevalence of LP is estimated to be in the range of 0.22–5% of the population (Gorouhi et al., 2014). LP occurs in all age groups but affects adults significantly more than children (Gorouhi et al., 2014; Payette, Weston, Humphrey, Yu, & Holland, 2015). The disease, although not gender specific has been reported to affect more women than men (Payette et al., 2015). Cutaneous lichen planus (CLP) presents as the traditional 6 “P’s” of LP—pruritic, purple, polygonal, planar, papules and plaques, frequently affecting the flexures of the extremities (Gorouhi et al., 2009; Usatine & Tinitigan, 2011). Variants of CLP are site specific and include hypertrophic, pigmentosus, annular, atrophic, follicular, linear or actinic forms on skin surfaces (Weston & Payette, 2015). Generally, CLP is largely managed based on clinical experience, location and severity of the lesions, most of which resolve spontaneously within a few years (Weston & Payette, 2015). Despite treatment, recurrence is common (Usatine & Tinitigan, 2011). Generalised eruptions have reported to heal faster than limited cutaneous disease. Hypertrophic LP is typically unrelenting (Gorouhi et al., 2009).

CLP is associated with intense itching and often pigmentation, which affects the patients quality of life due to discomfort and cosmetic problems (Gorouhi et al., 2009). Despite numerous medicines available for the treatment of CLP, there exists a gap in the knowledge of recommended drugs as many of the prescribed treatments lack conclusive evidence for efficacy, accompanied by side effects and often produce disappointing results.

There have been four systematic reviews (SRs) (Antiga, Caproni, Parodi, Cianchini, & Fabbri, 2014; Atzmony, Reiter, Hodak, Gdalevich, & Mimouni, 2016; Cribier, Frances, & Chosidow, 1998; Fazel, 2014) and four review articles (Asch & Goldenberg, 2011; Lehman, Tollefson, & Gibson, 2009; I. Manousaridis, Manousaridis, Peitsch, & Schneider, 2013; Puza & Cardones, 2017) published over the past three decades which help in ascertaining evidence of efficacy of many treatment modalities. However, due to the varying inclusion and exclusion criteria amongst these reviews, and the advent of newer treatments being tested, no consolidated publication exists which provides reports of evidence of all types of studies carried out for CLP. This two-part overview presents the findings from all previously published SRs and reviews, including studies that have been omitted in these publications for unidentified reasons and novel studies that have become evident subsequent to these publications.

Part 1 addresses the current literature focusing on topical therapies and phototherapy for the treatment of CLP. Part 2 encompasses all systemic treatments for CLP. The aim is to provide clinicians with a summarised and consolidated evidence of the various treatments of CLP; hence most of the treatments have been tabulated providing information on the type of study, dosage used, study sizes, outcome, as well as the category of evidence.

2. Methodology

2.1. Data sources and search strategy

Related literature published up until January 2018 were obtained from the following electronic database searches: Cochrane Library, Google Scholar, Medline, PubMed, EBSCOHost and ScienceDirect. The following search terms were transcribed to yield articles of relevance:

“cutaneous lichen planus”, “treatment”, “systematic review” and “review” in combination with; “topical treatment”, “systemic treatment”, “UV light/phototherapy”; “low molecular weight heparin”, “alternative/complementary medicine”, “calcineurin inhibitors”. Screening of the literature was performed independently by two authors (YT and RM) in order to validate the reliability of the information and prevent author bias. Reference lists of included papers were scanned, and further relevant publications were retrieved. This review presents findings of all studies including the most recent current literature available.

2.2. Inclusion and exclusion criteria

We included all English studies that have been previously published in peer-reviewed journals up to January 2018. There was no restriction for the type of study and hence we included randomised controlled trials (RCTs), non-randomised control studies, cohort studies, case series, case reports and anecdotal studies. We included the following clinical subtypes of CLP—hypertrophic, pigmentosus, annular, atrophic, follicular, linear or actinic. Studies of oral lichen planus with cutaneous involvement were also included. We excluded those studies that focused on solely oral involvement without cutaneous lesions, lichen planopilaris, palmoplantar and lichen pemphigoids.

2.3. Formulation of study strategy

Upon retrieval of all published literature, CLP studies were collated according to the treatment modalities. We found four systematic reviews (SRs) (Antiga et al., 2014; Atzmony et al., 2016; Cribier et al., 1998; Fazel, 2014) and four review articles (Asch & Goldenberg, 2011; Lehman et al., 2009; Manousaridis et al., 2013; Puza & Cardones, 2017) published on CLP including additional studies not mentioned by the current reviews. To date, the most recent published SR by Atzmony et al. (2016) was used as a benchmark to compare data from previously published SRs and reviews, in addition of any relevant old or current literature obtained. Table 1 provides a summary of the criteria of selection of scientific publications for each SR and review previously published.

2.4. Level of evidence grading

Three different grading systems were used to describe the level of evidence in the various SRs. These included the Grading of Recommendation, Development and Evaluation (GRADE) system, American College of Physicians (ACP) guidelines grading system and Sackett’s system of grading (Table 1). For the purpose of standardisation for evidence-based medicine, we used the GRADE system (Guyatt et al., 2008) to categorise each study. The GRADE system offers an explicit and comprehensive grading criterion and provides clear characterisation of the levels of evidence and strength of recommendation for clinicians (Guyatt et al., 2008). Where studies were already graded (as in the respective SRs), we represented it using the GRADE format for consistency. The level of evidence is based on the quality of the study i.e. study design, consistency and degree of specificity. These are graded as High, Moderate, Low and Very Low. The strength of recommendation is graded as either **strong** or **conditional (weak)**, based on the treatment outcome in individual studies (Guyatt et al., 2008; Schunemann, Hill, Guyatt, Akl, & Ahmed, 2011).

- **High** level of evidence is allocated to studies that have a controlled trial study design which minimises the risk of bias and have a high confidence that the true effect may coincide with the estimated effect.
- **Moderate** level studies are in line with high level of evidence but there may be a possibility of change in the estimate.
- **Low** level of evidence may have limited confidence on the estimate of effect, while **Very low** levels of evidence in studies that have minimal confidence and that the true effect may be substantially different from the estimate of effect.

Table 1. Summary of published systematic reviews and reviews for CLP

Systematic reviews

| Reference citation | Data bases used | Date of search | Number of studies included | Inclusion criteria | Grading system used to assess strength of evidence |
|--|--|--------------------------------|---|--|---|
| Atzmony et al., 2016 | PubMed, CENTRAL, ClinicalTrials.gov registry | Till May 2014 | 16 Total: 12- RCTs 4-non RCTs | All randomised controlled trials, Non-randomised case-control studies, Cohort studies with more than one treatment arm | GRADE (Rai, Kaur, & Kumar, 2002) system (4 levels: high, moderate, low, very low) moderate to high = RCTs with strong evidence very low to low = cohort studies that provide observational evidence |
| Fazel, 2014; Turan, Baskan, Tunali, Yazici, and Saricaoglu, 2009 | PubMed EMBASE Cochrane Database of SRs Cochrane Central Register of Controlled Trials Database of Abstracts of Reviews of Effects Health Technology Assessment Database | Till 2012 | 2 SRs 9 RCTs | All SRs and RCTs of any design RCTs that compared at least one treatment arm with control, placebo, alternate therapy or no treatment | ACP guidelines grading system (Ansari, Henderson, Stott, & Parr, 2017) (2 levels; high, moderate) High = all RCTs that was equal or half the inclusion criteria moderate = meets the minimum inclusion criteria of RCTs |
| Antiga et al., 2014 | Medline | January 1999- November 2012 | 21 Total: 3- Level B studies 18—Level C studies | All papers published between 1999–2012 about treatment of CLP | Sackett's (Chauhan, De, Handa, Narang, & Saikia, 2017) system (3 levels; A, B, C) A = large RCT with defined conclusions, B = RCTs with uncertain results, C = trials without randomised controls |
| Cribier et al., 1998 | MEDLINE BIOSIS | Till 1998 | 27 Total: 1—Level B study 26—Level C studies | All papers published from inception of treatment till 1998 for CLP | Sackett's (Chauhan et al., 2017) system (3 levels; A, B, C) A = large RCT with defined conclusions, B = RCTs with uncertain results, C = trials without randomised controls |
| Reviews | | | | | |
| Puza and Cardones, 2017 | PubMed, CENTRAL, EBSCOhost | 1972–April 2017 | 21 Total: 9 RCTs 6 open trials 6 case series/cohort/case reports | All RCTs and therapeutic studies relating to CLP treatments | None |

(Continued)

Table 1. (Continued)

Systematic reviews

| Reference citation | Data bases used | Date of search | Number of studies included | Inclusion criteria | Grading system used to assess strength of evidence |
|---------------------------|----------------------------------|----------------|---|--|---|
| Manousaridis et al., 2013 | PubMed Cochrane Databases | 1976-2012 | 14 Total: 3 RCTs 2 non-RCTs 2 open trials 7 case series/cohort/case reports | All published literature in peer-reviewed journals on LP including CLP | Self-defined criteria (A) Prospective controlled trial (B) Retrospective study or large clinical series (C) Small clinical series or case reports (D) Unpublished clinical experience |
| Asch and Goldenberg, 2011 | PubMed, CENTRAL, Science direct, | 1998-2008 | 20 Total: 1 RCT 1 non-RCT 18 case series/cohort/case reports | All systemic therapies relating to CLP from 1998 till 2008 | None |
| Lehman et al., 2009 | PubMed, CENTRAL, Science direct | Till 2008 | 22 Total: 2 RCTs 20 case series/cohort/case reports | All CLP treatments from inception up until 2008 | None |

Randomised Control Trial (RCT), systematic reviews (SRs), Grading of Recommendation, Development and Evaluation (GRADE), American College of Physicians (ACP).

3. Treatment regimens

3.1. Topical interventions for cutaneous lichen planus

Topical treatments for CLP include corticosteroids, calcineurin inhibitors e.g. tacrolimus and Vitamin D3 analogues, e.g. calcipotriol. Also included in this review are phototherapy treatments.

3.2. Topical corticosteroids

Class 1 (ultra-high potency) and Class II (high potency) topical corticosteroids are still considered the first line of treatment for CLP due to their anti-inflammatory properties that focus on localised lesions and reduce pruritus (Ramachandran, 2014). Six studies on topical corticosteroids were identified in the literature. Only one RCT was reported by Atzmony et al. (2016) which included betamethasone valerate 0.1% vs calcipotriol. In addition to that, four studies reported in the Atzmony et al. SR were non-randomised case-control trials (Atzmony et al., 2016). Two studies conducted before 1970 were reported by Cribier et al. (1998) but were excluded by Atzmony et al. (2016). A preceding study conducted in 1976 by Björnberg and Hellpen (1976) was only reported in a review by Manousaridis et al. (Hazra et al., 2013).

Upon evaluations of studies that explore the effectiveness of topical corticosteroids, it is apparent that majority of these studies have low patient sample size with the largest study group of 25 patients. Only a single RCT was conducted (Theng et al., 2004), following two non-RCTs (Chopra, Mittal, & Kaur, 1999; Sharma & Mishra, 2003), two open, non-comparative trials (Björnberg & Hellpen, 1976; Marsden, 1968) and one case-controlled study (Brock & Cullen, 1967). Results varied across studies with different corticosteroid formulations used. Response across each of these studies demonstrated no significant difference with a lower response between the topical corticosteroid betamethasone valerate 0.1% and topical calcipotriol (Theng et al., 2004). Similarly, with betamethasone dipropionate 0.05%, no significant difference was observed in a comparison against PUVAol (Sharma & Mishra, 2003). Furthermore, in an open trial by Björnberg and Hellpen (1976), a large effect (73.7% improvement) with betamethasone-17,21-dipropionate 0.05% was demonstrated, although there was no comparative measure (Björnberg & Hellpen, 1976). Other studies with topical fluocinonide acetone reported a low (28.6%) complete response (Marsden, 1968) and with triamcinolone 0.5%, a lower percentage of patients had a better response with the topical steroid (Brock & Cullen, 1967). Topical Clobetasol propionate lotion together with a hydrocolloid occlusive dressing was used in patients with chronic skin diseases including CLP. It was reported that in those patients with CLP, 2.8 weeks was the average time to remission (Volden, 1992).

Grading of the studies showed that none of the studies published reported a high level of evidence. Apart from the one RCT conducted by Theng et al. (Theng et al., 2004), all other studies demonstrated either a low or very low level of evidence. Considering that no high-level evidence exists for the use of topical corticosteroids in CLP, its routine use by clinicians as first-line treatment for CLP is primarily based on their own experiences. The use of topical corticosteroids under occlusion and intra-lesional corticosteroid injections are primarily anecdotal and there are no published trials demonstrating their efficacy. The strength of recommendation for topical corticosteroids is discretionary, and its role as first-line therapy is therefore arguable. Table 2 provides a summary of all published topical corticosteroid studies to date.

3.3. Phototherapy

Phototherapy is often used in the treatment of various inflammatory skin disorders (Vangipuram & Feldman, 2016). It is a specialised technique that can act as an alternative treatment to assist in clearing of lesions observed in CLP. The mechanism of its action is controversial since sunlight is known to aggravate certain variants of CLP (Taneja & Taylor, 2002), although at different wavelengths, treatment using phototherapy is widely explored. Following the very first SR in 1998 by Cribier et al. (1998), only one RCT on phototherapy was conducted by Irajii et al. (2011) and reported in the three subsequent SRs (Antiga et al., 2014; Atzmony et al., 2016; Turan et al., 2009). Since then, there have been no additional RCTs on phototherapy. Atzmony et al. (2016) also

Table 2. Summary of topical corticosteroid published studies

| Corticosteroids (Topical) | | | | | | |
|---------------------------------------|-----------------------------|---|--|---|-------------------|--|
| Study design | Author/year | Type of Lichen planus | Treatment (n) | Comparative Treatment (n) | Level of Evidence | Result |
| RCT | Theng et al., 2004 | Generalised | Betamethasone valerate 0.1% bds for 12 weeks (n = 16) | Topical Calcipotriol 0.05% bds for 12 weeks (n = 15) | Moderate | 50% lesion flattening with betamethasone. However, no difference between groups were reported after 12 weeks. |
| Non-RCT | Sharma and Mishra, 2003 | Hypertrophic, Guttate, atrophic | Betamethasone dipropionate 0.05% daily for 12 weeks (together with cetirizine 10mg daily) (n = 24) | PUVASol 4mg/kg on alternate days 3 X week for 12 weeks (n = 23) vs Metronidazole 200mg tds for 3 weeks (n = 23) | Low | Good and excellent response was noted with betamethasone in 54.2% of patients. This was comparable to PUVASol and a better response compared to metronidazole. |
| Non-RCT | Chopra et al., 1999 | Various types including Classic, lichen actinicus, linear LP, LPP, mucosal LP | Betamethasone 0.1% bds for 3 months (n = 25) | Oral Dapsone 50mg tds for 3 months (together with chlorpheniramine maleate 4mg bds and coconut oil) (n = 50) | Low | Response to betamethasone was less compared to dapsone (40% good response with betamethasone vs 58% dapsone). |
| Open trial | Björnberg and Hellpen, 1976 | NS | 0.05% betamethasone-17,21-dipropionate ointment once or twice daily for 2-3 weeks (n = 19) | None | Very Low | Patients treated were those whom previously demonstrated resistance to prolonged treatment with 0.05% betamethasone -17-valerate ointment. 73.7% improvement was noted. The remaining 26.3% had no response. |
| Open trial | Marsden, 1968 | NS | Fluocinonide acetone 0.2% tds (n = 7) | None | Very Low | 28.6% had complete response (after unknown delay) |
| Case controlled (double blind) | Brock and Cullen, 1967 | NS | Triamcinolone 0.5% in flexible collodion acetone. One half of body (n = 7) | Excipient Other half of body | Very Low | 42.8% had a better response on the corticosteroid side |

Randomised control trial (RCT), Lichen planus Pemphigoids (LPP), Twice daily (bds), Three times daily (tds), Not stated (NS)

reported on three non-RCTs, and although part of the inclusion date, this SR did not include the Gonzalez, Momtaz-T, and Freedman (1984) study in 1984 which was reported by Cribier et al. (1998). Further studies which were predominately case series, non-comparative open trials and retrospective studies were reported in SRs by Cribier et al. (1998) and Antiga et al. (2014). These studies did not meet the Atzmony et al. (2016) SR inclusion criteria.

Additionally, we found the other two studies (case series), which explored the efficacy of phototherapy, that were not mentioned in any of the SRs and reviews despite meeting their inclusion criteria. One older study by Gamil, Nassar, Saadawi, El-Qashishi, and Ahmed (2009) and a novel treatment by Fan et al. (2015). A four-year retrospective study by Solak, Sevimli Dikicier, and Erdem (2016) which demonstrated a significant positive response with NBUVB for generalised lichen planus was only reported in the Puza and Cardones review (Samyia & Lin, 2012). Table 3 summarises all documented phototherapy studies.

3.3.1. Ultraviolet B (UVB) therapy

Commonly used in the treatment of CLP, Narrow-band UVB (NBUVB) and Broad-band UVB (BBUVB) radiation exposure are known to reduce skin lesions by causing apoptosis of the affected cells and interfering with immunological functions that inhibit the expression of related inflammatory factors (Berneburg, Röcken, & Benedix, 2005). Post 2002 and to date, there were seven published studies conducted with NBUVB with sample sizes up to a maximum of 43 patients. Results from the only RCT conducted with phototherapy demonstrated that NBUVB had a better response to systemic prednisolone therapy (Iraji et al., 2011). This evidence was considered moderate. NBUVB was compared to oral PUVA in one non-RCT where it was reported to be comparable to oral PUVA (Wackernagel et al., 2007). The evidence of efficacy was considered low. Three case series demonstrated a positive response to NBUVB. Evidence of efficacy from these was very low (Gamil et al., 2009; Saricaoglu, Karadogan, Baskan, & Tunali, 2003; Taneja & Taylor, 2002). Three retrospective studies, although regarded as low evidence studies, reported a favourable outcome for NBUVB treatment; two of which were non-comparative studies by Solak et al. (Majid, 2017) and Habib et al. (2005), with one comparative to BBUVB reported by Pavlotsky, Nathansohn, Kriger, Shpiro, and Trau (2008).

Despite the level of evidence in majority of studies with NBUVB being considered low, an improved outcome with NBUVB was reported in six of the seven studies. In only one study, NBUVB was comparable to oral PUVA in the long term in terms of efficacy and relapse rates, with oral PUVA demonstrating an initial superior response. Oral PUVA may have a better response in patients with hypertrophic LP who do not respond to NBUVB. The recommendation based on these results is that NBUVB should be considered as an effective treatment option for CLP before proceeding to use systemic corticosteroids or systemic immunosuppressants. However, the high costs associated with outpatient phototherapy and the frequency of sessions required, need to be considered.

3.3.2. Psoralen plus Ultraviolet A (PUVA) therapy

Photochemotherapy using Ultraviolet A light in conjunction with psoralen (as a photosensitizer) enhances the efficacy of UVA in the treatment of CLP (Vangipuram & Feldman, 2016). There are no RCTs with psoralen plus ultraviolet A (PUVA) reported, with either oral or bath therapy. Although, one non-RCT conducted in 1987 by Helander, Jansen, and Meurman (1987) established that there is no significant difference between oral PUVA and bath PUVA with no significant difference in the long-term outcomes between PUVA and no treatment. In contrast to NBUVB, while oral PUVA initially showed a clinically better response, there was a very similar overall response in long term observation (Wackernagel et al., 2007). Sharma and Mishra (2003) reported that PUVA is comparable to treatment with topical betamethasone and cetirizine combined. In other studies, a favourable response to PUVA was evident in one non-RCT (Gonzalez et al., 1984) and four case series (Karvonen & Hannuksela, 1985; Kerscher, Volkenandt, Lehmann, Plewig, & Röcken, 1995; Ortonne, Thivolet, & Sannwald, 1978; Väättäinen, Hannuksela, & Karvonen, 1981) between 1978

Table 3. Summary of phototherapy published studies.

| Phototherapy | | | | | | |
|-------------------------------------|---------------------------|--|---|---|-------------------|--|
| Narrow/Broad Band UVB (NBUVB/BBUVB) | | | | | | |
| Study design | Author/ year | Type of Lichen planus | Treatment regime (n) | Comparative treatment(n) | Level of Evidence | Result |
| RCT | Iraji et al., 2011 | Generalised | NBUVB 3 times a week at 70% MED 9J/cm ² 6 weeks (n = 23) | Prednisolone 0.3mg/kg 6 weeks (n = 23) | Moderate | NBUVB had 52.2% complete response and 47.8% partial response. This was better than prednisolone treatment. |
| non-RCT | Wackernaegel et al., 2007 | Generalised; Hypertrophic (2 patients) | NBUVB (22.5 exposures) 0.34 J/cm ² (n = 13) 8.2 weeks | Oral oxisoralen 1.2mg/kg + UVA 1J/cm ² (n = 15) 10.5 weeks | Low | 67% complete response with PUVA and 33% partial response. 30.1% complete response with NBUVB and 46.2% partial response. Longterm follow-up showed that the effectiveness of oral PUVA is comparable to NBUVB. |
| Case series | Gamil et al., 2009 | Generalised | NBUVB 3 times weekly 40 sessions (0.411–0.707 J/cm ²) (n = 16) | None | Very low | Complete response was observed in 69% of patients, partial response in 12% of patients and 19% had no response. |
| Case series | Saricaoglu et al., 2003 | Localised (either trunk or extremities) | Narrow band UVB 3–4 times weekly (30 sessions) (n = 10) mean cumulative dose = 17.7 J/cm ² | None | Very low | 50% patients responded completely 40% were partially responsive, while 10% showed no improvement. |
| Case series | Taneja and Taylor, 2002 | Localised (mostly trunk and extremities); with oral lesions (2 patients) | Narrow band UVB 2–3 times weekly (mean = 40 sessions) (n = 5) mean cumulative dose = 87.2 J/cm ² | None | Very low | Pruritus responded early in all patients. Flattening of lesions was achieved in local cutaneous lesions but not in oral lesions. |
| Retrospective | Solak et al., 2016 | Generalised | NBUVB (duration varied) (n = 24) | None | Very low | 45.8% complete response to NBUVB, 20.5% partial response and 33.7% no response. |
| Retrospective | Pavlotsky et al., 2008 | Generalised | NBUVB three times weekly Mean cumulative dose 31.5 joules/cm ² (n = 43) | BBUVB three times weekly Mean cumulative dose 11 joules/cm ² (n = 7) | Very low | NBUVB had 85% complete response and BBUVB had 70% complete response after 34.7 months of remission. |

(Continued)

Table 3. (Continued)

Phototherapy

Narrow/Broad Band UVB (NBUBV/BBUBV)

| Study design | Author/ year | Type of Lichen planus | Treatment regime (n) | Comparative treatment(n) | Level of Evidence | Result |
|---------------------|-------------------------|--|--|--|-------------------|--|
| Retrospective | Habib et al., 2005 | Disseminated LP | NBUBV three times weekly for 2-6 months (n = 20) mean cumulative dose 36 ± 4.8 joules/cm ² | None | Very low | 55% had complete response, 20% had partial response. relapse was seen in 18% after 42 months after treatment |
| Psoriasis with UV-A | | | | | | |
| non-RCT | Sharma and Mishra, 2003 | Classic, Hypertrophic, Guttate, atrophic | Oxoralen + PUVASOL 4mg + 30min sun 3 times weekly for 12 weeks (n = 23) | Metronidazole 200mg tds, 3 weeks (n = 23) Cetirizine once daily 12 weeks Betamethasone dipropionate cream 0.05% (n = 24) | Low | High and comparable clinical improvement rates with PUVAsoL (69.6%) and betamethasone dipropionate cream + oral cetirizine for 12 weeks (70.1%). Metronidazole was found to be less effective (34.8% responded to treatment) than PUVAsoL and cetirizine + topical betamethasone |
| non-RCT | Helander et al., 1987 | Generalised, Localised | Oral methoxsalen 0.6mg/kg + UVA (n = 10) 50mg with methoxsalen bath + UVA (n = 13) | no PUVA treatment (n = 20) | Low | 76.9% good response with bath PUVA. 50% good response with oral methoxsalen. This difference in response however was non-significant. 55% of the no treatment group showed complete clearing. The late overall outcome of UV treatment is no better than with no treatment. |
| non-RCT | Gonzalez et al., 1984 | Generalised | Oxsolaren + PUVA on one half of the body (n = 10) Mean cumulative dose = 256J/cm ² | Untreated/unexposed other half of body | Low | 30% partial response to PUVA 50% complete cure within 6 months. |
| Case series | Kerscher et al., 1995 | NS | PUVA bath therapy (methoxsalen 1mg/L) with maximum single dose of 1.2 J/cm ² (n = 4) | None | Very low | Complete clearance seen within 6 weeks of treatment. |

(Continued)

Table 3. (Continued)

| Phototherapy | | | | | | |
|--|-------------------------------|---|--|---------------------------------|--------------------------|--|
| Narrow/Broad Band UVB (NBUBV/BBUBV) | | | | | | |
| Study design | Author/ year | Type of Lichen planus | Treatment regime (n) | Comparative treatment(n) | Level of Evidence | Result |
| Case series | Karvonen and Hannuksela, 1985 | NS | PUVA bath therapy (trioxsalen + UVA) (n = 75) | None | Very low | 65% cure rate (after 2 cycles) 15% improvement rate 25% relapse rate |
| Case series | Väätäinen et al., 1981 | papular/hypertrophic | PUVA bath therapy (trioxsalen 3mg/L) (n = 19) | None | Very low | Complete recovery from papular LP noted in all 16 patients 67% complete response and 33% partial response seen in 3 patients with hypertrophic LP |
| Case series | Ortonne et al., 1978 | NS | PUVA (0.4mg/kg methoxsalen + UVA) mean cumulative dose = 107 J/cm ² (n = 7) | None | Very low | 85.7% had complete response. No further details reported. |
| Laser diode therapy | | | | | | |
| Case series | Fan et al., 2015 | Localised (5 males localised on penis, 1 female localised forehead, nose, mouth and other localised on wrist) | 10% 5-aminolevulinic acid + 635 nm laser diode (ALA-mediated photodynamic therapy) applied topically (n = 7) | None | Very low | 71.4% complete response 28.6% partial response overall patients responded well to treatment. |

Randomised control trial (RCT), minimal erythema dose (MED), Three times daily (tds), Not stated (NS)

and 1995. The level of evidence in these studies with PUVA is considered low. PUVA is not considered the ideal choice of treatment for CLP. NBUVB is a preferred phototherapeutic option however patients that do not respond well to NBUVB may be susceptible to PUVA treatment.

3.3.3. *Laser diode therapy*

A novel treatment for CLP in a 2015 study by Fan et al. (2015) examined the use of photodynamic therapy with 10% 5-aminolevulinic acid (ALA) cream mediated under photodynamic therapy (PDT). The study consisted of seven CLP patients who were previously recalcitrant to topical steroid creams. ALA cream was applied to affected lesions and then incubated for 3 h after which irradiation using 635nm laser diode was used to target affected areas. The majority (71%) demonstrated complete response to treatment in which complete disappearance of the lesions was observed. The remaining two patients exhibited partial response. Patients demonstrated complete response after just one course consisting of two-week intervals of three sessions. After 6 months follow up, there was no recurrence in those who had complete response to treatment. The side effects experienced were pain and burning sensations which were tolerable with the use of a topical lidocaine spray. Moderate erythema was observed during recovery and clearing was seen within 10 days. The mechanism on how treatment action occurs on the skin is unclear but may accelerate apoptosis of targeted affected cells.

Considering high relapses with other treatments, associated side effects with high potency steroids and possible carcinogenic side effects with constant PUVA exposure; ALA-mediated PDT provides a minimal invasive treatment option with little side effects and recurrence. Larger studies are required to confirm its efficacy and understand its mechanisms (Fan et al., 2015).

3.3.4. *Fractional CO₂ laser*

In a recent study (Majid, 2017) in patients with hypertrophic LP, complete resolution of lesions was found with the use of fractional CO₂ laser-assisted corticosteroid delivery. This was administered at 4-week intervals (60 J/cm²) in combination with either triamcinolone suspension 10mg/ml or topical clobetasol propionate gel applied to the lesion immediately after laser treatment and then twice daily. Topical corticosteroid alone was not very effective as a stand-alone treatment, but fractional CO₂ complete relief was observed with noticeable improvement in skin lesions. This study shows that treatment with corticosteroids is more effective in CO₂ laser assisted drug delivery.

3.4. *Topical calcineurin inhibitors (TCIs)*

Topical calcineurin inhibitors (TCIs) are widely explored as a potential substitute for corticosteroids because of the potent side effects of corticosteroids in dermatological treatment. Their immunomodulatory and anti-inflammatory properties are attributed to the inhibition of the protein calcineurin phosphatase, which is known to regulate cytokine production and T-cell activation (Wong & Kurian, 2016). Despite the strong evidence of its use in double-blind and open studies for oral lichen planus (More et al., 2017), there are no trials on calcineurin inhibitors for CLP that were reported in any of the SRs or reviews. The only SR to mention treatment of CLP using calcineurin inhibitors was by Fazel (2014). The studies were sourced from an SR by Samyia and Lin (2012) for the treatment of CLP using TCIs however no analysis of the included studies from this was reported by Fazel (2014). Samyia and Lin (2012) identified 1 open prospective trial, 11 case reports and 1 case series of TCIs and discusses their efficacy in various types of CLP. We identified an additional study which was not included in the Samyia and Lin (2012) SR on TCIs by Coman, Benea, and Georgescu et al. (2005) who had explored the use of 1% pimecrolimus for LP treatment. The level of efficacy for all of the individual reports was considered very low.

From all 11 studies evaluating the efficacy of tacrolimus, ineffective treatment was reported in only one study which treated for classic LP and LPP (Kim et al., 2008). A positive response was noted in all remaining studies with tacrolimus. Pimecrolimus was effective in all 3 case reports. Improved study designs which are randomised and controlled with larger patient numbers are

required to define and formalise the role of calcineurin inhibitors in CLP. Based on the findings from numerous reports and its mechanism of inhibition of cytokine production and proliferation which in turn limits T-cell propagation, it may be advisable to use topical calcineurin inhibitors in CLP in conjunction with topical steroids and thereby possibly reducing the need for long term topical steroids. Table 4 summarises all reported topical calcineurin inhibitor studies.

3.5. Topical cyclosporin

Topical cyclosporin acts as an immunomodulatory drug which suppresses the direct effects of T-lymphocytes that are associated with immunoregulatory dysfunctions associated with CLP (Faulds, Goa, & Benfield, 1993). Only one study of 5% w/v intravenous cyclosporin (Grattan, Boon, & Gregory, 1989) used topically under occlusion was reported in the study by Cribier et al. (1998). This was a case series of four chronic hypertrophic LP patients. Improvement was noted in all patients. No further studies were conducted using intravenous cyclosporin topically since 1989. Evidence for its use is thus very low. Long term use of cyclosporin is not advised as renal toxicity and arterial hypertension may occur. Minimising the dosage may reduce the risk of adverse effects (Dehesa, Abuchar, Nuno-Gonzalez, Vitiello, & Kerdel, 2012). Results are summarised in Table 5.

3.6. Vitamin D₃ analogues

Vitamin D₃ analogues have shown to have immunomodulatory properties affecting cell growth and have been used in clinical trials for the treatment of CLP (Turan et al., 2009). We identified a total of three RCTs using topical Vitamin D₃ analogues, specifically, calcipotriol and KH1060 (Vitamin D₃ analogue) of the treatment of CLP. Only one RCT by Theng (Theng et al., 2004) using calcipotriol treatment was reported by Atzmony et al. (2016). The remaining two RCTs that explored the efficacy of KH1060 were included in the SR by Fazel (Turan et al., 2009). Furthermore, one open study using calcipotriol by Bayramgürler, Apaydın, and Bilen (2002) was reported in a review by Puza (Ansari et al., 2017).

All three RCTs with moderate to high level of evidence showed no significant difference between topical Vitamin D₃ to placebo or betamethasone valerate. Vitamin D₃ analogues are therefore not a strongly recommended treatment for CLP. It is further suggested by Berneburg et al. (2005) that the combination treatment of Vitamin D₃ in conjunction with phototherapy may enhance efficacy of treatment outcomes. Table 6 summarises all studies with topical Vitamin D₃.

4. Conclusion

Despite various treatment modalities available, CLP remains a therapeutic challenge. On analyses from previously published literature, we identified studies not reported on and included newly published evidence. For topical treatment options, we report on all available clinical trials, however, the quality of evidence of many of the treatments remain low. Attributable to the fact that large randomised prospective controlled trials with rigorous methods are insufficient, we rely on evidence from single RCTs if conducted, smaller trials, non-randomised trials, retrospective studies as well as case series and reports. Although the level of evidence is low in the majority of studies, our recommendation for use is based on a combination of factors including side effects, patient satisfaction and cost-effectiveness.

While routinely used as first-line treatment for CLP by clinicians, strong evidence that supports the use of topical corticosteroids is absent and its role as first-line therapy is controversial. NBUVB is the preferred phototherapeutic treatment option for CLP and should be considered before commencing with systemic treatment. Vitamin D₃ is not recommended for the treatment of CLP due to poor patient outcomes. TCIs show promising results despite evidence only available from case reports. Once-off studies with novel treatments like ALA-mediated PDT (Fan et al., 2015) for localised lesions, fractional CO₂ laser (Majid, 2017) and intravenous cyclosporine (Grattan et al., 1989) used topically for hypertrophic LP have demonstrated favourable results and further investigation into the use of these is recommended. Complementary and alternative treatments for concomitant skin diseases have been explored (Thandar, Gray, Botha, & Mosam, 2017) but there is

Table 4. Summary of topical calcineurin inhibitors published studies

| Study design | Author/year | Type of Lichen planus | Treatment regime (n) | Level of evidence | Result |
|---------------------|---|------------------------------|---|--------------------------|--|
| Open trial | Al-Mutairi and El-Khalawany, 2010 | LPP | Tacrolimus 0.03% ointment bds (n = 13) 16 weeks | Low | 54% showed improvement in pigmentation of lesions |
| Case report | Sälvästru and Tiplica 2010 | Ulcerative plantar | tacrolimus 0.1% bds (n = 1) 6 months | Very low | Significant improvement in 4 weeks |
| Case series | Ujje, Shibaki, Akiyama, and Shimizu, 2010 | Nail | Tacrolimus 0.1% bds ointment (n = 5) 15-71 months | Very low | Good effect in all patients. Improvement in 1-6 months |
| Case report | Fortina, Giuliani, and Tonin, 2008 | Lower leg | Tacrolimus 0.03% bds (n = 1) 3 weeks | Very low | Significant improvement in 2 months |
| Case report | Al-Khenaizan and Al Mubarak, 2008 | Ulcerative plantar | Tacrolimus 0.1% bds (n = 1) 2 years | Very low | Complete resolution in 4 weeks |
| Case report | Kim et al., 2008 | LPP inversus, groin | Tacrolimus 0.1% bds (n = 1) 4 weeks | Very low | No response to tacrolimus or Clobetasol |
| Case report | Dominguez, Mateu, and Vieira et al., 2006 | Trunk | Tacrolimus 0.1% bds (n = 1) Duration NS | Very low | Complete clearing with tacrolimus |
| Case report | Meyer et al., 2005 | Plantar, palmer | Tacrolimus 0.1% bds (n = 1) 1 month | Very low | Lichen Planus cleared with tacrolimus. Reoccurrence occurred due to metoprolol |
| Case report | Eisman and Orteu, 2004 | Ulcerated Flexural | Tacrolimus 0.1% bds (n = 1) 5 months | Very low | Some improvement in 8 weeks. With added thalidomide cleared in 3 months |
| Case report | Watsky, 2003 | Perianal | Tacrolimus 0.1% bds (n = 1) 1 month | Very low | Complete clearing. |
| Case report | Nazzaro and Cestari, 2002 | Ulcerative plantar | Tacrolimus 0.1% bds (n = 1) 4 weeks | Very low | Complete healing of ulceration in 4 weeks. Still in remission at 8 months |
| Pimecrolimus | | | | | |
| Case report | Ezzedine, Simonart, Vereecken, and Heenen, 2009 | Facial actinic | Pimecrolimus 0.1% bds (n = 1) 2 years | Very low | Improvement after 2 weeks. No relapse in 2 years |

(Continued)

Table 4. (Continued)

| Tacrolimus | | | | | |
|---------------------|--------------------|------------------------------|--|--------------------------|---|
| Study design | Author/year | Type of Lichen planus | Treatment regime (n) | Level of evidence | Result |
| Case report | Lim and Love, 2004 | Plantar palmar | Pimecrolimus 0.1% bds (n = 1) 1 month | Very low | Greatly improved in one month. No improvement with clobetasol. |
| Case report | Coman et al., 2005 | NS | Pimecrolimus 1% bds (n = 3) 6 months | Very low | Initial worsening of lesions in first 3 days (in 2 patients). Improvement was seen after 2 weeks and complete response within 8–10 weeks. No relapse after 3 months of discontinued use |

Lichen planus Pemphigoids (LPP), Twice daily (bds), Three times daily (tds), Not stated (NS)

Table 5. Summary of topical cyclosporin published studies

| Cyclosporin | | | | | |
|---------------------|----------------------|------------------------------|--|--------------------------|---|
| Study design | Author/year | Type of Lichen planus | Treatment regime (n) | Level of evidence | Result |
| Case series | Grattan et al., 1989 | Chronic hypertrophic LP | 5% w/v intravenous cyclosporin used topically under polythene occlusion within 4 weeks (n = 4) | Very low | Reduction in scaling was noted in all patients. Thinner plaques in 75% of patients and irritation reduced in 50%. |

Table 6. Summary of topical Vitamin D published studies

Vitamin D

| Study design | Author/year | Type of Lichen planus | Treatment regime (n) | Comparative treatment(n) | Level of Evidence | Result |
|-------------------|--|-----------------------------|---|---|-------------------|--|
| RCT | Theng et al., 2004 | Generalised | Topical Calcipotriol 0.05% bds for 12 weeks (n = 15) | Betamethasone valerate 0.1% bds for 12 weeks (n = 16) | Moderate | 46.7% lesion flattening with calcipotriol. However, no difference between groups were reported after 12 weeks. Adverse events were higher for calcipotriol (irritation and increased pruritis) |
| RCT | Bouloc, Revuz, Bagot, Wechsler, and Natta, 2000 | NS | Topical KH1060 1ug/g (Vitamin D3 analogue) bds for 8 weeks (n = 38) | Placebo (n = 36) | High | 37% clearance with topical KH1060 compared to 42% clearance with placebo. No significant difference between treatment and placebo groups was noted. |
| RCT | Glade, Van Der Vleuten, van Erp, De Jong, and van de Kerkhof, 1998 | NS | Topical KH1060 1ug/g (Vitamin D3 analogue) bds for 8 weeks (n = 5) | Placebo (n = 5) | Moderate | No clinically significant difference between treatment and placebo groups. On a cellular level, the treatment may inhibit epidermal growth and reduce mesenchymal cells |
| Open trial | Bayramgurlier, 2002 | Different clinical subtypes | Topical calcipotriol ointment bds for 2-3 months (n = 18) | None | Low | 31.25% had complete response, 25% partial response. 43.75% had no response. |

Randomised control trial (RCT), Not stated (NS), bds (twice daily).

no available evidence exploring the efficacy of these treatments in CLP. The second part of this review will investigate the efficacy of systemic treatments for CLP in the current literature.

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