Treatment of Lichen Planus

An Evidence-Based Medicine Analysis of Efficacy

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Objective: To critically appraise the body of literature concerning treatment of lichen planus (LP).

Design: Review of MEDLINE and BIOSIS databases to identify articles published with at least an English abstract before March 1998 that examined treatment of LP.

Main Outcome Measures: Forming a primary database on which most recommendations are based. We thus selected 83 clinical trials or small series of patients in the medical literature that referenced clinical data on patients treated for LP.

Results: There are no large randomized trials with definitive results in the medical literature examining the efficacy of the various drugs or physical treatments of LP. There are only 3 level B trials (small randomized trials with uncertain results because of moderate to high \( \alpha \) or \( \beta \) error) that address efficacy of treatment in LP, ie, 1 with acitretin in cutaneous LP and 2 with topical corticosteroids in mucosal LP. The remainder of the published trials are observational and are not always prospective. Many of the recommendations of the experts are based on their personal experience.

Conclusions: Although LP may be associated with substantial morbidity and altered quality of life, especially the erosive mucosal LP, definitive clinical trials have not been performed. Acitretin is the first-line therapy in cutaneous LP. The efficacy of systemic corticosteroids and psoralen plus UV-A therapy has not been established with a high level of proof. Topical corticosteroids are the first-line therapy in mucosal erosive LP. Other treatments, such as topical cyclosporine or extracorporeal photopheresis, remain to be evaluated. European-US cooperation is warranted to perform large randomized controlled trials in cutaneous and mucosal LP.

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Lichen planus (LP) is a well-characterized dermatological condition affecting the skin, mucosa, hair, and nails, but its treatment is often disappointing and controversial. Various drugs or physical treatments have been proposed in the past 30 years, but the majority of these reports consist of small series of patients or anecdotes. Controlled studies on large numbers of patients are rare, probably because LP is not a common disease; it has many different clinical forms that have different natural courses and may require different treatments. As a result, large and randomized studies are difficult to perform. Furthermore, no standardized methods exist for the evaluation of the severity of the disease, there are no consensual criteria of improvement or cure, and the course of the disease is variable from one patient to another and varies according to the clinical form. To correctly interpret the results, the natural course of the disease must be kept in mind. According to large series in the literature, spontaneous remissions of cutaneous LP after 1 year occur in 64% to 68% of the cases. On the other hand, spontaneous remissions of oral LP are much rarer and were estimated to occur in less than 2.8% of the cases in a series of 570 patients and in 6.5% of 214 patients with a mean follow-up of 7.5 years. The reported mean duration of oral LP is about 5 years, but the erosive form does not spontaneously resolve. The reticular form has the best prognosis, since spontaneous remission occurs in 40% of cases. Recurrences are occasionally observed, but their prevalence has never been studied in large prospective studies. Malignant transformation of oral LP has been described but remains controversial. Among all articles published on the treatment of LP, we have found only a minority of them to be controlled studies, the largest series comprising 65 patients.
RESULTS

CUTANEOUS LP

Retinoids

Acitretin. A double-blind vs placebo trial was carried out on 65 patients with cutaneous LP. Treatment consisting of 30 mg of acitretin per day for 8 weeks demonstrated the drug's efficacy, as 64% (18/28) of the treated patients experienced significant improvement or remission in contrast to 13% (4/31) of the placebo group. The criteria for remission and marked improvement are not detailed. One figure clearly showed that papules persisted in the majority of patients under acitretin. Nevertheless, the intensity of pruritus, papulosis, and erythema was significantly lower in the treated group, with the difference being most evident during the first 12 weeks of acitretin treatment. In a 9-year-old boy who suffered from exanthematous LP, acitretin allowed complete clearance or major improvement in 6 of 8 patients with cutaneous LP treated with 30 mg/d for 8 weeks. Dramatic improvement was noted after 12 weeks of acitretin treatment in a 9-year-old boy who suffered from exanthematous LP. Acitretin has also been used successfully in 1 case of palmar-plantar lichen nitidus.

Etretinate. An open study tested the efficacy of etretinate, 50 mg/d for 2 to 3 weeks, followed by 25 mg/d in 28 patients with cutaneous LP. No criteria for evaluation were provided in this study, which showed a "good effect" in 23 cases, and the time of withdrawal of the drug was chosen "more or less at random." Two small groups of patients with "chronic" cutaneous LP or eruptive LP had good or excellent responses, but patients with LP were mixed with patients affected by various other skin diseases. The efficacy of etretinate was also noted in 4 anecdotal reports: 2 cases of cutaneous LP, 1 case of ulc- erative LP, and 1 case of LP affecting the nails.

Oral Isotretinoin and Tretinoin. Oral isotretinoin, 0.5 mg/kg per day, was effective in 2 cases of severe LP with both cutaneous and oral lesions, but we could not find a controlled study using this drug. More recently, a small series of 13 patients with cutaneous LP were treated with oral tretinoin in an open study. The dosage was 10 to 30 mg/d for 1 to 10 months. Twelve of the 13 patients experienced complete remission, without side effects other than cheilitis in 3 cases. A complete failure was observed in 1 additional patient who had only nail involvement. The use of oral tretinoin in the treatment of LP was introduced as early as 1971. It is difficult to evaluate critically the efficacy of tretinoin in those studies, since (1) patients were treated either locally or orally or both for unknown reasons, (2) the dose and duration of treatment were not available in all patients, and (3) the criteria for response were not clearly stated. The results seemed to be encouraging, although multiple systemic side effects were recorded. Hypertrophic cutaneous lesions did not respond to oral tretinoin.

Temarotene, a new member of the retinoid family, has been tried in 13 patients, of whom 10 had complete or near-complete remission after 2 to 3 months of treatment. Transient increases in transaminase levels, nausea, and vomiting were recorded in 6 cases. A placebo-controlled assay was in progress in 1989, but results have not been published yet.

Before definitive conclusions can be drawn, the various oral retinoids should be compared, but of all systemic retinoids, only acitretin has shown a relatively good level of evidence of its efficacy in the treatment of cutaneous LP. The association of retinoids with psoralen plus UV-A (PUVA) therapy has not been evaluated.

Photochemotherapy

A cure rate of 75% after 8 weeks was reported in 2 open studies conducted in 7 and 70 patients, but no criteria for a cure were described. Only 1 small controlled trial was published, in 1984; it used hemicorporeal UV-A irradiation after ingestion of psoralen (dosage un-
nails, and megadoses of methylprednisolone (1 g in regimens were also proposed: prednisone, 5 to 10 mg/d after the end of the second cycle. There were 5 other open studies with small populations. In one,10 patients after 10 minutes of bathing. After 2 to 5 years of follow-up, the relapse rate was 25%, occurring 3 weeks to 3 years after the end of the second cycle. There were 5 other open studies with small populations.11-13 In one,14 10 patients received conventional PUVA and 13 had bath PUVA. Although the response rate was a little higher in the bath PUVA group, the retrospective comparison of nonrandomized patients in an uncontrolled study did not allow any clear-cut conclusion. Moreover, at 1 year of follow-up, 74% of the treated patients had papules again, while 55% of untreated control patients were cured, suggesting an exacerbation or a relapse of the disease after withdrawal of therapy.15 In the most recent open study,32 of 11 patients with resistant LP were cured or had significant improvement with bath PUVA, with the use of methoxsalen at 1 mg/L.

The level of evidence of PUVA efficacy in the treatment of cutaneous LP is therefore weak. In some cases, PUVA is able to decrease pruritus during the first weeks of treatment26 or to rapidly cure patients with resistant long-standing LP. Bath PUVA could be more effective than oral PUVA, but the possibility of exacerbation of the disease induced by PUVA27 or after the treatment33 has been raised; thus, the results must be interpreted cautiously.

Corticosteroids

Examination of the literature, especially general reviews devoted to LP, shows numerous recommendations concerning the use of oral corticosteroids, but, surprisingly, no published study evaluated their efficacy until 1990.37 In contrast, many patients were treated with various drugs (oral cyclosporine, retinoids, immunosuppressors, dapsone) after the failure of systemic corticosteroid therapy or the inability to discontinue it without relapse. Corticosteroids remain the most widely used treatment in LP.38-41 Prednisolone dosages of 30 to 60 mg/d are recommended,39 with an efficacy threshold of 15 to 20 mg/d.40,41 The mean duration of treatment is 6 weeks, but it has been stated that corticosteroid therapy does not affect the total duration of the disease.32 Different dosage regimens were also proposed: prednisone, 5 to 10 mg/d for 3 to 5 weeks, was successful in 3 cases of LP of the nails,53 and megadoses of methylprednisolone (1 g intravenously on 3 consecutive days) resulted in a favorable response in a patient with severe resistant LP of the skin, genitalia, and scalp.44 The most recent study was made in 38 patients who received either prednisolone, 30 mg/d (without gradual reduction), or placebo for 10 days and whose LP was evaluated by a linear scale of severity.37 After a follow-up of 2 years, data for 28 patients (14 in each group) could be evaluated. The median time for LP to clear was 18 weeks in the corticosteroid group and 29 weeks in the placebo group (P = .02), and 3 of 14 patients in the placebo group vs none in the corticosteroid group failed to clear after 2 years. The changes at 6 weeks were significantly higher in the treated group (P < .05). Two patients treated with prednisolone had severe relapse after discontinuation of the drug, so that a more prolonged course of corticosteroid therapy was necessary. No other controlled study could be found in the literature. It is not known whether the conventional 4- to 6-week treatment is superior to the short-course prednisolone regimen.

Topical corticosteroids are also frequently applied to reduce itching, but we could not find any clinical trial addressing this issue. For some authors,39 clobetasol propionate has the ability to clear skin lesions when used frequently, leading them to recommend triamcinolone acetonide under occlusion for generalized disease. Intralesion injections of triamcinolone acetonide, 10 mg/mL, are used in hypertrophic lesions.39 Topical corticosteroids are the most popular form of therapy in children.40 Others recommend topical corticosteroids only in case of limited involvement, with occlusion overnight to increase efficiency.7 Surprisingly, none of these recommendations is based on clinical trials.

There are few studies published before 1970 dealing with topical corticosteroids in various cutaneous diseases in which patients with LP were included. Two of 7 patients treated with fluocinolone acetonide, 0.2%, 3 times per day, cleared after an unknown delay.45 Fluocinonide was administered to 29 patients with LP in a double-blind trial vs betamethasone valerate and hydrocortisone topically, but the patients were mixed together with 811 other patients suffering from various dermatoses.46 The results in the patients with LP were not available. Triamcinolone acetonide, 0.025%, in 70% dimethyl sulf oxide was tested in 224 patients, including 13 patients with LP, but their specific results were not detailed.47 Triamcinolone acetonide, 0.5%, in flexible collodion was administered on 1 side to 7 patients with LP compared with excipient on the opposite side.48 Only 3 of them had clear benefit on the corticosteroid side.

Intradermal injections of triamcinolone acetonide, 5 mg/mL, in the posterior nail fold were given 3 times at intervals of 2 to 4 weeks in 11 patients with LP of the nails.49 seven of them were “greatly improved,” but 2 relapsed after 8 and 12 months.

We could not find any clinical trial specifically dedicated to the treatment of cutaneous LP with topical corticosteroids.

Although the level of evidence of corticosteroid efficacy is low, unpublished clinical experience has showed that short-course systemic therapy can be effective in reducing the duration of the disease. The frequency and level of relapse of LP after withdrawal have also never been established. Topical corticosteroids are widely used, but there is no convincing evidence of their efficacy in the literature.
Griseofulvin
Griseofulvin, 1000 mg/d, was administered for 1 to 10 months in 15 patients with cutaneous LP associated or not with oral lesions and in 25 patients with cutaneous LP. In the first open study, 12% of the patients improved and 12% experienced exacerbation of the disease. In the second study, 86% of the patients had complete disappearance of the lesions after a 3-month delay. Two trials in which the methods were incompletely detailed have been published. The first study included 2 groups of 17 patients each who received either placebo or griseofulvin for 4 to 6 weeks. “Complete regression” was observed in 71% of griseofulvin-treated patients vs 30% of placebo-treated patients, but the definition of a cure was based only on flattening of lesions and reduction of itching. In the second study, 44 patients with cutaneous LP were treated with griseofulvin, 1 g/d, or placebo for 8 weeks. Griseofulvin resulted in “complete improvement” in 82% of patients and partial remission in 18%, whereas partial remission occurred in only 23% of placebo-treated patients. The extension and type of lesions are unknown. The methods used in both studies do not allow definitive conclusions.

Cyclosporine
Oral cyclosporine has been used only in 4 small uncontrolled series and 1 isolated case. In every instance, these patients had severe cutaneous LP resistant to retinoids or systemic corticosteroid therapy. In a total of 21 patients treated, a complete response was obtained with doses ranging from 1 to 6 mg/kg per day, without relapse during several months of follow-up in the majority of the patients. Pruritus disappeared after 1 to 2 weeks of treatment, and clearance of the rash was noted in a mean of 6 weeks, which could be interpreted as a strong argument in favor of cyclosporine efficacy. It seems that low doses (1-2.5 mg/kg) are sufficient to cure or control the disease, since relapses could be controlled by topical corticosteroids only. We found only 1 study evaluating the effects of topical cyclosporine under occlusion in 4 cases of chronic hypertrophic LP. Although the plaque thickness was reduced, none of the treated areas cleared completely, and the effect of occlusion alone was not compared with that of cyclosporine.

Various Drugs
Dapsone, 200 mg/d for 16 weeks, was used in 92 patients with various forms of LP, and this treatment was followed by 65% complete clearance and 19% partial response. This study was not a true open trial, but rather a summary of the experience of these authors in the use of dapsone. No criteria for efficacy were available in this letter. Successful treatment of actinic LP was occasionally reported with the use of hydroxychloroquine sulfate, 200 to 400 mg/d, but often in association with topical corticosteroids. In 1 patient, LP involving the nails was cleared with chloroquine hydrochloride only, but there were no controlled studies that could assess the efficacy of antimalarials. Metronidazole was used in 3 small groups of patients, producing complete clearance in 7 of the 10 patients described. In 1 study of 30 patients with cutaneous LP associated or not with oral lesions, phenytoin, 100 to 300 mg/d, was administered for 8 to 24 weeks. Inclusion and efficacy criteria are lacking, but the authors described 14 patients with complete clearance and 11 with improvement. In 1 case of severe LP and in 1 case of LP associated with pemphigoid, azathioprine plus systemic corticosteroids proved effective, and cyclophosphamide was effective in 3 cases of resistant cutaneous LP. In 2 isolated cases of LP pemphigoid, the lesions were cleared by tetracycline and nicotinamide, and by dapsone in combination with prednisone. In both cases, the treatment was effective in controlling the relapse observed after reduction of dosage. There is 1 anecdotal report of thalidomide efficacy after 12 weeks in a patient with cutaneous LP associated with erosive penile lesions. Since a few cases of LP occurring in patients infected by hepatitis C virus cleared with interferon alfa 2b, 3 patients with generalized LP who were negative for hepatitis C virus received this cytokine. Clearance of all papules was achieved after 10 weeks, and recurrences after dosage reduction were controlled by re-administration of interferon. Finally, in an open study enoxaparin sodium, a low-molecular-weight heparin, proved successful within 4 to 10 weeks in 8 of 10 patients. The itch disappeared within 2 weeks in these patients.

MUCOUS LP
Topical Corticosteroids
Fluocinonide and Fluocinolone. Fluocinonide in an adhesive base, applied 6 times per day for 9 weeks, was compared with its vehicle in 40 patients with oral LP. Thirteen of the 20 treated patients entered complete remission or had a good response, compared with 4 good responses in the placebo group. The efficacy of the corticosteroid was better than that of the excipient on functional signs (15 of 20 complete responses vs 7 of 20). This study included 12 patients with erosive LP, 13 with reticular LP, and 15 with a combination. Four of the patients with erosive LP or the combined form treated with the corticosteroid had no response to treatment. No adverse effects were recorded. Although this controlled study included relatively few patients, the clinical data and the criteria of efficacy are well documented, demonstrating the efficacy of this corticosteroid (level B trial).

Fluocinonide in an adhesive gel used for 6 months resulted in improvement of erosive and atrophic LP in 18 of 20 patients who also received chlorhexidine gluconate mouthwashes and miconazole nitrate gel. The clinical results remained stable in 61% of these patients after a 6-month follow-up. In a review of 214 patients, 22 patients with oral LP received fluocinonide, and all of them had a 50% to 75% reduction of their lesions, but clinical details are not available in this study. The same authors also studied 67 patients with oral LP who were treated with fluocinonide in an adhesive base. Initially, 11 patients participated in a double-blind trial with crossover. A partial response was observed in 5 of them and a complete response in the other 6 treated with the corticosteroid, compared with 1 partial response with placebo. Subsequently, 56 other patients were treated openly;
29 obtained a complete response after 2 weeks of therapy; and some of the patients had relapse but the exact number is impossible to calculate because various oral diseases were mixed in the follow-up study. The type of oral LP was probably erosive, since these patients with LP were mixed together with patients with other “vesiculolerosive” diseases, but clinical data are not available.

The efficacy of 0.1% fluocinolone acetonide was tested against that of 0.1% triamcinolone acetonide (4 applications per day for 4 weeks) to treat oral LP in 40 patients with erosive (18 cases) and atrophic (22 cases) LP. The efficacy was based on the reduction of the surface of lesions. Fluocinolone was found to be more effective, with 13 of 19 patients cured vs 8 of 19 with triamcinolone, but the rate of success in the 2 forms of LP was not detailed. Oral candidiasis was observed in 13 patients, 9 of whom were in the fluocinolone group, which was cured in all cases with topical antifungals. After a 1-year follow-up, only 2 patients in the fluocinolone group remained completely cured. This is the second level B study we found in the treatment of oral LP.

Fluocinolone acetonide 0.05% was also compared with 0.05% clobetasol propionate (in orabase) in 60 patients with “oral vesiculolerosive lesions,” 35 of whom had LP of unknown extent and duration. All patients were mixed together, and specific results of patients with LP are not available. Both medications significantly lessened pain and decreased the size and number of lesions, but clobetasol seemed to reduce pain better. Because the results are not reported in detail, the superiority of clobetasol in LP cannot be definitively concluded.

Betamethasone Valerate. In an open study, 30 patients with oral LP were treated topically 4 times daily, of whom 20 were significantly improved after 1 to 12 months of treatment, but no objective criteria were used in this study. A double-blind clinical study compared betamethasone valerate aerosol, 4 sprays per day for 2 months, with a placebo in 23 patients with oral LP, 18 of whom had erosive lesions. After 2 months of therapy, 8 of 11 patients had a “good or moderate” response (6 of them having erosive LP) vs 2 moderate responses in the placebo group, but these ratings were obtained by means of a subjective, overall evaluation.

Injections of Corticosteroids or Administration Under Occlusion

Anecdotal reports have described the administration of corticosteroids topically by injections within the lesion or under occlusion by flexible soft tray, vaginal prosthetic device, or cloth strips in severe erosive LP of the buccal or vaginal mucosa. In a retrospective analysis, 24 patients were treated with topical corticosteroids by means of cloth strips on the mucosal lesions and an adhesive paste on gingival lesions. All but 1 were improved by repeated applications.

Systemic Corticosteroids

There are no controlled studies that evaluated the efficacy of oral corticosteroids in mucous LP. Systemic corticosteroid therapy seems to be effective against erosive vulvovaginal LP. 10 patients responded favorably after 3 weeks of prednisone (0.5 mg/kg per day), but they had relapses as soon as the dose was lowered to 10 mg/d. In a report on 55 patients with “inflammatory and erosive lesions of the mouth,” prednisone dosages of 10 to 50 mg/d were successfully used; however, no clear conclusions can be drawn from this study because various diseases of unknown diagnosis were mixed. Systemic corticosteroids were associated with topical corticosteroids in oral LP but the superiority of this combination over local or systemic corticosteroid therapy has not been demonstrated. Because oral LP in its erosive form can be highly symptomatic, prednisone, 30 to 80 mg/d, is recommended by many authors. Prednisone, 0.75 mg/kg per day, has also been used in LP of the esophagus. Secondary candidiasis is frequent and relapses are common when the dosage is lowered, but it is believed that benefits outweigh side effects in severe cases. Mouthwashes with prednisolone are also currently used but have not been evaluated by clinical trials.

As noted in cutaneous LP, the efficacy of systemic corticosteroids in mucous LP has not been demonstrated by rigorous trials, and the level of evidence of their efficacy is poor, despite widespread use based on clinical experience. The efficacy of fluocinonide and fluocinolone has been assessed by controlled assays in small groups of patients. Triamcinolone seems to be less effective than fluocinolone. The alternative choices are clobetasol and betamethasone. Topical corticosteroids are considered to be the most useful drugs in oral LP.

RETINOIDS

Five open studies have tested the efficacy of etretinate in 58 cases of oral LP. The initial dosages ranged from 0.6 to 1 mg/kg per day for various durations. A good outcome, difficult to assess because of the lack of precise criteria, was reportedly obtained in 4 of the 5 studies. In a series of 10 patients, the benefits were minimal and were considered to be outweighed by side effects. Only 1 small controlled trial has been published; it was conducted on 28 patients suffering from severe oral LP who were treated with etretinate, 75 mg/d, vs placebo for 2 months, followed by crossover with etretinate in 9 cases. Six of 23 patients treated with etretinate stopped the treatment prematurely because of side effects. This therapy led to improvement (reduction of more than 50% of the erosions and infiltration) in 93% of lesions as opposed to 5% of the lesions in the control group. The majority of lesions were “atrophic and erosive,” but it is unclear whether all patients had erosive lesions. Percentages of patients who had good improvement are not available, and complete cure did not seem to occur. Moreover, 3 months after the end of treatment, 66% of the patients had had relapses.

Oral tretinoin has been administered in 3 open studies at doses ranging from 10 to 60 mg/d. Although favorable results have been reported, the lack of clinical data and detailed criteria of efficacy, the various dosages, and the association with topical tretinoin make it impossible to assess the efficacy of systemic tretinoin. Only anecdotal reports on the efficacy of oral isotretinoin have been published with good

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results in patients whose lesions were resistant to other treatments. In a series of 6 patients, only minimal benefits were reported with isotretinoin.107

Topical retinoic acid has been used in a few open studies lacking details on dosages or clinical evaluation.104,108 Two comparative studies have examined 0.1% retinoic acid vs placebo to treat oral LP.109,110 The majority of erosive and atrophic lesions of 23 nonrandomized patients improved,109 but relapses were common after 3 months, as confirmed by an unpublished experience mentioned in the study.109 The most recent study was randomized and double-blind, comparing 0.1% retinoic acid in 10 patients and the excipient in 10 others.112 All patients with plaquetlike LP lesions. After 4 months of therapy, 9 patients in the tretinoin group had improved or were cured as opposed to 4 in the placebo group. The diminution of the lesions, evaluated in a test area, was 91% in the tretinoin group vs 21% in the placebo group. Unfortunately, the sizes of the groups compared do not allow any definitive conclusions to be drawn. Another randomized double-blind study evaluated topical 0.05% tretinoin vs fluocinonide in 33 patients with atrophic and erosive LP.113 The reduction of severity score was significantly higher with fluocinonide than with topical tretinoin (P = .01). The results according to the clinical form of LP are unclear. Among the 15 patients who received tretinoin, there was only a small decrease in the severity score. It could be hypothesized that the concentration of 0.05% is too low, as previously suggested.94

Isotretinoin gel was administered in 20 patients with mucous LP, 4 of whom had lesions of the penis.112 After 8 weeks, “clinical and symptomatic” improvement was noted in 80% of patients, mainly on nonerosive areas, but a 45% recurrence rate was observed. In a double-blind study, 20 patients with oral LP were randomized to receive either isotretinoin gel or the excipient alone for 2 months; the respective improvements obtained in their severity scores were 90% and 10%.112 After administration of isotretinoin to patients who had initially received the placebo, their scores dropped significantly to reach 90% improvement (P < .05).

The results of a limited trial using the new retinoid fenretinide have been published but allow no conclusions to be drawn, since only 2 patients with oral LP were studied.114 Complete disappearance of local pain and burning sensation was described.

In conclusion, etretinate seems to be effective in reducing the lesions of oral LP. Both 0.1% tretinoin and 0.1% isotretinoin seem to be effective when applied topically to oral LP. All of these findings need further confirmation, since very small groups of patients were examined in the available controlled studies. The efficacy of 0.05% tretinoin is poor. After withdrawal of systemic or topical retinoids, recurrences are common.

**CYCLOSPORINE**

Topical application of cyclosporine on mucous LP was evaluated in multiple, small, uncontrolled trials115-124 that are very difficult to compare because of the highly disparate forms of lichen treated, application modalities practiced (mouthwash, manual administration with local massage), various doses (ranging from 50-1500 mg/d), and excipients. Indeed, no galenical formulation adapted to topical application is currently available. The findings are controversial. Most studies reported favorable results in severe recalcitrant oral LP, mainly erosive LP responsible for severe pain. Nevertheless, poor efficacy was reported in 3 of these studies.119,122,125 A possible efficacy in genital LP, with or without erosion, has been suggested,118,127-129 but 1 case of squamous cell carcinoma arising on the penis during cyclosporine treatment was reported.130 The dose administered probably plays a role because, with the same modality of administration, the favorable outcome obtained with 1500 mg/d was not observed with 600 mg/d. As a consequence, it was postulated that only systemic administration of cyclosporine could generate a beneficial response; however, this hypothesis was refuted by the results of a study that showed that the efficacy of topical applications was not correlated with cyclosporine blood levels.127

Four controlled trials evaluated topical cyclosporine.131-134 The first demonstrated the efficacy of 3 washes per day (1500 mg/d) against symptomatic oral LP in 16 patients.131 Compared with the control group, which received a placebo, erythema (P = .003), reticulated lesions (P = .007), erosions (P = .02), and functional signs (P = .002) were significantly attenuated after 8 weeks of treatment. In a subsequent controlled trial132 that included 13 patients, the same modality of cyclosporine application was compared with triamcinolone paste; no difference between the efficacies of the 2 regimens was noted. The application of an oil-based cyclosporine solution (50 mg 3 times daily) compared with an aqueous 1% triamcinolone acetonide solution in 20 patients133 did not show any difference between the drug efficacies, but it must be emphasized that no statistical analysis of the results was provided. Fourteen patients with erosive oral LP were treated either with 5 mL of cyclosporine (500 mg) or with placebo in different sites.134 After 4 weeks of treatment, there was a significant difference in the rate of healing in favor of cyclosporine, with reduced pain.

In conclusion, topical cyclosporine washes seem to be effective against oral LP, especially the severe erosive forms, but they do not appear to be better than local corticosteroid therapy. The lack of statistical power in these studies limits their contribution, especially in light of the high cost of this drug, which is neither formulated for topical mouth applications nor approved for treating LP.

**ORAL PHOTOCHROMOTHERAPY AND EXTRACORPOREAL PHOTOCHROMOTHERAPY**

Oral PUVA therapy with low-dose UV-A was effective in treating oral LP of various forms (erosive, atrophic, or reticular) in 4 open studies.135-138 A total of 65 patients were treated in these studies, which showed improvement or clinical cure in the majority of cases. After a follow-up of 12 to 24 months, complete remission was observed in only 5 of 17 patients in 1 study.137 This treatment remains experimental, since irradiation was provided by an apparatus designed for light-cured dental fillings. A controlled study of oral PUVA therapy using the same

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irradiation source was conducted on 18 patients with erosive or ulcerative oral LP after ingestion of psoralen (0.6 mg/kg) and randomized unilateral irradiation. The end point of the trial was the comparison in the same patient of the unilateral treated side vs the nontreated other side used as a control. After 12 sessions (total dose, 16.5 J/cm²), the treated side showed marked or slight improvement in 13 patients and the control side improved in 6 patients. Side effects, mainly nausea, were related to oral ingestion of psoralen.

A series of 7 patients with severe resistant erosive oral LP were treated successfully with extracorporeal photochemotherapy, a method usually applied to patients with cutaneous T-cell lymphomas. Complete remission of erosive lesions was obtained in all patients.

**VARIOUS DRUGS**

Griseofulvin was of little benefit in 2 groups of 7 and 23 patients with various forms of oral LP treated openly. but 3 cases of severe erosive LP with dramatic response to 1 g/d for 8 to 10 weeks were described. Dapsone proved effective in 2 isolated cases of recalcitrant erosive oral LP. Among a small group of 10 patients with erosive and reticular oral LP, 9 had an excellent response after 1 to 2 months of hydroxychloroquine, and 3 of the 6 who had erosions achieved healing. In 1 case, LP of the lower lip was improved after treatment with chloroquine phosphate for 3 months. Thalidomide was administered in 2 patients with erosive oral LP and produced major reduction or complete healing, without recurrence after 15 and 36 months of follow-up. Six patients with oral LP were treated with levallosole hydrochloride, but it is not known whether the patients improved. Levamisole hydrochloride, 150 mg/d, was also given with prednisolone, 15 mg/d, for 3 days each week in 23 patients with recalcitrant oral LP. Pain relief and healing of erosions were noted in all patients after 4 to 6 weeks, and they remained lesion free 6 months after withdrawal of the drugs. This combination was not tested against prednisolone alone, and the interest in levamisole therefore remains speculative.

**COMMENT**

The Table, which summarizes the main published results, shows that we did not find any level A trial in the medical literature examining the efficacy of the various drugs or physical treatments of LP. There are only 3 trials with satisfactory methods including more than 20 patients in each group. The remainder of the published trials are controlled trials with imprecise methods or extremely small populations, uncontrolled studies, or observational series that are not always prospective. Therefore, critical analysis of the literature is disappointing. Most reports include favorable responses to the studied treatment, suggesting possible publication bias in the reports. Finally, it is extremely difficult to compare all the studies, because different criteria were used to define a cure or attenuation. Rigorous evaluation of efficacy is often lacking, since efficacy criteria were mainly based on imprecise global evaluation. Many studies lack precise clinical data, especially the type and extent of lesions and the duration of disease before inclusion. There are no studies using quality-of-life scales, despite the extremely severe pain often present in oral LP. Meta-analysis is therefore impossible in the field of LP therapy.

Taking into consideration only the controlled studies, an attempt can be made to set forth therapeutic indications, using evidence-based medicine analysis.

**CUTANEOUS LP**

The first-line therapy in cutaneous LP is acitretin. All other methods or drugs are of uncertain efficacy. Based on clinical experience worldwide, systemic corticosteroid therapy is recommended by many authors and could be classified as second-line treatment in cutaneous LP. All other treatments, mainly PUVA therapy and griseofulvin, should be evaluated by rigorous controlled trials before being recommended in an evidence-based medicine review.

**ORAL LP**

The first-line therapy in oral LP is topical corticosteroid therapy. No treatment has demonstrated convincingly its superiority over topical corticosteroids. This first-line choice is accepted in most reviews. The second-line therapy in plaquelike LP should be topical retinoids or etretinate, but strong evidence of efficacy is lacking. All others are unapproved treatments, of uncertain or doubtful efficacy. The use of topical cyclosporine could...
be recommended as third-line therapy in severe multiply drug-resistant cases.

Finally, this review shows the lack of clear-cut results in the treatment of LP, even for those drugs considered to be classical standards. For future studies, oral and cutaneous LP should clearly be separated, since the modalities of clinical evaluation and treatment are different. The duration of disease before inclusion, the type of lesion, and the involved body surface should be detailed. The major criteria for efficacy should be based on objective criteria, and global evaluation should be considered only as accessory criteria. Erosive and reticulate mucous membrane LP must be separated and research concerning adapted topical treatments continued. The new promising treatments, such as topical cyclosporine, extracorporeal photochemotherapy, or even retinoids plus PUVA therapy should be tested in large controlled trials. Quality-of-life studies could be helpful in the evaluation of oral LP therapy. Finally, European-US cooperation is warranted to perform large randomized controlled trials in cutaneous and mucosal LP to improve the treatment of these patients.

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