Influence of treatments on prognosis for vulvar lichen sclerosus: Facts and controversies

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Abstract
Lichen sclerosus (LS) is an inflammatory dermatosis with a predilection for the anogenital skin. Vulvar LS can be a debilitating disease, causing pruritus and pain, and it carries the potential for atrophy, scarring, and significant functional impairment. Recently, many advances have been made regarding the etiology and natural history of the disease process; however, much debate still exists regarding the most advantageous medical and surgical management of this disorder. In an effort to provide a comprehensive review on current vulvar LS literature, the following three controversies will be discussed: (1) optimal disease treatment, (2) theories behind LS's oncogenicity and treatments for minimizing malignancy, and (3) the value of surgical treatment for LS.

Ultra-potent topical corticosteroids (TCSs) are the first-line treatment for vulvar LS, while topical calcineurin inhibitors (TCIs) remain second-line agents for patients for whom TCS treatment resulted in incomplete resolution of symptoms or adverse events. Due to the relapsing nature of the disease, long-term maintenance therapy is often required. In addition, recent advances have contributed to the understanding of the association between LS and squamous cell carcinoma (SCC). While the exact mechanism responsible for LS-associated SCC is not known, immune dysregulation and inflammation may play an important role; therefore, successful treatment of LS should be directed towards alleviation of symptoms and reversal of the underlying histopathologic changes. Patients with LS-associated malignancy, as well as patients who need correction of functionally restrictive, scarring processes, can successfully undergo surgical intervention with tissue conservation.

Introduction
Lichen sclerosus (LS) is an inflammatory dermatosis characterized by localized dense lymphocytic infiltrates and vasculitic processes with a predilection for the anogenital skin. Vulvar LS can be a debilitating disease, causing pruritus and pain, and it carries the potential for atrophy, scarring, and significant functional impairment. The exact prevalence of vulvar LS is not known, but recent estimates suggest that 1 in 60 (1.7%) women presenting to a general gynecology practice have LS.1 Recently, many advances have been made regarding the etiology and natural history of the disease process, including the association between LS and squamous cell carcinoma (SCC); nevertheless, many controversies still exist regarding the most advantageous medical and surgical management of this disorder. This contribution will discuss three controversies surrounding LS: (1) optimal disease treatment, (2) theories behind LS’s oncogenicity and treatments for minimizing malignancy, and (3) value of surgical treatment for LS.

What is the optimal treatment for LS?

Historically, LS was treated with topical hormones due to the strong association with its onset and hormonal changes.
Observational reports have described that the highest prevalence of LS coincides with physiological low-estrogen states (pre-puberty and menopause). In addition, vulvar androgen receptor expression was shown to be decreased in a subset of LS patients, and early onset LS was linked to the use of oral contraceptive pills. In a randomized control trial, 2% progesterone and 2% testosterone were found to be no more effective than petroleum ointment and significantly less effective than 0.05% clobetasol propionate in treating LS. Similarly, another study showed that women treated with 2% dihydrotestosterone showed no improvement in their symptoms. In one study investigating topical testosterone for maintenance therapy, women with vulvar LS achieved remission after 24 weeks with clobetasol propionate 0.05% cream but showed a worsening of symptoms and appearance with subsequent 24-week testosterone maintenance therapy as compared with a placebo. Given the results of these studies, it is evident that topical hormones do not have a role in the treatment of LS.

In more recent years, significant research has emerged that demonstrates that LS is an autoimmune inflammatory process. Given this etiology, it is not surprising that ultra-potent topical corticosteroids (TCSs), such as clobetasol or halobetasol, have repeatedly been shown to be effective and safe in the treatment of vulvar LS. In one prospective cohort study of 244 patients with LS treated with ultra-potent TCSs, the symptoms of 96% of the patients improved. In this study, 168 (66%) of patients became symptom free and 76 (30%) experienced partial response to treatment. Total resolution of the clinical signs, including return to normal color and texture, occurred in 23% of the women, and partial resolution of the hyperkeratosis, purpura, fissuring, and erosions associated with this disorder occurred in 68% of the women. In a retrospective study of 81 patients who received ultra-potent TCS treatment for refractory LS, in which average duration of prior treatment for disease (including hormonal or steroid treatment) was 6 +/- 6.9 years, patients treated with 0.05% clobetasol propionate for three months had a 77% chance of complete remission of symptoms and a 47% chance of improvement in the clinical appearance of the vulva.

Similarly, a prospective study conducted between 1981 and 2001, analyzed the rates of remission, recurrence, and risk of malignancy of 83 women with vulvar LS treated with 0.05% clobetasol propionate ointment. Complete remission was obtained in 45 patients (54%). The probability of remission was significantly associated with age such that the estimated incidence of remission at three years was 72% in women under 50, 23% in women between the ages of 50 and 70, but in women older than 70 years of age, none achieved remission. The incidence of relapse was estimated to be 50% at 16 months and 84% at four years from initial treatment; moreover, patients’ tolerance of long-term ultra-potent TCSs in this cohort was excellent and no atrophic events were observed. The eight observed vulvar SCC occurred in previously untreated or irregularly treated vulvar LS lesions.

In addition to the ultra-potent TCSs, less potent TCSs, such as mometasone furoate and triamcinolone acetonide, have also been shown to be effective in the treatment of vulvar LS. Thirty-one consecutive patients with biopsy-proven vulvar LS seen in a vulvar clinic were treated with a regimen of 0.1% mometasone furoate cream once daily for four weeks and then twice weekly for eight weeks. All the patients had a significant improvement in the gross aspects of the disease and a very dramatic decrease in symptoms, with nearly all the subjects having complete symptomatic remission. When triamcinolone 0.1% ointment was applied once or twice daily for three months, complete symptom resolution was reported in 19 (86.4%) of 22 women with vulvar burning, 23 (71.9%) of 32 women with vulvar pruritus, 12 (92.3%) of 13 women with vulvar pain, and 8 (47.1%) of 17 women with dyspareunia.

To address their LS symptoms, patients traditionally have been instructed to apply a TCS reactively on demand after their LS has been stabilized with an ultra-potent TCS, but newer studies support a proactive approach to long-term therapy. A randomized controlled study demonstrated that the relapse rate was significantly lower in patients who applied mometasone furoate 0.1% ointment biweekly (0%) for 52 weeks, in comparison to women treated with cold cream once daily (55.6%) or vitamin E once daily (62.5%). The median time to relapse for both groups was the same, 21.6% weeks. Mometasone furoate and triamcinolone may act as alternatives to clobetasol propionate for treatment of vulvar LS, especially for long-term therapy, with similar efficacy but higher levels of safety and tolerability. Although no randomized controlled trials have determined the optimal potency and regimen for TCSs, standard practice begins with once-daily application of TCSs for 4 weeks, tapering to alternate days for 4 weeks, followed by once or twice weekly application as maintenance. While some practitioners recommend twice-daily application of TCSs, pharmacodynamic studies have demonstrated that once-daily application of a TCS is sufficient. In general, a typical 30-g tube of a TCS should last approximately 3 to 6 months.

Despite their effectiveness, it has been suggested that long-term use of TCSs may be associated with an increased risk of skin atrophy, and consequently, an anti-inflammatory alternative to topical steroids may be desirable. Pimecrolimus and tacrolimus are two nonsteroid topical calcineurin inhibitors (TCIs) that act as immunomodulators that block the release of inflammatory cytokines from T lymphocytes in the skin, while promoting cutaneous innate host defense. TCIs do not inhibit collagen synthesis by keratinocytes, so unlike TCSs, they do not cause atrophy of the skin. The initial case reports of successfully treating vulvar LS with twice-daily pimecrolimus cream 1% were small-case series in children and adults. A larger pilot study evaluated the safety and efficacy of pimecrolimus cream 1% applied twice daily for up to 6 months in women.
with severe LS who were previously unsatisfactorily treated with TCSs. Of the 26 patients who completed the follow-up, 42% (11 out of 26) experienced complete remission, with relief from itching, pain, and inflammation. Nine women (35%) achieved remission within 2 months of the start of treatment. Biopsy specimens from 16 patients demonstrated increase collagen synthesis after 2 months with pimecrolimus 1% treatment in comparison with baseline. The only noted adverse side effect was mild burning and itching, which was reported in 50% of participants during the first 3-14 days of treatment. At the 2-month visit, blood concentrations of pimecrolimus were undetected in all 10 assessed patients Another prospective study evaluating the safety, efficacy, and tolerability of pimecrolimus 1% in 16 postmenopausal women with biopsy-proven vulvar LS found that after 3 months of twice-daily treatment, complete disease remission was reported in 11 patients (69%). Seven of those 11 patients were in remission for over a year, and repeat biopsies performed on eight women showed reversal of the histological features of LS. Another four patients (25%) achieved partial remission. The most common adverse event was mild to moderate burning, which was experienced by one-third of the women at the site of application during the first week.

Four case reports, two pilot studies, and one multicenter open-label trial all demonstrated the efficacy and tolerability of tacrolimus ointment 0.1% in the treatment of anogenital LS. All patients in the case reports experienced resolution of symptoms. In the first pilot study, 16 women with histologically proven vulvar LS, who had previously demonstrated an incomplete response to fluorinated steroids (10 patients) or poor compliance with TCS treatment (five patients), were treated with tacrolimus 0.1% twice daily for 3 months. Among these patients, 12.5% achieved a complete response (maintained at 12 months), 50% experienced a partial improvement, and 37.5% were nonresponders. Additionally, one-third of the participants reported a transient, mild, local burning sensation. A second pilot study investigated 11 women with vulvar LS treated with tacrolimus ointment 0.1% twice daily for the first 6 weeks, followed by treatment reduction over the next 6 weeks. Complete or partial remission was observed in four of six patients at the end of 3 months. Last, a larger multicenter, phase II, open-label trial was conducted on 84 patients (49 women, 32 men, and 3 girls) with long-standing anogenital LS. Participants were treated with tacrolimus ointment 0.1% for 16 weeks and, if deemed beneficial, treatment was continued to 24 weeks. Clearance of active lesions occurred in 43% of patients, and an additional 34% experienced partial resolution. Transient itching and burning during the first few days of treatment were the most commonly reported adverse events. Infections, such as genital herpes and vulvovaginal candidiasis, each occurred in 2% of patients. During the 18-month follow-up, the recurrence rate in participants was less than 10% and no malignancy was observed. In contrast, a long-term study monitoring patients for 54 months reported aggravation of cutaneous lesions in six out of nine patients (66.7%), who initially experienced clinical improvement, suggesting continuous and long-term treatment with tacrolimus is necessary for LS management.

The only study thus far to compare TCI versus TCS was a double-blind randomized controlled trial comparing the efficacy and safety of clobetasol versus pimecrolimus in the treatment of vulvar LS. Seventeen women in the pimecrolimus arm of the study and 19 women in the clobetasol arm had biopsy-proven vulvar LS. Patients in the pimecrolimus 1% group applied the medicine twice daily, and the patients in the clobetasol group applied an unmedicated vehicle in the morning and the clobetasol cream 0.05% in the evening daily for 12 weeks. Improvement in inflammation on pre- and post-treatment biopsies was assessed by a dermatopathologist and was found to be significant for the clobetasol and pimecrolimus groups ($P = .001$ and .008, respectively). Both groups showed clinical improvement in pruritus and burning/pain as assessed by the investigator and by the patients themselves. Clobetasol was more effective than pimecrolimus in decreasing histologically measured inflammation. Based on this observation, the investigators concluded that clobetasol should remain the first-line agent for the treatment of vulvar LS.

To add to the controversy surrounding the use of TCIs versus TCSs for treatment of vulvar LS, concern has been raised about the use of immunomodulating therapies, such as TCIs, in the therapy of a disease with an inherent malignant potential. Although there have been no reports of systemic immune suppression or increased risk of malignancies in LS patients treated intermittently with TCIs for up to 4 years, cases of vulvar SCC after TCI treatment have been reported. The US FDA collated worldwide reports and found 19 malignancy-related adverse events with the use of topical tacrolimus and 10 cases with the application of topical pimecrolimus, but it has not been established that these reported cancers are associated with the TCIs. Consequently, the FDA recommends using pimecrolimus and tacrolimus only as second-line agents for short-term and intermittent treatment in patients who are unresponsive to or intolerant of other treatments.

If TCSs or TCIs are not well tolerated or available, third-line agents, such as topical or systemic retinoids, may be used to treat vulvar LS. Despite the fact that topical and systemic retinoids are generally avoided due to their well-known potential to cause severe teratogenicity, several studies have demonstrated their efficacy. After 1 year of treatment with topical 0.025% tretinoin once daily 5 days a week, 22 women experienced improvements in symptoms, clinical appearance, and histopathologic features. Nineteen women with vulvar LS previously unsuccessfully treated with topical estrogen and corticosteroids experienced excellent results (90% symptom resolution) when treated with oral etretinate. In a double-blind placebo-controlled study, acitretin 20 to 30 mg/day for 16 weeks led to treatment...
response in approximately two-thirds of women. All patients experienced some degree of typical retinoid adverse effects, such as dry mucous membranes and sun sensitivity.

Why is LS potentially oncogenic and is there evidence that optimal treatment lowers malignant transformation?

Strong support has accumulated for the notions that there are two different etiopathogenic pathways for the development of vulvar squamous cell carcinoma (SCC) and vulvar intraepithelial neoplasia (VIN). The first is associated with infection by human papilloma-virus (HPV), and the second is independent of HPV infection. HPV-associated vulvar SCCs are of the basaloid or warty type and arise from VIN of the usual type. LS-associated SCC originates from a well-differentiated vulvar intraepithelial neoplasia (d-VIN). The risk of SCC arising in LS is approximately 5%, but histopathological examination of vulvar SCCs indicates that 45% to 61% occur on the background of LS. In cases of LS-associated SCC, rapid progression to invasive SCC often occurs within 6 months, making early detection difficult because many atypical intraepithelial lesions are not seen as premalignant at the time of biopsy. Development of SCC in LS appears more dependent on stage and duration of LS, as well as activity of LS, than on the age of patients. The exact mechanism of LS-associated carcinogenesis is uncertain, but one hypothesis proposes that ineffective local immune surveillance creates a permissive environment allowing for immunological escape of early invasive malignant tumors.

Links between LS and immune dysregulation have been fortified by the increased prevalence of autoimmune disorders in LS patients, especially when the onset of LS is between the ages of 41 to 60. One study of 350 patients with vulvar LS revealed 22% had autoimmune disease, 42% had autoantibodies, and 60% had one or more autoimmune-related phenomena. More recent studies conducted in Oxfordshire, UK, revealed 28.4% of the 189 patients treated at the vulvar clinic for LS had at least one autoimmune disease. Thyroid disease, vitiligo, alopecia areata, and pernicious anemia are among the most often reported in LS patients. The molecular mechanism responsible for LS progression to SCC remains elusive, yet the uncontrolled inflammation is clearly deleterious. LS therapy should aim to reduce lymphocyte infiltrate and decrease cytokine secretions that may contribute to disease progression. The current available evidence cannot address the question whether local therapy with topical corticosteroids or immune modulators can prevent the development of primary vulvar SCC or decrease the recurrence of cancer. Clobetasol has been shown to be more effective than pimecrolimus in decreasing histologically measured inflammation, so presumably clobetasol may also be more successful in the prevention of malignant transformation of LS. No studies have been adequately powered to determine whether medical suppressive therapy will prevent LS progression to SCC. Additional studies have noted that SCC is not seen in patients who comply with treatment, suggesting early extensive treatment with TCSs may prevent malignant changes. Additionally, one study noted the mean duration of vulvar symptoms before diagnosis of SCC was...
When is surgical treatment of LS warranted?

In the past, vulvectomies were considered acceptable surgical interventions for LS, but with recurrence rates as high as 50% and often mutilating results, the procedure is no longer advocated. Contributing to the failure of surgical treatment of LS is the Koebner phenomenon, a pathologic process in which normal skin becomes sclerotic after injury or trauma. Consequently, surgery can lead to additional scarring. More recently, ultra-potent TCSs have been applied after surgery to mitigate the risk of Koebnerization, thereby making surgery a more viable option. Currently, there is a role for surgery in LS where urinary or sexual dysfunction is compromised by adhesions or scarring of the vulva. Because conservative treatments can be quite effective, as noted in a 2010 study showing labial fusions softened and divided after surgery to mitigate the risk of Koebnerization, thereby allowing the treated areas to re-epithelialize from adjacent noninvolved epithelium and leaves little to no scar formation. In two cases of LS, both women became symptom free after re-epithelialization and remained in remission after 2 years. Additionally, in another study, six of seven patients were free of recurrent symptoms at follow-up, which ranged from 12 to 37 months. In contrast, another group noted recurrence in both of their patients treated for genital LS.

Conclusions

While the etiology remains uncertain, mounting evidence suggests that immune dysregulation is involved in the pathogenesis of LS. Treatments aim to alleviate symptoms,
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prevent architectural damage, and reverse the underlying histopathologic changes. Ultra-potent TCSs have been the first-line treatment for over 15 years. Although effective in improving symptoms and reversing histological changes, concerns remain about the safety of long-term use despite a paucity of adverse events observed in vulvar LS patients. Less-potent TCSs may be an alternative to ultra-potent TCSs for treatment of vulvar LS with similar efficacy but higher levels of safety and tolerability. Approximately 96% of patients will respond to TCSs initially, but there is a high rate of relapse without long-term maintenance therapy. TCIs remain second-line agents for patients for whom TCS treatment resulted in incomplete resolution of symptoms or adverse events. Existing long-term follow-up studies suggest early diagnosis and early treatment with good compliance result in lower rates of malignancy and scarring. The exact mechanism responsible for LS-associated SCC is not known; however, immune dysregulation and inflammation may play a role in cancer development, so symptom resolution and reversal of histologic changes should be obtained. Patients with LS-associated malignancy, as well as patients who need correction of functionally restrictive, scarring processes, can successfully undergo surgical intervention with tissue conservation. Preoperative and postoperative medical suppressive therapy is recommended.

References

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