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# Lichen planus and lichenoid dermatoses



## Conventional and emerging therapeutic strategies

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### Learning objectives

After completing this learning activity, participants should be able to describe briefly the evidence-based therapeutic options available for lichen planus and related disorders and discuss emerging therapies and reflect on recent molecular advances in related disorders that might contribute to advancing therapies in lichen planus and variants.

### Disclosures

#### Editors

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Having reviewed the diverse clinical subtypes of lichenoid disease and the postulated molecular basis thereof in the first article in this 2-part continuing medical education series, we discuss herein the existing and emerging treatment strategies in the most common clinical forms of lichenoid inflammation and provide an overview of their pharmacodynamics and evidence base. The scope of this review is not to exhaustively discuss treatment modalities for all lichenoid variants discussed in the previous article of this series. Instead, the focus will be on frequently encountered subtypes of lichen planus and on linking mechanisms of disease with mechanisms of drug action. Future directions and potential avenues for translational research will also be discussed. (*J Am Acad Dermatol* 2018;79:807-18.)

**Keywords:** emerging drugs for lichenoid inflammation; lichen planus therapeutics; lichenoid variant therapeutics.

## LICHEN PLANUS: DISEASE BURDEN AND NATURAL HISTORY

### Key points

- Lichen planus is associated with significant morbidity, especially the mucosal, erosive, and appendageal subtypes

- Although cutaneous lichen planus is known to resolve spontaneously, there are many persistent, treatment-refractory clinical variants

Whether genital, oral, follicular, or classic cutaneous, lichen planus (LP) is associated with

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*Abbreviations used:*

LP:	lichen planus
LPP:	lichen planopilaris
NB-UVB:	narrowband ultraviolet B light
NLP:	nail lichen planus
PUVA:	psoralen plus ultraviolet A light phototherapy
RCT:	randomized controlled trial
TCI:	topical calcineurin inhibitor
TCS:	topical corticosteroid

significant morbidity among affected individuals, both physical and psychological.<sup>1</sup> The considerable impact on patient quality of life may result from symptoms related to active inflammatory, often erosive disease, such as intense pruritus, burning, trichodynia, or odynophagia.<sup>2</sup> Aside from the symptomatic aftermath, the impact of disfiguring lesions, especially associated with some cicatricial variants,<sup>3</sup> can also be detrimental to psychological well-being. Certainly, the side effects associated with potent systemic immunosuppressants or prolonged courses of topical corticosteroids may per se impact patient quality of life, and therefore the benefit-to-risk ratio should always be considered carefully before initiating therapy.

Most cases of classic cutaneous disease are thought to resolve spontaneously within 1 to 2 years, although mucosal and appendageal disease tends to be more persistent and refractory to treatment.<sup>4,5</sup> Oral, hypertrophic cutaneous and genital lichenoid disease have been thought to bear the potential for malignant transformation in some individuals; nevertheless, there is marked inconsistency among published studies and no consensus has been reached.<sup>6,7</sup> We tend to take an individualized approach when it comes to surveillance for carcinogenesis but, in practical terms, refractory cases are followed up and thus monitored regularly for neoplastic transformation.

## CONVENTIONAL THERAPEUTIC STRATEGIES

### Key points

- **Conventional treatment agents for lichenoid disease include topical and systemic corticosteroids, phototherapy, retinoids, topical calcineurin inhibitors, and systemic immunosuppressants**
- **Oral, genital, and follicular LP are less likely to resolve spontaneously and are more likely to require systemic treatment**
- **Well-conducted clinical research is sparse, although the lack of evidence does not necessarily indicate a lack of efficacy**

LP collectively represents a significant and unresolved clinical entity that has been sparsely researched, and therefore the evidence base underlying many of the currently used treatment modalities remains by and large inadequate. The evidence base alongside the basic pharmacology of conventional, commonly used treatment strategies will be reviewed separately for each broad clinical lichenoid subtype. An overview of conventional therapeutic strategies, their pharmacodynamics, and evidence base is provided in [Table 1](#).

## Cutaneous LP

**Topical and systemic corticosteroids.** The aim of treatment in the self-limiting classic cutaneous LP is to accelerate resolution while providing symptomatic relief from pruritus. Medium- to high-potency topical corticosteroids (TCSs) are the standard first-line treatment choice for this purpose, primarily reflecting physician experience and confidence with prescribing these agents rather than robust clinical trial data.<sup>10</sup> Commonly used TCSs include clobetasol propionate, fluocinolone acetonide, betamethasone dipropionate, and triamcinolone acetonide, the latter also delivered as an intradermal injectable in stubborn cases of hypertrophic cutaneous LP.<sup>7,2</sup> We generally recommend ointment-based formulations because of the added emollient benefit and the less complex formulation compared to creams. Application of topical steroids can only be practicable if the body surface area involvement is <10% to 15%, above which systemic options may be preferable.

Systemic corticosteroids, whether oral or intramuscular, may be used for TCS-resistant cases of LP, with prednisone typically being used at a dose of 30 to 60 mg/day for a treatment period of variable duration, depending on severity and refractoriness by clinical impression. A placebo-controlled randomized clinical trial (RCT) of patients with TCS-refractory disease has demonstrated that a 10-day course of prednisone at 30 mg/day is associated with significantly improved clinical outcomes.<sup>9</sup> We tend to use treatment regimens of up to 4 to 6 weeks in our center for severe cases of LP, but treatment duration tends to be shorter for less severe cases. The adverse effects of systemic steroid therapy should be borne in mind, particularly when administered for an extended duration, and blood pressure monitoring and regular urinalysis for glucosuria is common practice for many physicians. Repeated courses of corticosteroids should be (and are) generally avoided where possible, but clinical signs of chronic steroid exposure and toxicity should be looked for, with appropriate surveillance

**Table I.** Proposed mechanisms of action and comments on evidence base for commonly used conventional and less commonly used experimental treatment modalities for lichenoid inflammation

Modality	Mechanism of action	Comments	Level of evidence
Cutaneous lichen planus			
Topical and systemic corticosteroids	Nonspecific suppression of a multitude of proinflammatory mediators at a gene expression, protein, and cellular level <sup>8</sup>	Small (n = 38) but well-conducted double-blind, placebo-controlled, RCT for prednisone <sup>9</sup> ; evidence for medium to potent topical agents mostly empirical <sup>10</sup>	IB (systemic corticosteroid therapy) and IV (topical corticosteroids)
Photo(chemo)therapy	UV radiation exerts immunomodulation by triggering the photoproduct generation, interfering with DNA replication (PUVA) and synthesis; culminates in cell cycle arrest and suppression of inflammatory presence <sup>11</sup>	RCT of UVB vs corticosteroids (N = 46) <sup>12</sup> ; evidence for PUVA from retrospective study of small sample size (N = 28) <sup>13</sup>	IB (narrowband UVB) and III (PUVA)
Retinoids	Downregulates epidermal cell maturation and inflammatory pathways via effects on retinoic acid receptor <sup>14</sup>	Randomized, double-blind, placebo-controlled trial on acitretin (N = 65) <sup>14</sup>	IB (acitretin)
Sulfasalazine	Antiinflammatory effects via metabolites (5-aminosalicylic acid and sulfapyridine) interfering with arachidonic acid metabolism; inflammatory cytokine production; leukocyte function; and free radical scavenging <sup>15</sup>	Randomized, double-blind, placebo-controlled trial (N = 52) <sup>16</sup>	IB
Griseofulvin	Mostly unknown; in vitro antiinflammatory effects not replicated in vivo; main in vivo effect observed on polymorphonuclear cell migration <sup>17</sup>	Randomized, double-blind, placebo-controlled trial (N = 38) <sup>18</sup>	IB
Azathioprine	Converted to 6-mercaptopurine, a purine metabolism antagonist exerting immunosuppressive effects via effects on (rapidly proliferating) B and T cells <sup>19</sup>	Reports of cases <sup>20</sup>	IV
Methotrexate	Inhibits tetrahydrofolate reductase and interferes with purine and pyrimidine synthesis, although its antiinflammatory effects are mediated via enhancing adenosine release and effects at cellular, protein, and immune response level <sup>21</sup> ; inhibiting effects on JAK/STAT pathway recently described <sup>22</sup>	Nonrandomized, uncontrolled, small sample-sized studies <sup>23,24</sup>	IIB

Continued

Table I. Cont'd

Modality	Mechanism of action	Comments	Level of evidence
Topical calcipotriol	A vitamin D analogue exerting antiproliferative effects on keratinocytes and immunomodulatory actions via the nuclear vitamin D receptor expressed on lymphocytes, macrophages, and Langerhans cells; direct cellular effects via an increase in intracellular calcium <sup>25</sup>	Randomized open-label controlled trial comparing calcipotriol and betamethasone (N = 31) <sup>26</sup>	IB
Thalidomide	Inhibits TNF $\alpha$ * and suppresses lymphocytic response <sup>27</sup>	Small sample-sized, uncontrolled cases	IIB
Adalimumab	TNF $\alpha$ blocker	Case report <sup>28</sup>	III
Apremilast	Inhibits PDE4 and leads to the accumulation of intracellular cAMP, which activates protein kinase A and suppresses downstream, such as TNF $\alpha$ , interferon- $\gamma$ , IL-2, -5, -8, and -12 <sup>29,30</sup>	Open-label case series (N = 10) <sup>30</sup>	IIB
OLP			
Topical and systemic corticosteroids	As above	Triple-blind RCT evidence for TCSs <sup>31-33</sup> ; triple-blind study (N = 30) demonstrating superiority of clobetasol propionate (0.05%) vs TCI tacrolimus orabase (0.3%) and triamcinolone acetonate (0.1%) <sup>34</sup>	IB (topical corticosteroids)
Topical calcineurin inhibitors	Inhibit T cell activation via multiple effects at the transcription factor level <sup>35</sup>	No evidence for pimecrolimus vs placebo (Cochrane metaanalysis of 3 RCTs) <sup>36</sup> ; no evidence for tacrolimus superior to TCSs <sup>37</sup>	IA
Topical and systemic retinoids	As above	Placebo-controlled RCTs <sup>6,38</sup> for use of topical retinoids; small series for oral retinoids	IB (topical retinoids) and IIB (systemic retinoids)
Sulfasalazine	As above	Uncontrolled study (N = 21) demonstrates benefit of topical sulfasalazine in steroid-refractory OLP <sup>37</sup>	IIB
Azathioprine	As above	Case series <sup>39</sup>	IIB
Hydroxychloroquine	Permeates cell membrane and concentrates in cytoplasmic vesicles of macrophages and other antigen-presenting cells resulting in intravesicular pH elevation, which may downregulate autoantigenic immune response; also modulates Treg-related gene expression <sup>40,41</sup>	Open-label study (N = 10) <sup>42</sup>	IIB

Continued

**Table I.** Cont'd

Modality	Mechanism of action	Comments	Level of evidence
MMF	Inhibits IMPDH in activated B and T lymphocytes, antagonizing purine synthesis and T and B cell proliferation <sup>43</sup>	Retrospective study <sup>43</sup> (N = 10) for OLP	III
Biologics (adalimumab, etanercept, infliximab, alefacept, basiliximab, efalizumab, and rituximab)	Adalimumab, etanercept, and infliximab block TNF $\alpha$ ; alefacept blocks CD2 on T cell membrane, thereby blocking T cell activation; basiliximab inhibits IL-2; efalizumab inhibits lymphocyte activation by interfering with the CD11a subunit of lymphocyte function-associated antigen 1 (withdrawn in 2009); rituximab interferes with CD20 on B cells <sup>44-46</sup>	Overall, scant evidence; single case reports for each molecule <sup>44-46</sup>	III
Topical thalidomide	As above	Randomized, double-blind, positive controlled trial for topical thalidomide <sup>47</sup>	IB (topical thalidomide)
Purslane	Likely multifactorial mechanism of action <sup>48</sup> ; antiinflammatory constituent alkaloid recently reported <sup>49</sup>	Randomized, double-blind, placebo-controlled trial (N = 37) <sup>48</sup>	IB
Curcuminoids	Antiinflammatory effects, <sup>50</sup> including systemic IL-6–lowering effects <sup>51</sup>	Randomized, double-blind, placebo-controlled trial (N = 20) <sup>50</sup>	IB
ECP	Complex immunomodulatory properties including induction of lymphocyte apoptosis <sup>52</sup>	Nonrandomized, uncontrolled study (N = 12) <sup>52</sup>	IIB
BCG-PSN	Immunoregulatory effects via T cell subset modulation <sup>53</sup>	RCT (N = 56) <sup>53</sup>	IB
Genital lichen planus			
Topical corticosteroids	As above	Descriptive, prospective, cohort study (N = 114) <sup>54</sup> ; recommended in national guidelines <sup>55,56</sup>	III
PUVA	As above	Nonrandomized, uncontrolled study (N = 12)	IIB
PDT	Direct effects on highly proliferating immune cells, where photosensitizer accumulates <sup>57</sup>	Randomized, double-blind, controlled trial demonstrating superiority of PDT vs topical corticosteroids (N = 20) <sup>58</sup>	IB
MMF	As above	Single case report of erosive female genital lichen planus (N = 1)	III
Follicular lichen planus			
Topical, intralesional, and systemic corticosteroids	As above	Case series, <sup>59-61</sup> but also parallel-group, assessor-blinded, randomized trial (N = 60) <sup>62</sup>	IB

Continued

**Table I.** Cont'd

Modality	Mechanism of action	Comments	Level of evidence
Hydroxychloroquine	As above	Retrospective studies of efficacy only <sup>63,64</sup>	III
MMF	As above	Found to be beneficial in retrospective study (N = 12), <sup>65</sup> although a RCT demonstrated inferiority to TCS (clobetasol) <sup>62</sup>	IB (MMF vs TCS) and III
Cyclosporine	Block T lymphocyte function <sup>66</sup>	Small series (N = 3) observed benefit in follicular lichen planus <sup>67</sup>	III
Doxycycline	Tetracycline antibiotic with antiinflammatory properties <sup>68</sup>	Mixed treatment response in small series (N = 4)	III
Nail lichen planus			
Topical, intralesional and systemic corticosteroids	Nonspecific antiinflammatory effects, as above	Sporadic cases; retrospective study (N = 67) <sup>16</sup>	III
Alitretinoin	First-generation retinoid; mode of action as above	Case reports <sup>69,70</sup>	III

*cAMP*, Cyclic adenosine monophosphate; *ECP*, extracorporeal photophoresis; *IL*, interleukin; *IMPDH*, inosine monophosphate dehydrogenase; *JAK/STAT*, Janus tyrosine kinase/signal transducer and activator of transcription; *MMF*, mycophenolate mofetil; *OLP*, oral lichen planus; *PDE4*, phosphodiesterase type 4; *PDT*, photodynamic therapy; *PUVA*, psoralen plus ultraviolet A light phototherapy; *RCT*, randomized controlled trial; *TCl*, topical calcineurin inhibitor; *TCS*, topical corticosteroid; *TNF $\alpha$* , tumor necrosis factor- $\alpha$ ; *Treg*, regulatory T cell; *UV*, ultraviolet.

\**TNF $\alpha$*  is thought to be upregulated in lichen planus (see Tziotzios et al<sup>71</sup>).

measures put in place as necessary. The mode of action of corticosteroid therapy is rather nonspecific by exerting immunosuppressive and antiinflammatory effects through regulating a milieu of proinflammatory mediators at gene, cytokine, and cellular levels.<sup>8</sup> The lack of pharmacologic specificity underlies the plethora of side effects, testament to the notion that research toward targeted treatments is a necessity.

**Photo(chemo)therapy.** Photo(chemo)therapy has been used for its complex immunosuppressive effects in inflammatory dermatoses, including cutaneous LP, for many years.<sup>11</sup> Recently, RCT data have demonstrated superiority of phototherapy over oral corticosteroids; in a study of patients with TCS-refractory disease, a 6-week course of narrowband ultraviolet B light phototherapy (NB-UVB) was associated with a 52% complete response rate versus 13% with a similar duration of oral prednisone therapy,<sup>12</sup> although the latter was used at a slightly lower dose than typically used in common practice. A retrospective cohort study suggested that NB-UVB and psoralen plus ultraviolet A light phototherapy (PUVA) are of comparable clinical efficacy in cutaneous LP,<sup>13</sup> although NB-UVB is often preferred at our center over PUVA because of its more convenient administration mode and favorable safety profile.<sup>72</sup>

**Retinoids.** Systemic retinoids have been used successfully in cutaneous LP, with acitretin being the most commonly used drug. The pharmacologic effects of acitretin are thought to be effected via the activation of retinoic acid receptor subtypes, controlling epidermal maturation and inflammatory responses in the skin.<sup>14</sup> A placebo-controlled double-blind RCT in patients with cutaneous LP reported that an 8-week course of acitretin (30 mg/day) was associated with significantly greater disease remission.<sup>14</sup> A higher adverse event incidence was nonetheless reported in the treated arm,<sup>14</sup> the occurrence of which in clinical practice may explain why acitretin and other systemic retinoids are not commonly used in patients with cutaneous LP despite evidence of efficacy. Various case series have cited the beneficial effects of other oral retinoids, including etretinate, isotretinoin, and tretinoin, although their actual usage in practice is limited.<sup>10</sup>

### Oral LP

**Topical and systemic corticosteroids.** TCS therapy is first-line therapy for localized forms of oral LP.<sup>31-33</sup> Potent or highly potent TCSs, comprising preparations based on clobetasol, triamcinolone, betamethasone, fluocinonide, fluticasone, and prednisone, have been shown to be effective and



safe.<sup>31-33</sup> These preparations are commonly applied twice daily either neat (eg, clobetasol propionate 0.05%) or mixed with orabase (eg, triamcinolone) for 1 to 2 months, before tapering to a maintenance regime subject to clinical response.<sup>72</sup> Corticosteroids can also be injected intralesionally, although there are few data to suggest any benefit other than case series reports.<sup>73,74</sup> Systemic therapy, usually with oral glucocorticoids, may be considered in cases of sufficient severity or that remain refractory to topical treatments, though the evidence is sparse, with no adequate placebo-controlled studies conducted.<sup>75</sup> Because of the side effects associated with systemic steroid use, oral glucocorticoids are used on a short-term basis before commencing or reverting to topical therapy.<sup>76</sup>

**Topical calcineurin inhibitors.** Topical calcineurin inhibitors (TCIs) have been of interest primarily because of their steroid-sparing antiinflammatory properties. These effects are thought to be through blockage of T-cell activation via effects at the transcription factor level.<sup>35</sup> The published accounts on efficacy have been somewhat contradicting: a 2012 metaanalysis of 3 RCTs concluded that there was no evidence that pimecrolimus provided benefit over placebo.<sup>36</sup> Subsequent accounts were mixed but were more positive by reporting that TCIs were noninferior<sup>77-79</sup> or superior<sup>80-82</sup> an alternative to topical corticosteroids in oral LP. Pimecrolimus was found to somewhat outperform tacrolimus in a 2014 RCT<sup>83</sup> but not in a later study, where they were found to be pharmacodynamically equipotent.<sup>84</sup> These findings were affirmed in 2017 in a randomized open-label study,<sup>85</sup> a 3-arm pilot RCT,<sup>77</sup> and a subsequent metaanalysis,<sup>86</sup> and, in fact, many experts realize and report that tacrolimus is associated with better clinical outcomes than pimecrolimus in practice. Side effects of TCIs include local irritation and burning, particularly on eroded skin, prohibiting their wider use in erosive disease,<sup>80</sup> but otherwise their side effect profile is not less favorable than that of chronically used TCSs. Their favorable steroid-sparing pharmacodynamics encouraged their increasingly widespread use in clinical practice.<sup>87-89</sup>

**Topical and systemic retinoids.** Retinoids are known to exert their immunomodulatory properties by direct effects on T cells via the nuclear retinoic acid receptor.<sup>90</sup> Topical retinoids are an alternative to TCSs in nonerosive oral LP and are recommended as second-line therapy in oral LP by the World Workshop in Oral Medicine IV. Although 0.1% topical preparations of both tretinoin and isotretinoin have demonstrated efficacy in

placebo-controlled RCTs,<sup>6,91</sup> a comparative study showed inferiority to TCS therapy, albeit with a relatively low potency retinoid preparation.<sup>92</sup> Side effects include local irritation, photosensitivity, and teratogenicity,<sup>10</sup> and disease relapse 2 to 5 weeks after discontinuation limits the wider uptake of topical retinoid therapy in practice.<sup>91</sup> Systemic retinoids, such as etretinate and isotretinoin,<sup>38,93-96</sup> have been used in the treatment of oral LP, but their benefit-to-risk ratio is suboptimal and their clinical utility minimal, although alitretinoin may be more promising.<sup>97</sup>

### Genital LP

The treatment of genital LP is, in principle, similar to that of its oral mucosal counterpart. The major objective of therapy is to prevent or minimize scarring, synechiae, and vaginal stenosis in women and phimosis in men. While standard antipruritic measures can be used for symptomatic relief, TCSs are widely used as the initial line of therapy in genital LP.<sup>98</sup> An initially intensive regime, typically with clobetasol twice daily for 1 to 2 months, aims to assertively arrest the inflammatory process before tapering to a maintenance regime of twice to thrice weekly. The above treatment strategy is germane to the recommended therapeutic approach for lichen sclerosis<sup>99</sup> and is supported by data from case series.<sup>54</sup> The intravaginal application of emollients can help in reducing friction and pain, while foam and suppository corticosteroid formulations can be used in anal disease.<sup>100</sup>

In cases of treatment-resistant, severe, genital disease, systemic (oral) corticosteroid therapy can be used in the form of a tapering course followed by maintenance topical therapy. Topical retinoids are irritating and rarely tolerated in erosive (ano)genital disease. There have been retrospective studies and case reports of genital LP responding to TCIs<sup>101,102</sup> which, despite being associated with burning on eroded skin, are better tolerated than topical retinoids and are used widely for genital LP.

### Follicular LP

The objective in treating follicular LP or lichen planopilaris (LPP) and its variants is to arrest the inflammatory process as early as possible to minimize epithelial hair follicle stem cell loss via inflammation-driven apoptosis, while also controlling associated symptoms and awaiting spontaneous clinical remission.<sup>103</sup> Topical potent and ultrapotent corticosteroids are frequently used as first-line therapy in clinical practice, and there is reasonable evidence to support established clinician familiarity.<sup>59,60,62</sup> Intralesional corticosteroid therapy



is used by many clinicians despite lack of strong evidence and concerns about scalp skin atrophy in cases of prolonged use.<sup>61</sup> A dual regime of an ultrapotent and a potent topical corticosteroid instead, daily for 6 to 8 weeks, followed by tapering to thrice weekly or as per skin response, is favored by some clinicians. Systemic steroids (30–80 mg daily of prednisone or equivalent) are often administered in aggressive, rapid disease and sometimes systemic cyclosporine (3–10 mg/kg/day), although their actual evidence base is sparse.<sup>104–106</sup> A tapering course of prednisone (commencing with 40 mg daily) in addition to TCS therapy may be prescribed when there is a prominent inflammatory base for LPP, while also introducing hydroxychloroquine. The latter is thought to downregulate the immune response to autoantigens while also modulating regulatory T cell–related gene expression.<sup>40,41</sup> Its immunomodulating effect can be of benefit in LPP, and its relatively good overall adverse effect profile<sup>63,64,105</sup> renders it a preferred therapeutic option in this context. Tetracycline antibiotics can be used in cases where hydroxychloroquine is either not tolerated or contraindicated and is our preferred second-line agent,<sup>61,63</sup> followed by mycophenolate mofetil<sup>62,63,65,106</sup> and cyclosporine.<sup>67,107,108</sup>

### Nail LP

Despite the significant functional and cosmetic impact associated with nail LP, there is significant scarcity of evidence-based treatments. The objective to prevent or minimize permanent scarring is on par with follicular LP, and it is similarly important to arrest the inflammatory process as soon as possible to achieve the best overall outcome. Intralesional, topical, and systemic corticosteroids are favored as first-line, with the latter being reserved for cases in which the extent of involvement goes beyond a few nails.<sup>16,109</sup> Alitretinoin has also been reported to be of benefit.<sup>69,70,110</sup> For many dermatologists, including the authors, pulsed or short and tapering systemic corticosteroid treatment is preferred to intralesional delivery because of its efficacy and convenience, while we have also found that occlusion enhances the efficacy of moderately and highly potent topical corticosteroids.

## EXPERIMENTAL AND EMERGING THERAPEUTIC STRATEGIES

### Key points

- **Many treatment modalities have been used experimentally to treat cutaneous, mucosal, and follicular LP, such as sulfasalazine, mycophenolate mofetil, azathioprine, griseofulvin, and adalimumab**

- **Most attempted treatment strategies have not progressed to clinical practice because of suboptimal benefit-to-risk ratios**
- **The prerequisite to success for any future advances is molecular insight into the pathobiology of the condition**

### Cutaneous LP

There is a plethora of experimental agents that have not made it to standard clinical practice either because of unfavorable benefit-to-risk ratios or because of unconvincing overall cost effectiveness. An example of such a drug is sulfasalazine, which has not yet been widely adopted as mainstay treatment despite the relatively good evidence base and lack of serious side effects.<sup>111,112</sup> Griseofulvin seemed promising in early trials<sup>18,113</sup> but was later researched only sporadically<sup>114,115</sup> before being reported to be inferior to hydroxychloroquine.<sup>116</sup> Antifungals such as itraconazole and terbinafine, thought to interfere with inflammatory cytokines, have also been investigated and showed some benefit but were never followed-up more thoroughly.<sup>117–119</sup> Systemic immunosuppressive antiinflammatory agents, such as azathioprine and methotrexate, have been used with success in generalized, severe forms of LP and they tend to only be resorted to in such cases, given their associated toxicity.<sup>20,23,24</sup> Topical calcipotriol has been found to be noninferior to a potent TCS in a randomized controlled trial,<sup>120</sup> although there are inconsistent reports about its efficacy.<sup>26,121</sup> By immunomodulating effects on multiple cytokine and immune targets, including interferon-gamma loops, thalidomide has been postulated as efficacious in treating LP,<sup>27,122</sup> although it has not been further researched or developed. Adalimumab has been reported to be efficacious in cases of cutaneous LP,<sup>28</sup> although tumor necrosis factor–alpha blockade is not always therapeutic<sup>123,124</sup> and its precise role in lichenoid inflammation is not fully understood. Phosphodiesterase 4 is a key enzyme to cyclic adenosine monophosphate processing in several immune cell types,<sup>29</sup> and apremilast, an oral phosphodiesterase 4 inhibitor, has been reported to be effective in treating cutaneous LP.<sup>30</sup>

### Oral and genital LP

As mucosal and cutaneous disease share the same molecular underpinning, there is considerable overlap in therapies used in experiments in both conditions. Agents such as sulfasalazine, azathioprine, hydroxychloroquine, mycophenolate mofetil, tumor necrosis factor–alpha inhibitors and

other biologics, and topical thalidomide have been studied in oral and genital lichenoid inflammation and are of varying efficacy.<sup>39,42,44-47,112,125</sup> Pharmacognosy-derived agents, such as purslane<sup>48</sup> and curcuminoids,<sup>50</sup> have been demonstrated to be clinically efficacious in oral LP, although an uptake in clinical practice following larger-scale studies has not yet materialized. The list of experimental drug therapies for mucosal lichenoid disease would be incomplete without mentioning PUVA,<sup>126</sup> extracorporeal photochemotherapy,<sup>52</sup> and intralesional bacillus Calmette–Guérin,<sup>53</sup> which, although practically obsolete and reserved for refractory cases, may provide insights into the molecular signature of disease and how this might determine pharmacodynamic responses. Photodynamic therapy has also been reported to be of benefit in genital disease, although it is still regarded as experimental and is not widely used.<sup>57</sup>

### Follicular LP

While molecular research into the pathogenesis of follicular LP and its variants is as sparse as or perhaps sparser than in the other lichenoid inflammatory conditions, there has been an example whereby gene expression studies formed the basis of adopting an experimental treatment in clinical practice.<sup>127</sup> The implication of peroxisome proliferator-activated receptor gamma in the etiopathogenesis of LPP encouraged clinicians to use pioglitazone, a peroxisome proliferator-activated receptor gamma receptor agonist, for refractory cases. Controversy soon arose about whether the gene expression studies were relevant,<sup>128</sup> and reports of inconsistency in clinical outcomes when treating LPP with pioglitazone followed.<sup>129</sup> By the same token, finasteride was reported to be of help in patients with frontal fibrosing alopecia after overinterpretation of the clinical benefit in reversing the androgenetic element coexisting with frontal fibrosing alopecia, a claim that was later dismissed and failed the litmus test in clinical practice.<sup>130,131</sup> These scenarios highlight how significant and sought after well-conducted molecular research is in the modern era of evidenced-based therapeutics by informing pharmacodynamics and enabling targeted drug development and utilization.

### FUTURE DIRECTION

The profound morbidity associated with most forms of LP necessitates clinically efficacious therapies. The latter will only arise if robust molecular research elucidates novel pathways that inform targeted drug development and therapeutics. In many respects, the desired objective would be to

achieve molecular dissection of the etiopathogenesis of LP before exploring gene expression and druggable targets for targeted therapeutics in a manner germane to the disease. Large-scale studies aimed at gleaning fresh insights into the mechanistic basis of lichenoid inflammation will need to be orchestrated, with the aid of modern multiomic technologies that can help inform specific molecular pathways. There is paucity of such investigative approaches, possibly because of the lack of commercial interest and relative dearth of research funding to support basic scientific exploration before moving forward to conceptualizing and experimenting or testing appropriate molecular targets in clinical trials.

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