Lichen Planus

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Key Points

- Lichen planus (LP) is an acquired chronic disease characterized by small cutaneous papules and mucosal striae affecting 0.3–0.8 % of the population.
- Topical treatments are usually employed on limited lesions, especially the oral ones. The most useful medications are corticosteroids and tacrolimus.
- Systemic treatments are rarely needed. Oral cyclosporine is probably the most active.
- Biologics are interesting but only exceptionally needed.

Definition and Epidemiology

Lichen planus (LP) is an acquired chronic disease characterized by small cutaneous papules and mucosal striae. It affects 0.3–0.8 % of the population, occurring in all races and both genders. Children are rarely affected.

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Basic Concepts of Pathogenesis

LP is a specific pattern of cell-mediated cutaneous hypersensitivity to a variety of antigens expressed on keratinocytes (possibly on other epitheliocytes as well), which are the target of CD8 lymphotoxicity. Antigens may be viruses (hepatitis C and hepatitis B virus in the Mediterranean countries, the USA, and Japan), drugs, and contact antigens. LP may associate with visceral diseases, in particular chronic active hepatitis, primary biliary cirrhosis (in the UK), and ulcerative colitis and with other autoimmune disorders of the same cell-mediated nature, like alopecia areata.

Clinical Presentation

Lesions are small violet, polygonal papules, which coalesce into larger papules and plaques. On their surface, a whitish reticulum can be observed. On the skin, a typical site is the volar aspect of the wrist, but widespread lesions are not uncommon. Mucosae are often involved, usually by the whitish reticulum, more rarely by erosions (Figs. 53.1 and 53.2). Nail plates may be dystrophic. Clinical features vary according to the body region. On the shins, LP is verrucous, while on the scalp it presents as a scarring alopecia plaque. Unusual varieties include:

- Annular LP of the scrotum
- Ulcerative form of the sole
- Lichen planopilaris

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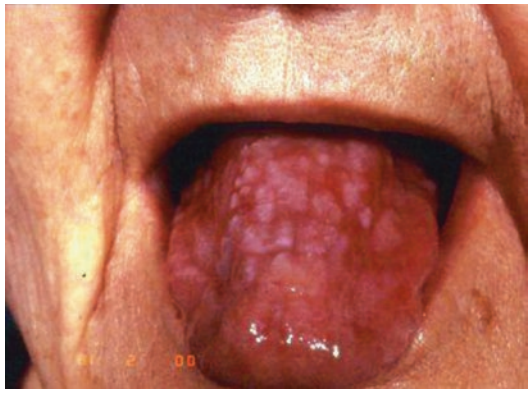

Fig. 53.1 Nonerosive oral lichen planus. Note the whitish irregular plaques on the dorsal surface of the tongue

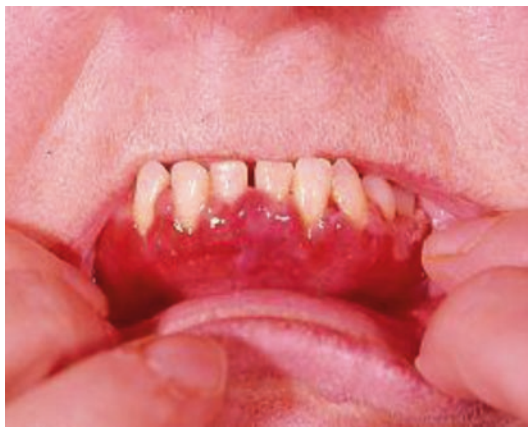

Fig. 53.2 Erosive oral lichen planus. Gums are intensely erythematous and deepithelialized

- Vesicobullous lichen
- Pigmentary forms (lichen actinicus, lichen pigmentosus)

The course is chronic, accompanied by pruritus of varying severity. Mucosal erosion may result in squamous cell carcinoma.

Diagnosis

Diagnosis is mainly clinical. Histopathology may help in doubtful cases but is mandatory in erosive forms. It reveals a typical mononuclear infiltrate (CD4-positive initially then CD8-positive), which impinges the keratinocyte basal line, disorganizing the epidermal architecture. Immunofluorescence shows an IgM deposit at the dermoepidermal junction.

Differential Diagnosis

- Lichenoid drug eruptions: they show parakeratosis and eosinophils in the infiltrate.
- Lupus erythematosus: a lupus band in direct immunofluorescence is distinctive, but there may be overlapping cases.
- Secondary syphilis: lymph nodes are constantly involved and serology is distinctive.
- Psoriasis: there are parakeratotic scales and a typical histopathology.
- Leukoplakia: often asymmetrical, with a rough velvet surface and dysplasias on histopathology.
- Candidiasis: whitish patches are easily removed; there is a severe immunodeficiency.
- Erythema multiforme: skin lesions are target-like and histopathology is distinctive.
- Bullous diseases: histopathology and direct immunofluorescence are distinctive.

General Principles of Treatment

Usually, LP is a chronic but benign and often symptomless disease, which does not require systemic treatment. As an immune disease, LP responds to all immunosuppressants. Those should be used only if a severe visceral involvement is documented or whenever the mucosal erosions prevent eating and speaking.

Topical Treatments

A number of medications have been tried and recommended. They are summarized in Table 53.1.

Topical Corticosteroids

Corticosteroids are in most cases the treatment of choice, but there is no convincing evidence of their efficacy in the literature (Cribier et al. 1998). Class I and II corticosteroids should preferably

Table 53.1 Treatments

Corticosteroids	Retinoids	Calcineurin inhibitors	Physical	Others
Triamcinolone acetonide	Tretinoin	CyA A	Laser therapy	Aloe vera
Fluocinolone acetonide	Tazarotene	Pimecrolimus	Photodynamic therapy	Hyaluronic acid
Fluocinonide	Isotretinon	Tacrolimus		Calcipotriol
Clobetasol proprionate	Fenretinide	Sirolimus		Mesalazine
Fluticasone proprionate				Thalidomide
Betamethasone phosphate				Amlexanox
Mometasone furoate				Tetracycline
				Herbal medicines
				Extracorporeal photochemotherapy

be employed. Occlusive dressings with class I drugs are recommended on verrucous plaques. Intralesional preparations have been advocated, but they should be used only in very resistant verrucous plaques. They have been useful in pitted nails, but discomfort discourages the patients. In any case, injectable triamcinolone, properly diluted, is preferable (5–0 mg per mL injection and 0.5–1 mL per 2 cm lesion). On lichen planopilaris of the scalp, corticosteroids may be more useful at the periphery of the plaque rather in its center, which is usually scarring. Foamy preparations of betamethasone or clobetasol are useful in this particular location.

Oral mucosal lesions (OLP) occur in 50–70 % of the patients with LP, affecting 2 % of the population with the highest incidence in women (2:1), in the age range from 40 to 70 years. It is understandable therefore that most of the literature is devoted to oral lesions rather than to other locations. Topical steroids are still the widely accepted first-line therapy for erosive OLP. A recent Cochrane collaboration systematic review found, however, only weak evidence for their effectiveness (Thongprasom et al. 2011). The lack of good-quality well-conducted trials and the small number of participants prevented good evidence to be obtained. In any case, none of the studies involved genital or oesophageal disease.

Several side effects are reported. With topical corticosteroids, the main side effects are oral candidiasis and dyspepsia, but even a severe neuropsychiatric disorder has been reported due to the exceeding absorption of clobetasol through the oral mucosa. Fluticasone propionate spray caused nausea, swollen mouth, bad taste and smell, dry mouth, and a sore throat in a small proportion of participants.

Anecdotal reports describe the efficacy of the injections of triamcinolone within the lesion of OLP. In a study of 11 patients with lichen of the nail plate (Abell 1973), 5 mg/mL were injected in the posterior nail fold at intervals of 2–4 weeks. Seven of them greatly improved, but eight experienced relapses after about 1 year.

Retinoids

A recent literature review (Petruzzi et al. 2013) of data on topical retinoids in patients with OLP found 16 studies with 280 patients topically treated with different classes of retinoids. Isotretinoin 0.1 % gel is the most frequently employed one, but tretinoin (0.025 %), tazarotene, and fenretinide have been also tried.

In a double-blind study, ten patients with biopsy-proven OLP were treated for 4 months with 0.1 % isotretinoin gel and another ten patients with placebo. All patients treated with isotretinoin showed a significant improvement of the oral lesions, whereas in the placebo group, the size of the lesions remained the same (Piattelli et al. 2007). The best concentration has been also studied in 70 OLP patients who were randomly divided into two groups with 0.05 and 0.18 % drug concentrations. None of the cases of reticular LP improved, while in 26 patients with the

atrophic-erosive forms (at 0.18 % concentration) and in nine patients (at 0.05 % concentration), the erosions or ulcers disappeared both clinically and histologically. The disappearance of dysplastic phenomena was observed at 0.18 % concentration. Topical application of the drug was accompanied by a transitory increase in soreness and pain, as well as greater sensitivity to hot foods. The presence of dysplastic features, however, raises some doubts on the correct diagnosis (Scardina et al. 2006).

Tretinoin in an oral base 0.05 % was compared in a randomized controlled study with fluocinolone acetonide 0.1 % in the treatment of atrophic and erosive OLP. Of 33 patients, 18 improved with fluocinolone acetonide, whereas 15 patients receiving topical retinoic acid showed little change. The difference was significant. In a randomized, placebo-controlled study, 12 patients with OLP were randomly treated with tazarotene gel 0.1 % b.i.d. or with placebo for eight consecutive weeks. The tazarotene group had their lesions significantly reduced as compared with the control group (Petruzzi et al. 2002).

Fenretinide was used in a small heterogeneous study (eight patients) and two of them had complete remission after 1 month.

Cyclosporin A

Four controlled trials evaluated topical CyA (Eisen et al. 1990; Sieg et al. 1995; Lopez Lopez and Rosello Llabrés 1995; Harpenau et al. 1995). Three washes per day (1,500 mg/day) proved beneficial in 16 OLP patients. In another trial, no difference between CyA and triamcinolone paste was noted in 13 patients. Likewise, there was no difference in comparing an oil-based CyA solution (50 mg three times daily) with an aqueous 1 % triamcinolone acetonide solution in 20 patients. A significant difference was instead found when 14 patients with erosive OLP treated with 5 mL of CyA (500 mg) were compared with placebo after 4 weeks of treatment.

Multiple, small, uncontrolled trials studied topical CyA on OLP, while only one evaluated its effect under occlusion in chronic hypertrophic LP. The different forms of OLP, the different modalities of application (mouthwash, manual administration with local massage), the different doses (50–1,500 mg/day), and vehicles all bias the results. Those are favorable in most studies, although poor efficacy was also reported in three. Also genital LP seems to benefit from topical CyA, but a case of squamous cell carcinoma was registered during treatment. Efficacy seems to be dose dependent (1,550 mg/day), but not blood level dependent. CyA A solution significantly reduced pain in erosive OLP over 0.1 % triamcinolone acetonide in orabase; the study, however, was very small (11 patients). A significant difference was seen in favor of the 1.5 % CyA gel compared to 0.025 % clobetasol propionate gel. However, seven patients with long-standing atrophic/erosive OLP were treated for 4 weeks with CyA A as a mouthwash. At the end of the 3-month follow-up period, no improvement was recorded. In any case, the evidence to support the contention that topical cyclosporine reduces pain and clinical signs of oral lichen planus has been defined as weak and unreliable (Le Cleach and Chosidow 2012).

Calcineurin Inhibitors

A recent systematic review for calcineurin inhibitors examined 5 double-blind studies, 1 investigator-blinded study, 10 open prospective studies, 6 retrospective studies, and 28 case reports (Cheng et al. 2012).

Strong evidence (double-blind and open studies) (level A) has been found for tacrolimus ointment in OLP, with efficacy at least equal to topical clobetasol propionate 0.05 % ointment. Blood levels of tacrolimus are demonstrable but without clinically significant adverse events. Strong evidence (level A) has been also found for pimecrolimus 1 % cream with efficacy equal to that of topical triamcinolone acetonide 0.1 % paste. For vulvovaginal LP, pimecrolimus was superior to placebo in one double-blind study but less active than clobetasol (Goldstein et al. 2011). Only case reports support the efficacy of topical calcineurin inhibitors in cutaneous LP.

Topical rapamycin (1 mg/ml) was studied in an open prospective study involving seven women with oral and vulvar erosive lesions twice a day for 3 months. Complete remission was obtained in four women. Only one had stopped treatment due to local discomfort. Only one woman had detectable blood sirolimus level (Soria et al. 2009).

Other Topical Preparations

Calcipotriol

Eighteen LP patients applied calcipotriol ointment twice daily. Of the 16 patients that completed the study, 5 obtained complete clearing of the lesions, while 4 had partial improvement. No improvement was observed in seven. In a randomized open-label trial, 15 LP patients were given calcipotriol 50 μg/g and 16 betamethasone 0.1 % ointment twice daily for 12 weeks. Calcipotriol was no more effective than betamethasone (Theng et al. 2004).

Mesalazine

Mesalazine (5-aminosalicylic acid) 5 % was compared with clobetasol propionate 0.05 % in 25 patients with OLP. Both preparations were active without statistical difference. Mesalazine resulted in total remission in 57 % of patients. Only 9 % of patients had no benefit (Sardella et al. 1998).

Thalidomide

In a randomized double-blind, positive-control trial, 24 patients received thalidomide 1 % paste vs. dexamethasone 0.043 % paste of controls. After 1 month of treatment, 66.7 % of thalidomide patients had fully healed. The erosive area size and the Visual Analogue Scale scores were similar between groups. Only two patients in each group experienced discomfort with treatment (Wu et al. 2010).

Amlexanox

Amlexanox is an anti-inflammatory drug which selectively inhibits TBK1 and IKK-ε. It has been studied in a randomized, positive-controlled clinical trial in which 20 patients with erosive OLP received amlexanox paste and 18 dexamethasone paste. After 7 days of treatment, both groups showed significant reduction in erosive area. None of the patients had severe adverse reactions (Fu et al.2012).

Aloe Vera

Aloe vera gel was tried in a randomized, double-blind study involving 40 patients with OLP (18 erosive, 14 atrophic). After 8 weeks of therapy, aloe vera gel proved more effective than triamcinolone acetonide (Choonhakarn et al. 2010). In another double-blind, placebo-controlled trial, 27 patients with OLP applied *Aloe vera* twice daily for 8 weeks. Lesions disappeared in two patients treated with *Aloe vera* vs. none of the placebo group.

Hyaluronic Acid

In a blinded parallel-group randomized clinical trial (Woo 1985), a local hyaluronic acid preparation (0.2 %) was evaluated in 120 patients with erosive OLP four to five times daily for 28 days. In patients treated with hyaluronic acid, a decrease of pain for up to 4 h post application and a reduction of ulcerative areas were registered (Nolan et al. 2009).

Tetracycline

A 78-year-old woman with erosive OLP gargled a 0.25 % tetracycline solution three times a day. Within a week there was a considerable relief from pain, and after 6 weeks the erosions had disappeared.

Herbal Medicines

Zheng et al. investigated the concomitant administration of the Chinese herb *Liuwei Dihuang* and retinoic acid cream in 43 patients with OLP with more effective results than retinoic acid cream alone, particularly in patients with a shorter history of lichen. Lichen pemphigoides, however, has been reported to occur after Chinese herb medication.

Physical Treatments

Laser Therapy

A diode laser (940 nm) was also successfully used to relieve symptoms in a single case of LP.

The excimer laser 308 nm UVB was used in 8 patients with OLP with 9–32 applications and fluency 75–175 mJ/cm^2. Six patients improved, with

complete remission in two. One patient relapsed after 4 weeks (Köllner et al. 2003). Also Trehan and Taylor (2004) successfully managed nine patients with the excimer laser therapy (initial fluencies 100 mJ/cm^2). Unsatisfactory results have been instead reported in four patients treated with the 308 nm excimer laser twice a week for 12 sessions. The lowest dose was 50 mJ/cm^2, increased by 50 mJ/cm^2 every two sessions up to 200 mJ/cm^2. Only one patient showed positive results.

A total of 82 lesions of OLP of 30 patients were treated in an open study (Cafaro et al. 2013) with low-level laser therapy delivered with a 980 nm gallium-aluminum arsenide diode laser. Eighteen patients (60 %) obtained a total resolution of the clinical signs, ten patients (33.3 %) a partial resolution, and two patients (6.6 %) did not respond at all. In another study, low-level laser therapy proved as effective as topical corticosteroid therapy without any adverse effects.

The CO2 laser was investigated in 39 superficial OLP lesions (1.5–2.0 J/mm^2). During a mean follow-up period of 8 years, 24 lesions showed no more signs of pain or burning sensation. In all patients, the treatment led to complete epithelialization in 3 weeks (Van der Hem et al. 2008).

Photodynamic Therapy

Twenty-three patients with OLP were submitted to photodynamic therapy performed using a semiconductor laser, with power up to 300 mW and a wavelength of 660 nm. After treatment, improvement was observed in 39 sites, including 14 with complete regression. The reduction in the size of lesions was statistically significant in both genders and in smokers and nonsmokers. On the gums and tongue, the effect was slighter and not statistically significant.

Extracorporeal Photochemotherapy

Extracorporeal photochemotherapy (ECP) or photopheresis efficacy has been studied in four patients with erosive OLP. All patients improved their symptoms and lesions after seven to nine cycles. Guyot et al. (2007) submitted 20 patients with erosive OLP to ECP twice weekly for 3 weeks while the following sessions were planned according to clinical improvement. All patients reported clinical improvements. In another study ECP has been used successfully in the treatment of two patients with erosive OLP and cortico-resistant LP.

The Problem of Carcinogenicity of Calcineurin Inhibitors

Approximately 1–5 % of oral LP lesions will develop squamous cell carcinoma (SCC) of the mouth. Also about 1–3 % of vulval LP lesions develop into SCC and a small, but unknown, percentage of penile LP lesions transform into SCC. High-risk factors include smoking, excessive alcohol ingestion, erosive or atrophic clinical types, presence of erythroplakic lesions (reddened patches with a velvety surface found in the mouth), and sites involving the tongue, gingival, or buccal mucosa. No risk factors are known for progression of vulval LP into SCC. In a 7-year prospective study on 327 OLP patients, 8 patients developed an SCC in OLP areas (0.36 %/year) during a mean follow-up of 81.7 months, especially in women.

In 2006, the Food and Drug Administration warned about the potential cancer risk with topical calcineurin inhibitors tacrolimus and pimecrolimus. The reasons were an animal study indicating a risk for malignant transformation and lack of long-term studies on the safety of tacrolimus in treatment of atopic dermatitis. The advice to physicians was to use tacrolimus only as a second-line agent for short-term and intermittent treatment. The European Medicines Agency followed the same strategy.

Such strategy raised a discussion in which the reliability of the OLP diagnosis and whether the lesion would have become malignant even without tacrolimus were debated.

As Eisemberg (2000) put it, often "the microscopy not only fails to confirm the given diagnoses of antecedent OLP, but also it depicts previously unappreciated maturation abnormalities that augur malignant potential." In other words, "if the reported carcinomas evolved from atypical or dysplastic lesions that were confused with OLP at outset, the

case for malignant degeneration in OLP is decidedly undermined." I came recently across a case in which a patient was treated for OLP on the basis of a microscopic description and developed SCC. Further histological sections demonstrated that the original "OLP" was in fact already SCC. The asymmetry of the clinical lesions is against OLP diagnosis as they are the presence of dysplasia and the absence of persistent reticular striations in the periphery. As for the second point, the problem is whether or not tacrolimus may enhance SCC risk. Fleischer (2006) emphasized that not a single SCC case has been found in data from randomized control studies and that the risk is smaller than with use of topical steroids. In fact, topical steroids, which are usually recommended in OLP, are not free from risk of cancer (about 5 % in lichen sclerosus), and the incidence of lymphomas in the general population is far higher than in patients treated with topical tacrolimus. In conclusion, OLP, especially in its erosive variety, compromises the quality of life of the patient and even prevents any social activity (pain, severe dysphagia, fetid breath) demanding a treatment. Calcineurin inhibitors could be regarded at least as safe as topical steroids.

Systemic Treatments

Rarely LP requires systemic treatment. In the office patients, lesions are usually limited in size and spread; pruritus is hardly a real problem and the quality of life is commonly preserved. That is probably the reason why large controlled studies are scarce in the literature. Nonetheless, a number of systemic drugs have been proposed (Fig. 53.3).

Corticosteroids

Corticosteroids are the treatment of choice for most dermatologists, but surprisingly enough until recently, there were no double-blind placebo-controlled randomized studies to support such a practice. Two large studies have been recently conducted. In the first study by Kelett and Ead (1990), 38 patients received either prednisolone (30 mg/day) or placebo for 10 days. After 2 years, LP cleared in 18 weeks with prednisolone and, surprisingly, also in 29 weeks with placebo. Only three failed to clear with placebo. Probably because the treatment was stopped without tapering, severe relapses occurred. In the second study (Pitche et al. 2007), 73 patients with generalized cutaneous LP received three injections of betamethasone every 2 weeks. At 6 weeks, 84 % cleared and 8 % partially remitted. The failure rate was of 8.2 %. At 6 months, the relapse rate was 31.5 %. No major side effects were reported.

Cyclosporin A

Being specifically aimed at cell-mediated hypersensitivity reactions, systemic CyA is expected to be the drug of choice on severe cutaneous LP. It may be surprising therefore that only four small uncontrolled series and one anecdotal case are available. In a total of 21 patients treated with 1–6 mg/kg/day, the lesions cleared in a mean of 6 weeks. No relapse were noted after several months of follow-up in most patients. Lower doses 1–2.5 mg/kg/day proved to be equally effective.

Azathioprine

Azathioprine (50–100 mg/day) may be used in erosive OLP with chronic active hepatitis. Usually, transaminase level and oral lesions improve simultaneously. If the patient is hepatitis C virus positive, however, immunosuppressive treatments should be avoided to prevent hepatocarcinoma to develop. In any case, favorable therapeutic effects for LP found in the literature reach only a low quality of evidence (level C).

Thalidomide and Analogues

Oral administration of thalidomide seems to be effective in two short series and in anecdotal reports. Moura et al. (2009) treated eight patients with cutaneous LP with 100 mg/day. Five (62.5 %)

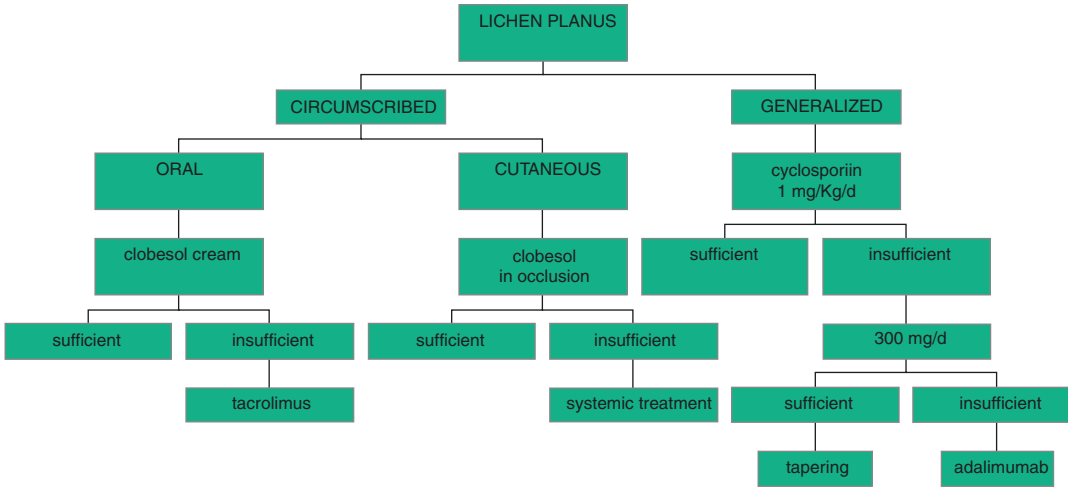

Fig. 53.3 Therapeutic algorithm

patients completed the trial. Three withdrew mainly due to neuropathy affecting the legs and weakness after the first days of treatment. These symptoms spontaneously regressed within days after treatment was stopped. Mean time for complete remission was 3 months. No recurrences were seen at follow-up 1 and 6 months after the end of treatment.

Macario-Barrel et al. (2003) used thalidomide in six patients with severe erosive OLP resistant to oral corticosteroids. They started at 50–100 mg/day to taper to the minimal effective dose. Complete healing of erosive lesions was observed in four patients after a mean duration of 4 months.

Perez reported a patient with generalized LP who, after treatment with thalidomide (initial doses 300 mg/day for 2 weeks and 200 mg/day for further 10 weeks), had his lesions cleared. Naafs and Faber (1985) treated one patient with oral LP in whom clearance was achieved. Another patient with generalized LP failed.

Dereure et al. (1996) treated two patients with severe erosive OLP with 150 mg thalidomide per day with impressive improvement in 4 months in the first case and with nearly complete healing in 3 months in the second. Tapering to 50 mg did not cause relapse. Side effects were minimal, except a mild reduction of T lymphocytes in the first case. Camisa and Popovsky (2000) used thalidomide in a patient with mild OLP at a starting dosage of 50 mg/day for 2 weeks and gradually increased the dosage over 3 months to 200 mg/day. Improvement was noted after 4 months. At the 11th month, the desquamative gingivitis and striae were nearly cleared. Dizziness, edema of the lower extremities, and a mild rash of the face and trunk recommended decrease to 100 mg/day.

Hydroxychloroquine

Although well known to include LP as adverse effect, hydroxychloroquine has been used in OLP at 200–400 mg/day for 6 months as a monotherapy in ten patients. Nine had an excellent response to therapy. Erosions required 3–6 months to clear. There were no adverse effects.

A 9-year-old girl with actinic LP was treated with hydroxychloroquine 200 mg daily for 3 months with complete and no relapse in the following years. The study was biased by the addition with 0.1 % methylprednisolone aceponate ointment for 2 weeks and with photoprotective measures (Ramírez et al. 2012).

A retrospective review by Chiang et al. (2010) of 40 patients with lichen planopilaris (or frontal fibrosing alopecia) who had been treated with hydroxychloroquine for up to 12 months found that after 6 months, 69 % had reduced symptoms and signs, a percentage that rose to 83 % at 12 months.

Retinal adverse effects should be considered, however, as they are often unpredictable and should be thoroughly monitored.

Retinoids

Etretinate provides more side effects than benefits. Five open studies have tested the efficacy of etretinate 0.6–1 mg/kg per day in 58 cases of oral LP (Miyagaki et al. 2013). Results were good in four of the five studies. In a series of ten patients, the benefits were minimal. In the only small controlled trial, 28 patients with OLP were treated with 75 mg/day etretinate vs. placebo for 2 months followed by crossover with etretinate in nine cases. Six stopped the treatment prematurely because of side effects. This therapy improved 93 % of lesions vs. 5 % of control lesions in the control group. Relapses occurred, 3 months after the end of treatment, in 66 % of cases.

In addition, scattered anecdotal reports can be found. A 68-year-old woman with oral and cutaneous LP and thymoma underwent thymectomy. Cutaneous LP lesions subsided spontaneously while oral lesions did not. Oral lesions responded well to oral etretinate therapy. No information on dosage are provided (Miyagaki et al. 2013). Another Japanese woman with ulcerative LP of the sole and Sjogren syndrome was treated with etretinate 30 mg/day for 2 months with nearly resolution of the ulcer (Tsuboi and Katsuoka 2007).

Oral tretinoin has been studied by three open studies. Doses ranged from 10 to 60 mg/day (Ott et al. 1996). Favorable results have been reported, but clinical data and criteria of efficacy are scantily mentioned; dosages are diverse, and topical tretinoin has been added, all biasing the assessment of tretinoin efficacy.

Oral isotretinoin has been reported anecdotally (Handler 1984), and in two small series, the dosage was 0.5 mg/kg/day and was effective in two cases. Benefits were minimal in the series of six patients.

Systemic therapy with acitretin 25 mg daily should be considered for patients with severe refractory LP. In the only placebo-controlled double-blind trial published so far, 65 patients with cutaneous LP were treated with 30 mg/day acitretin for 8 weeks. Sixty-four percent of them significantly improved vs. 13 % of controls. Clearance was doubtful, however, as papules persisted in most patients as one figure clearly shows. The trial had some defects as neither criteria for remission and improvement were detailed nor the duration and the extent of the lesions. Six of eight patients with LP treated with 50 mg/day acitretin for 8 weeks had a dramatic improvement, as did a boy with exanthematous LP (Brockowet al. 1997). A case of refractory hypertrophic LP, reported by Jaime et al. (2011), was treated with acitretin 40 mg/day and achieved total resolution on the upper limbs and partial resolution on the lower limbs after 9 months of therapy.

Because of the systemic side effects, acitretin has been replaced by oral alitretinoin. In one anecdotal report, a patient was treated with 30 mg/day with good results within 4 weeks. No severe side effects were registered, but oral striae and dysphagia recurred during treatment and LP relapsed after 4 months (Kolios et al. 2013).

Recently, some reports of recalcitrant lichen planus successfully treated with alitretinoin have been published (Kolios et al. 2013; Brehmer et al. 2011).

Temarotene obtained complete or nearly complete remission after 2–3 months in 10/13 patients. Dosage was 800–4,800 ng for between 31 and 441 days. Nausea and vomiting, with a transient increase of transaminase blood levels, afflicted six patients (Bollag and Ott 1989).

Dapsone

Dapsone (50–150 mg/day) proved to be more effective than topical corticosteroids in a prospective trial with 75 patients and in 2 isolated cases of recalcitrant erosive oral LP (Chopra et al. 1999). Attention should be paid to older patients for dapsone systemic side effects (hemolysis, methemoglobinemia). Its use is recommended in children and in bullous cases.

Methotrexate (MTX)

Only small retrospective series are available in the literature. Eleven patients with generalized

LP were treated with MTX 15–20 mg/week. Mucocutaneous lesions and pruritus improved within the first month in all patients, and complete response was achieved in ten patients at the end of the first month. Only one patient discontinued MTX because of intolerable adverse effects (nausea and fatigue) at the fourth week (Turan et al. 2009).

Adverse effects are in fact common, but they have been found only mild in a double-blind controlled study (Hazra et al. 2013) on 44 patients with LP treated with MTX (10 mg) (23 patients) or mini-pulse betamethasone (5 mg) (21 patients). Anemia (14.2 %), edema (57.1 %), dyspepsia 15 (71.4 %), acne 10 (47.6 %), mooning face 8 (38.1 %), striae 8 (38.1 %), menstrual abnormality (71.4 %), and hypertrichosis 4 (19.0 %) developed only with betamethasone. Intermittent diarrhea, headache, nausea, and fatigue were complained with both drugs but more often with betamethasone. Abnormality in platelet count and SGPT were registered only with MTX.

Tetracycline

In an open-label clinical trial, 15 patients with LP were treated with tetracycline 500 mg or doxycycline 100 mg, both twice daily. Of the 13 subjects who completed the study, 6 (46 %) reported no response to either doxycycline or tetracycline, 6 (46 %) a partial response, while only 1 experienced a complete remission in a mean treatment period for responders which was 3.6 months (range 1–6) (Hantash and Kanzler 2007).

An anecdotal report of a woman with lichen pemphigoides suggested the efficacy of doxycycline 200 mg/day and nicotinamide 1,500 mg/day, though the therapy included also intralesional triamcinolone.

Griseofulvin

Griseofulvin was largely studied in the past though no definitive conclusions were allowed. Griseofulvin, 1,000 mg/day, was given for 1–10 months in 15 patients with cutaneous LP and in 25 patients with cutaneous LP (Levy et al. 1986). 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. A study included two groups of 17 patients receiving either placebo or griseofulvin for 4–6 weeks. A partial regression was observed in 71 % of griseofulvin-treated patients vs. 30 % of controls. In the second study, 44 patients with cutaneous LP were treated with griseofulvin, 1 g/day 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. A case of intensely pruritic acute eruptive LP in a 51-year-old male failed to respond to griseofulvin, and of seven OLP cases treated with 500 mg/day griseofulvin for more than 2 months, none improved and four worsened.

Levamisole

Levamisole hydrochloride has been tried in two studies, but in one it is not known whether the patients improved and in another it was associated with prednisolone (Lu et al. 1995).

Curcuminoids

Curcuminoids (diferuloylmethane) are components of turmeric (*Curcuma longa*) that has anti-inflammatory properties and has been used in Indian traditional medicine for centuries. A randomized, double-blind, placebo-controlled clinical trial on 20 OLP patients compared 6,000 mg/day curcuminoids in three divided doses to placebo. The curcuminoids group showed a greater and significant reduction in erythema and total modified Oral Mucositis Index score and proportion showing improvement in the numerical rating scale of OLP signs and symptoms and total Modified Oral Mucositis Index score. Adverse effects were uncommon in both groups (Chainani-Wu et al. 2012).

Metronidazole

As LP is a standard Th1 cell-mediated reaction to a variety of antigens, it is of no surprise that cutaneous and oral lesions improved as the results of treatment of intestinal giardiasis with oral metronidazole. In an open-label trial (Rasi et al. 2010), 49 LP patients were given metronidazole, 750 mg/day. Forty-one percent of lesions fully cleared, 33 % had partial healing, and 26 % did not improve. In mucosal lesion, the overall response was 67 %. In another open study, 19 LP patients were treated with 1 g metronidazole for 20–60 days and were followed up for a period of 5–36 months. Complete response was observed in 13 patients. Lesions worsened in 1 of the 4 nonresponders.

Itraconazole

A prospective, open-label study of itraconazole 400 mg/day for 1 week of each month for 3 months in 16 patients with severe LP reported complete cessation of new lesions in 77.7 %, complete relief of pruritus in 55 %, and complete flattening of lesions in 33 %. The mechanism of action is believed to be due to the immunomodulatory effects of itraconazole (Khandpur et al. 2009).

Fumarate

In a retrospective study, two of three LP patients showed complete clearance of their lesions after being treated with fumarate (max three tablets a day for 8 months). In one case, side effect led to discontinuation.

Biologics

As the serum levels of TNF-alpha is higher in LP patients, some TNF-alpha inhibitors have been tried in particularly severe LP patients. Results are in general encouraging, although some relapses and even a rebound effect have been registered at the drug withdrawal (Table 53.2). Another apparent contradiction rests on the fairly frequent occurrence of LP as side effects of TNF-alpha inhibitors used for other reasons. Less understandable is why B-cell inhibitors like rituximab and mycophenolate mofetil can work in a Th1-mediated disease as LP. In any case, biologics should be used only as ultima ratio when all other therapies have failed or cannot be used.

UV Phototherapy

Narrowband UVB

Twenty patients with disseminated LP were included in a retrospective study treated with narrowband UVB thrice a week according to the standard protocol for psoriasis. Complete response was obtained in 11 patients and partial response in 4 after 3 months, with an accumulated dose of UVB of 36 ± 4.8 J/cm^2. Another retrospective analysis of 43 patients with generalized LP treated by narrowband UVB revealed that complete response was achieved in 70 % of cases. In a randomized study, 46 patients with generalized LP were treated with either systemic prednisolone 0.3 mg/kg for 6 weeks or narrowband UVB (max 9 J/cm three times a week for 6 weeks). Narrowband UVB was significantly more effective than systemic steroids (Iraji et al. 2011).

PUVA

In a retrospective study, 28 patients with disseminated LP treated with PUVA and 13 treated with UVB-311 nm were compared. All 15 patients treated with oral PUVA had a complete (10) or partial (5) clinical response. The ten patients treated with UVB-311 nm showed complete (4) or partial (6) clinical response. The initial response to PUVA was significantly superior. After a mean follow-up period of 20.5 and 35.7 months, respectively, the disease relapsed in 7 of 15 PUVA-treated patients in 3 and 3 of 10 UVB-311 nm-treated patients (Wackernagel et al. 2007).

Table 53.2 Biologics in LP

Drug	Author	Year	Cases	Type of LP	Dose	Duration (wks)	Result
Adalimumab	Chao	2009	1	LP + OLP		22	CR
	Ho and Hantash	2011	1	Vulvovaginal gingival syndrome	160 mg SC	12	CR
	Holló et al.	2012	1	LP	80 mg SC	24	CR
Alefacept	Fivenson and Mathes	2006	2	LP + OLP	15 mg/wk IM	12–20	CR
	Chang et al.	2008	7	Erosive	15 mg/wk IM	12	2 CR, 5 NR
Basiliximab	Rebora et al.	2002	1	Erosive	20 mg/ 4 days apart IV	1	CR but rebound in 4 wks
Efalizumab	Cheng and Mann	2006	1	Erosive	0.7–1 mg/Kg wk SC	10	PR
	Hefferman et al.	2007	4	Erosive	0.7–1 mg/Kg wk SC	11	PR
	Boehm and Luger	2007	1	LP	0.7–1 mg/Kg wk SC	4	CR
Etanercept	Yarom	2007	1	Erosive	25 mg/wk SC		PR but relapse
	Irla et al.	2010	1	Nail LP	25–50 mg/wk SC	24–36	PR
Infliximab	Muller et al.	2008	1	Erosive			PR
Rituximab	Parmentier et al.	2008	1		375 mg/m^2/wk IV	12	CR (relapse at 10th month)
	Erras et al.	2011	1	LPP	1 g/wk IV	24	CR
[AU2] Mycophenolate mofetil	Brehmer et al.	2011	16	LPP		>24	5 CR,5PR,2NR.4WD
	Emad et al.	2012	1	LP	1.5 g/day	24	PR[a]
	Wee et al.	2012	10	Erosive	2 g/day	3.7 years	7CR, 3 PR
BCG-PSN	Xiong et al.	2009	31	Erosive	0.5 ml every other day	2	CR (87 %)

LP lichen planus, *OLP* oral LP, *LPP* lichen planopilaris, *wks* weeks, *CR* complete remission, *PR* partial remission, *NR* nonresponder, *WD* withdrawal, *SC* subcutaneous, *IV* intravenous

[a]+systemic steroids

Conclusions

Generalized LP is rare and commonplace patients do not need particular treatments. This is probably the reason why most of the studies are based on very small populations. Recruiting larger populations and following them up for a long time is not a cheap endeavor. As a consequence, one may suspect that the few studies existing in the literature, which may be considered of level A, are probably supported by the firm that manufactures the studied drug. A conflict of interest may bias their results.

Keeping this on mind, acitretin is the first line of treatment for cutaneous LP. Systemic corticosteroids are the second-line treatment, and all other drugs or procedures, including PUVA and narrowband UVB, are still awaiting rigorous placebo-controlled randomized trials.

Oral LP, instead, especially in its erosive form, is the real therapeutic challenge, since it is painful, prevents eating and speaking, exhales a fetid odor, and, therefore, compromises the quality of life of the patient. In addition, it carries a non-negligible risk of carcinogenicity. This is the reason why a large literature exists, mostly by stomatologists, but there is a lack of strong evidence supporting the efficacy of any therapy for OLP, with the possible exception for calcineurin inhibitors. In OLP, topical corticosteroids are the first line of therapy, a choice which has been recommended by several studies (Cribier et al. 1998). The second line is represented by calcineurin inhibitors, which have replaced topical cyclosporine A. A number of other treatments, including biologics, require further rigorous studies.

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