

Systemic Treatment of Cutaneous Lichen Planus: An Update

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Lichen planus (LP) is a chronic and remitting dermatosis that may be idiopathic or associated with underlying systemic diseases, such as hepatitis C virus. Although numerous cases of LP resolve spontaneously, many cases require systemic treatment. Several therapeutic advances have occurred in the last 10 years: acitretin (30 mg daily for 8 weeks) remains a first-line therapy (level B, controlled clinical trial >20 participants); systemic corticosteroids are second-line therapies (level C, clinical trial <20 participants, or larger trial without appropriate controls); and new data recommend against the use of tetracycline (level C). This article reviews the current status of systemic therapies for cutaneous LP.

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Although many cases of lichen planus (LP) spontaneously resolve in approximately 1 year,¹ 15% to 20% of cases follow a relapsing and remitting course, making it a challenge to address response to treatment.² In 1998, Cribier et al³ reviewed the evidence-based treatments of cutaneous and oral LP. At that time, data only supported acitretin as a first-line agent; Cribier et al³ recommended systemic corticosteroids based on worldwide clinical experience but not based on controlled studies. In 2005, Zakrzewska et al⁴ reviewed the randomized controlled trial data for oral LP and concluded that there was only weak evidence for any given modality. To provide

a more recent update on the treatment of cutaneous LP with systemic therapies, we established the following inclusion criteria for evaluation in this article: (1) published in English (based on a PubMed search of articles indexed for MEDLINE using the term *cutaneous lichen planus*); (2) date of publication within the last 10 years (included 1998-2008 at the time the manuscript was written); (3) patients with cutaneous LP, not mucosal or oral LP; and (4) treatment with systemic therapies, not topical therapies. This article will review the current status of systemic therapies for cutaneous LP (Table).

Classic Therapies

Systemic Corticosteroids—Prednisolone at 30 mg daily was compared to placebo for 10 days; the treatment group showed shorter times to clearance (18 weeks vs 29 weeks [median time]) and fewer failures (0 patients vs 3 patients whose treatment failed to clear lesions in 2 years).³ Verma et al⁵ used oral betamethasone 5 mg for 2 consecutive days in a week for 3 months in 7 patients with only skin lesions; all of the patients had some response. There were no parameters outlined for less than 100% response, which was defined as flattening and decreased pruritus, but the authors noted that there were no patients without some response to treatment.⁵ An uncontrolled open trial of 35 patients on betamethasone oral mini-pulse therapy was conducted (6 mg of oral betamethasone phosphate once weekly for 3–6 months) and showed the following: 20 patients showed complete response of lesions and pruritus; 8 showed more than 50% improvement by decreased itching and no new lesions; and 3 did not improve.⁶ Twenty patients experienced side effects, 2 leaving the study due to weight gain, insomnia, and epigastric pain. Relapses were seen in 5 patients after discontinuation.⁶

Phototherapy and Psoralen Plus UVA—Several case series investigating the use of phototherapy treatments were published over the last 10 years.

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Summary of Data From Representative Studies on Cutaneous LP^a

Therapy (Level of Evidence)	No. of Patients	No. of Patients With Complete Remission	No. of Patients With Partial Remission	No. of Patients With Treatment Failure or Withdrawal From Study
Systemic corticosteroids ^{5,6} (Level C)	7+35=42	0+20=20	7+8=15	0+7=7
Phototherapy/PUVA ⁷⁻¹⁰ (Level D)	10+5+50+28=93	5+4+35+14=58	4+0+NA+11=15	1+1+NA+3=5
Retinoids ¹¹ (Level B)	28	18 (combined complete and partial)	NA	NA
Low-molecular-weight heparin ¹²⁻¹⁶ (Level D)	24+4+11+7 +10=56	20+3+7+0 +0=30	NA+NA+1 +3+2=6	4+1+3+4+8=20
Sulfasalazine ¹⁷ (Level D)	20	13	NA	4
Tetracycline ¹⁸ (Level C against) ^b	13	1	6	6
Metronidazole ¹⁹ (Level D)	19	13	2	4

Abbreviations: LP, lichen planus; PUVA, psoralen plus UVA; NA, not available.

^aLevel A, double-blind controlled study; level B, controlled clinical trial >20 participants; level C, clinical trial <20 participants, or larger trial without appropriate controls; level D, case series ≥5 participants; level E, anecdotal case reports (not listed in table; discussed in text).

^bEvidence against using tetracycline done at level C requirements, which showed that tetracycline was not effective and should not be used as a therapy for LP.

Saricaoğlu et al⁷ administered narrowband UVB (NB-UVB) phototherapy 3 to 4 times weekly to 10 histopathologically proven LP patients and examined them for disappearance of lesions. At the end of 30 sessions, 5 patients showed complete response and 4 showed partial response; 1 patient did not respond. Three of the partial responders became complete responders with further treatments (up to 51 sessions) and 1 partial responder did not improve further.⁷ A series of 5 patients with extensive LP reported success with 3 patients with no relapse at 5 months and 1 patient at 20 months after using NB-UVB phototherapy 2 to 3 times weekly.⁸

Pavlotsky et al⁹ retrospectively analyzed 50 patients treated with broadband- or NB-UVB therapy; complete response was achieved in 35 patients. However, as noted by the authors, it was a retrospective study of a usually self-limited disease.⁹ Wackernagel et al¹⁰ performed a chart review of 28 patients treated with either psoralen plus UVA or UVB 311-nm therapy. There was no significant difference between the 2 treatment groups in sustained clinical response.¹⁰

It is important to note that several cases of exacerbation of LP with phototherapy have been reported.²⁰⁻²²

Retinoids—The last published trial of oral or topical retinoids in the treatment of cutaneous LP, as described by Cribier et al³, was in 1991 with a series of 65 patients reported by Laurberg et al.¹¹ There was overlap between cutaneous and oral disease in this study. The patients demonstrated considerable improvement on 30 mg daily of acitretin for 8 weeks.¹¹ Thus, without further studies, the data remain that acitretin is the only retinoid proven to have efficacy in the treatment of cutaneous LP.

Newer Therapies

Enoxaparin Sodium (Low-Molecular-Weight Heparin)—Low-molecular-weight heparin (LMWH) has been used to treat cutaneous LP. In a 1998 report, Hodak et al²³ showed improvement in 8 of 10 patients treated with enoxaparin sodium. Further investigations have been undertaken since that time.

Akdeniz et al¹² published a series of 24 patients with cutaneous LP who were treated with 3-mg subcutaneous injections of enoxaparin sodium weekly for 4 to 14 weeks and then followed up for 1 year. Most patients had been previously treated with topical corticosteroids and/or oral antihistamines. Complete response was seen in 20 patients as assessed by disappearance of skin lesions; these patients also reported disappearance of itch after 3 weeks. Three patients with chronic hypertrophic LP showed no change. One patient showed no response to enoxaparin sodium but was successfully treated with systemic corticosteroids. This study suggests that enoxaparin sodium may be a good therapy for patients with disseminated LP; however, the duration of disease before beginning treatment was less than 6 months in all successfully treated patients and there were no control patients.¹²

Similarly, Pacheco and Kerdel¹³ reported a series of 4 patients with LP; 3 patients were treated with 30 mg weekly of enoxaparin sodium subcutaneous injection and 1 patient with 30 mg of enoxaparin sodium administered subcutaneously every other day. All LP patients in this series had long-standing disease (minimum of 1 year). Of the 4 LP patients, 3 responded to treatment with decreased pruritus and erythema. One patient showed no improvement. Of the 3 responders, 1 relapsed and showed improvement upon restarting enoxaparin sodium.¹³

Stefanidou et al¹⁴ published a series of 18 patients with cutaneous LP; 11 patients had only skin lesions. Seven patients had complete response after treatment with 3-mg subcutaneous LMWH injections (enoxaparin sodium) weekly for 6 to 13 weeks, 1 with marked improvement, and 3 with no change in their lesions. Ten of 11 patients had LP for less

than 1 year and there were no relapses; however, follow-up time varied greatly from 4 to 26 months.¹⁴

Some reports have shown disappointing results. Ferahbas et al¹⁵ reported a series of 7 patients with histologically proven LP treated with 5-mg subcutaneous injections of enoxaparin sodium for 6 weeks; 1 patient showed mild clinical improvement and reduced itch, 1 reported decrease of itch only, 1 had partial reduction of lesions clinically, and 4 others showed no improvement. In this study, 5 of 7 patients had the disease for 12 months or more.¹⁵ With similar disappointing results, in 2002 Rai et al¹⁶ presented a series of 10 patients treated with enoxaparin sodium for LP. Of them, only 2 showed any clinical response after 6 injections, both with LP for less than 1 year. The most notable response was relief of pruritus, which was only seen in 1 patient.¹⁶

The mechanism of action of LMWH in the treatment of cutaneous LP is only speculative. With enoxaparin sodium, the active player may be sulfated disaccharides, which act to influence anti-inflammatory and antichemotactic factors for T cells. Therefore, the clinical effect of enoxaparin sodium on LP may be dependent on the amount and nature of sulfated disaccharides in any given batch of enoxaparin sodium, which may account for the varied responses seen in the clinical setting.

Sulfasalazine—Bauzá et al¹⁷ reported a series of 20 patients in which sulfasalazine was used prospectively in cutaneous LP as monotherapy for 4 weeks to 14 months. Sulfasalazine was used at initial doses of 1.5 g daily and gradually increased to 3 g daily up to 16 weeks. Eleven patients were continued on decreasing doses for 2 to 12 months dependent on response. Four patients experienced side effects causing discontinuance of treatment and 3 other patients stopped treatment after achieving a complete response. In total, complete response was seen in 13 of 20 patients after 16 weeks or more of treatment and relapse was seen in 10 of 20 patients. Five patients with relapse were re-treated and obtained a complete response. All patients had decreased pruritus in 5 to 7 days and improvement in skin lesions; however, only 7 of 20 patients had the disease for more than 1 year.¹⁷ Of note, prior reports have associated sulfasalazine and a related compound mesalamine with inducing LP.^{24,25}

Tetracycline—While tetracycline is a commonly used treatment of LP, few data exist to support its use. In 2007, Hantash and Kanzler¹⁸ enrolled 15 LP patients in a prospective study on the use of tetracycline for LP. All patients were treated twice daily with either 500 mg of tetracycline or 100 mg of doxycycline for up to 6 months. Of the 15 patients,

13 completed the study; of those who completed the study, 6 had no response, 6 had partial response, and only 1 patient had complete remission. The authors observed that this level of remission is expected with the natural course of LP and concluded that given these preliminary results, a larger study is not warranted and tetracycline, in fact, is not an effective treatment of LP.¹⁸

Biologics—The advent of biologic therapies has changed the face of dermatologic disease over the last 10 years. Thus far, there are only case reports of these new therapies being utilized for LP.

Alefacept is a leukocyte function antigen-3/IgG dimeric fusion protein. In 2006, Fivenson and Mathes²⁶ used 12-week intramuscular therapy with alefacept in 2 patients with generalized LP. Both patients had improvement at 4 weeks, and by 20 weeks, both patients were free of itch and new lesions. Old lesions also showed some response.²⁶

Efalizumab is a monoclonal antibody to the CD11a chain of leukocyte function antigen-1 and was utilized in 1 patient with generalized relapsing remitting LP; weekly treatment with efalizumab was used with a decrease in pruritus and clearance of lesions.²⁷ However, in a series of 4 patients treated with efalizumab for 12 weeks, serious adverse events occurred including hospitalization for urticaria, staphylococcal hip abscess, and drug-induced subacute cutaneous lupus.²⁸ Of note, there are 2 case reports of induction of LP and lichen planopilaris associated with etanercept use for other inflammatory conditions.^{29,30}

Basiliximab, an anti-CD25 chimeric antibody, has not been tried in cutaneous LP but has been successfully used for erosive LP in one case report.³¹

Metronidazole—In one series of 19 patients, metronidazole was utilized for generalized LP.¹⁹ Complete response was defined as 80% to 100% clearance of lesions and alleviation of pruritus. Complete response without relapse during a median 2-year follow-up was observed in 13 patients. Of the remaining 6 patients, 2 patients had partial clearing of skin lesions and some alleviation of pruritus but localized recurrences in the period after treatment completion; 4 patients were unresponsive to metronidazole treatment. Treatment was discontinued after 20 days in 1 patient because of worsening of the disease.¹⁹

Thalidomide—In 2008, Doherty and Hsu³² provided a retrospective analysis of patients treated with thalidomide for various recalcitrant conditions at their institution. Six patients had LP and were treated with thalidomide for more than 1 month. Four of the treated patients had complete clinical improvement (defined as 90% improvement of lesions and no new lesions) with 1 patient relapsing at 6 months.

One patient had a partial response. All 5 patients responded within 3 months of initiation of therapy. One patient did not respond to thalidomide. In this report the nature of the LP, other than its recalcitrance, was not reported.³² One responding patient was previously reported in 2005; in that report, the patient was noted to have generalized LP.³³

Miscellaneous Treatments

As with other diseases without proven effective treatments, many therapies have been attempted for cutaneous LP. Therapy with azathioprine, itraconazole, and mycophenolate mofetil is reported in 1 or 2 case reports in the literature. All 3 therapies are reported with improvement or clearance of lesions, yet all as case reports without further studies to evaluate efficacy in larger numbers of patients.³⁴⁻³⁷ Surgery was used in 1 case in which squamous cell carcinoma arose in a chronic LP lesion; the local area of LP resolved with improvement of other lesions.³⁸ In a 1998 review, Cribier et al³ discussed data evaluating griseofulvin (not enough data to evaluate); cyclosporine (possibly efficacious, no controlled trials); and other attempted treatments including dapsone, hydroxychloroquine, phenytoin, cyclophosphamide, and interferons. There were not enough data to support use of any of these treatments as first-line therapy at that time and no data to further evaluate them have been published since then. One of the authors of this article (G.G.) has used methotrexate successfully to treat cutaneous LP.

Conclusion

The natural course of LP must be kept in mind when initiating any therapy for the dermatosis. Because many patients have spontaneous regression, the quality of data surrounding LP treatment must be carefully analyzed. The potential risk must be so low as to be negligible or the patient's condition so debilitating before a physician should attempt these unproven treatments. The quality of life of the patient with and without various treatments must be kept in the forefront of the physician's mind.

Based on available data, acitretin remains the only therapy that has shown sufficient efficacy to be considered first-line therapy. Corticosteroids remain a second-line therapy based on clinical experience and widespread use, though limited evidence-based data support their usage. The evidence is mixed on phototherapy, enoxaparin sodium, sulfasalazine, and tetracycline. Because such limited evidence is available for the biologics, calcineurin inhibitors, metronidazole, thalidomide, and other treatments discussed here, recommendations for their use cannot be made without further study.

ADDENDUM

After the manuscript was accepted for publication, 2 additional articles were published. Ochsendorf³⁹ commented on antimalarial agents in erosive LP, and Moura et al⁴⁰ addressed the use of thalidomide in cutaneous LP.

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