Recalcitrant Symptomatic Vulvar Lichen Planus

Response to Topical Tacrolimus

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Background: Topical tacrolimus has been reported to be an effective treatment for genital lichen planus in small case series. We retrospectively reviewed the medical records of 16 patients with symptomatic vulvar lichen planus who received treatment with tacrolimus ointment.

Observations: All patients had symptomatic vulvar lichen planus recalcitrant to other treatments. Of 16 patients, 15 (94%) experienced a symptomatic response to tacrolimus treatment within 3 months (mean, 4.2 weeks) and had a partial or complete resolution of the lesions. Six patients (38%) reported mild adverse effects, including irritation, burning, and tingling. With continued use of the medication, these adverse effects resolved. When patients stopped treatment, lichen planus returned in 10 (83%) of 12 patients within 6 months after discontinuation of therapy (median, 1 week; range, 0.3–24 weeks), but in 6 patients the lesions were less severe than the lesions before treatment; all 10 patients resumed use of topical tacrolimus.

Conclusions: In this retrospective series of 16 women with vulvar lichen planus, topical tacrolimus therapy effectively controlled symptoms and improved lesions in all but 1 patient. The effect may be temporary, requiring continued use of tacrolimus, which appears to be safe and effective in controlling disease activity.

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RAL LICHEN PLANUS IS A relatively common condition affecting approximately 1% of the population. Lichen planus is more common in women, and in 1 study it involved the genitalia in 25% of the women with oral lichen planus.

Genital lichen planus causes considerable discomfort, which may be debilitating. Typically, patients present in their fifth or sixth decade with pruritus, burning, pain, and dyspareunia. Physical examination findings range from erythema to erosions and frank ulcerations; in severe disease, vaginal adhesions and scarring develop, prohibiting sexual intercourse.

Besides the mouth and genitalia, other mucosal sites that may be involved with lichen planus include the esophagus, conjunctiva, and ear canals. Lichen planus in these sites may lead to scarring, resulting in disability and morbidity. Scarring usually does not occur with oral lichen planus.

Histopathologic examination reveals a lichenoid infiltrate, basal layer vacuolation, and scattered Civatte bodies. As expected, at mucosal sites many plasma cells may also be present. Direct immunofluorescence studies consistent with lichen planus and other lichenoid reactions reveal shaggy fibrinogen deposition at the dermal-epidermal junction, with cytokid bodies staining with 1 or more of the following conjugates: IgG, IgM, IgA, or C3.

Therapeutic management is challenging. Genital lichen planus may be more severe and recalcitrant to treatment compared with oral lichen planus. Variable benefit occurs with use of topical agents, such as corticosteroids, antifungal agents, retinoids, estrogens, and cyclosporine, as well as systemic agents, such as corticosteroids, retinoids, antifungal agents, hydroxychloroquine, and dapsone. Frequently, systemic treatments have unproven benefit, expose the patient to adverse effects, and are expensive.

Topical tacrolimus is an effective and safe therapy for oral lichen planus. This therapy has been used for other mucosal forms of lichen planus, and there are reports of its efficacy for genital lichen planus. We prescribed topical tacrolimus for 16 consecutive patients with symptomatic vulvar lichen planus; we report their responses to treatment in this study.
Increased
Tingling
Very Dissatisfied
Yes
Somewhat Satisfied
Came Back
3 Times Weekly
Once Daily
Cost of the

Mus capsules (Prograf; Fujisawa) were compounded in a bland tacrolimus prepared by the Mayo Clinic pharmacy: tacrolimus ointment. Before this product was available, 8 patients initially used topical tacrolimus for vulvar lichen planus. They were instructed to apply the ointment to affected areas twice daily.

We retrospectively reviewed the medical records of 16 consecutive female patients with symptomatic vulvar lichen planus who were treated with topical tacrolimus. All patients were evaluated and treated in the Department of Dermatology at Mayo Clinic in Rochester, Minn, by the same clinician (R.S.R.) between April 2000 and November 2002.

Patients fulfilled the following criteria: (1) vulvar lichen planus was diagnosed on the basis of history, physical examination, and, if available, histopathologic features of lichenoid mucositis with or without supportive direct immunofluorescence studies and (2) patients received treatment with topical tacrolimus for vulvar lichen planus.

Topical tacrolimus 0.1% ointment (Protopic; Fujisawa Healthcare, Inc, Deerfield, Ill) was prescribed for all patients. They were instructed to apply the ointment to affected areas twice daily. Before this product was available, 8 patients initially used topical tacrolimus prepared by the Mayo Clinic pharmacy: tacrolimus capsules (Prograf; Fujisawa) were compounded in a bland ointment base (Aquaphor; Beiersdorf, South Norwalk, Conn) in 2 concentrations, 0.1% (3 patients) and 0.03% (5 patients), until the commercial form became available. Neither the physician nor the patient perceived a difference between the Protopic ointment and the compounded product.

Follow-up data were obtained by means of a patient telephone questionnaire. The use of this questionnaire was approved by the Mayo Foundation Institutional Review Board. The topics of the questions included symptoms and lesions, use of the ointment, and patient satisfaction (Figure).

Response to treatment was evaluated according to change in symptoms and clearance of lesions. Symptoms were graded on the following scale: much better, somewhat better, about the same, somewhat worse, or much worse. Patients who responded that their symptoms were much better or somewhat better were considered to have had a symptomatic response.

Patients were asked whether the lesions were completely gone, almost gone, the same, or increased after treatment. Lesions were considered completely resolved if the patient believed that the lesions were completely gone; lesions were considered partially resolved if the patient believed that the lesions were almost gone. In addition to the patient questionnaire, a retrospective review of the patients’ medical charts was performed to obtain clinical examination findings after the use of topical tacrolimus.

If use of the medication was discontinued, the patient was asked whether the disease relapsed, when the relapse occurred, and how the severity of the relapse compared with the episode before treatment (worse than before, the same as before, or much better than before). Patient satisfaction with the use of tacrolimus was determined (very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, or very dissatisfied).

Demographic and clinical data from the patients studied are summarized in Table 1. All 16 patients were white women. Age ranged from 47 to 75 years (mean, 63 years). All patients had painful, erosive lesions of vulvar lichen planus. Reported symptoms included pain in 16 patients, soreness in 4, burning in 3, and bleeding in 1. The diagnosis of lichen planus was confirmed with biopsy results in 12 (75%) of the 16 patients. Of these 12 patients, 5 had direct immunofluorescence findings that showed changes consistent with lichen planus. One patient had nondiagnostic findings on direct immunofluorescence testing. Clinical diagnosis in others was made on the basis of the presence of concomitant oral, cutaneous, otic, or esophageal lichen planus.

The introitus was involved in 14 patients, and the vulva in 6. Labial involvement was present in 6 patients; in 2 of these patients the inflammation and destruction from lichen planus had obliterated the labia minora and majora. Lichen planus involved extragenital sites in most of these patients (Table 1): oral mucosa in 14 patients, skin in 5, ear in 3, esophagus in 2, and the perianal region in 2.

The mean duration of disease before initiation of therapy with topical tacrolimus was 4.3 years (range, 1-12 years). All patients had recalcitrant disease, and all patients had tried at least 1 form of treatment before receiving tacrolimus therapy. Prior treatments included use of topical corticosteroids (13 patients), antifungal medications (7 patients), topical estrogen (5 patients), systemic corticosteroids (5 patients), and hydroxychloro-
quine (4 patients). Two patients continued to receive systemic therapy during topical tacrolimus therapy: 1 received oral corticosteroids and the other received hydroxychloroquine. Both patients were able to decrease the dose of systemic medication when topical tacrolimus therapy was initiated.

A summary of the responses of the patients to initiation of therapy with topical tacrolimus is presented in Table 2. Of the 16 patients, 15 (94%) experienced a symptomatic response to treatment within 3 months (mean, 4.2 weeks; range, 0.3-12 weeks). These 15 patients also noted partial or complete resolution of the vulvar lesions. One had no symptomatic improvement. Patients were followed up for at least 2 months (mean, 15.7 months; range, 2-28 months).

Clinical examination findings are available in Table 2. Of the 16 patients, 13 returned for follow-up appointments. Of these 13, 10 had no clinical evidence of erosions and 3 had smaller erosions that were healing. Follow-up examination occurred in an average of 3 months (range, 1-12 months) after initiation of topical tacrolimus therapy.

Twelve patients stopped applying topical tacrolimus for various reasons (Table 3): 7 stopped because the lichen planus resolved, 3 forgot to apply it, 1 stopped because of adverse effects (burning and irritation), and

![Table 1. Data for Patients Using Topical Tacrolimus for Vulvar Lichen Planus](image)

<table>
<thead>
<tr>
<th>Patient No./ Age, y/ Duration, y</th>
<th>Site</th>
<th>Symptoms in Genital Area</th>
<th>Signs of Vulvar Lichen Planus</th>
<th>Extragenital Involvement</th>
<th>Biopsy Specimen</th>
<th>DIF Results</th>
<th>Prior Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/75/10 10</td>
<td>Introitus</td>
<td>Pain, bleeding</td>
<td>Erosions</td>
<td>Oral, gingival, cutaneous</td>
<td>None</td>
<td>Not done</td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td>2/69/1 13</td>
<td>Vulva</td>
<td>Pain</td>
<td>Erosions, scarring</td>
<td>Oral</td>
<td>None</td>
<td>Not done</td>
<td>Topical corticosteroids, oral corticosteroid, topical corticosteroids, antifungal</td>
</tr>
<tr>
<td>3/74/1 10</td>
<td>Vulva, including introitus</td>
<td>Pain, soreness</td>
<td>Erosions</td>
<td>Gingival, cutaneous</td>
<td>Nondiagnostic results</td>
<td>Not done</td>
<td>Topical corticosteroids, topical estrogen</td>
</tr>
<tr>
<td>4/72/1 7</td>
<td>Introitus</td>
<td>Pain, soreness</td>
<td>Erosions</td>
<td>Gingival</td>
<td>Gingiva and vulva</td>
<td>Positive</td>
<td>Topical corticosteroids, hydroxychloroquine, oral corticosteroid</td>
</tr>
<tr>
<td>5/60/6 10</td>
<td>Vulva, including labia</td>
<td>Pain</td>
<td>Erosions, scarring</td>
<td>Oral, gingival, otic</td>
<td>Gingiva</td>
<td>Positive</td>
<td>Topical corticosteroids, antifungal, hydroxychloroquine, topical estrogen</td>
</tr>
<tr>
<td>6/47/4 7</td>
<td>Introitus</td>
<td>Pain</td>
<td>Erosions</td>
<td>Gingival</td>
<td>Gingiva</td>
<td>Positive</td>
<td>Topical corticosteroids, antifungal</td>
</tr>
<tr>
<td>7/57/2 7</td>
<td>Vulva, including introitus</td>
<td>Pain</td>
<td>Erosions</td>
<td>Oral, gingival, perianal</td>
<td>Gingiva and labia</td>
<td>Positive</td>
<td>Topical corticosteroids, antifungal</td>
</tr>
<tr>
<td>8/47/2 7</td>
<td>Introitus</td>
<td>Pain</td>
<td>Erosions</td>
<td>Oral, gingival</td>
<td>Vagina</td>
<td>Not done</td>
<td>Antifungal, hydroxychloroquine</td>
</tr>
<tr>
<td>9/53/6 7</td>
<td>Introitus, labia</td>
<td>Pain</td>
<td>Erosions, stenosis</td>
<td>Oral, gingival, otic</td>
<td>Vagina</td>
<td>Not done</td>
<td>Topical corticosteroids, antifungal</td>
</tr>
<tr>
<td>10/74/6 7</td>
<td>Vulva, including introitus</td>
<td>Pain, soreness</td>
<td>Erosions</td>
<td>Gingival, perianal</td>
<td>Gingiva</td>
<td>Positive</td>
<td>Topical corticosteroids</td>
</tr>
<tr>
<td>11/66/5 7</td>
<td>Introitus, labia</td>
<td>Pain, burning</td>
<td>Erosions</td>
<td>Gingival, cutaneous</td>
<td>Wrist</td>
<td>Not done</td>
<td>Oral corticosteroid</td>
</tr>
<tr>
<td>12/49/1 7</td>
<td>Introitus, labia</td>
<td>Pain</td>
<td>Erosions, scarring</td>
<td>Oral, gingival, esophageal</td>
<td>None</td>
<td>Not done</td>
<td>Topical corticosteroids, antifungal, oral corticosteroid, hydroxychloroquine*</td>
</tr>
<tr>
<td>13/68/3 7</td>
<td>Introitus</td>
<td>Pain, burning</td>
<td>Erosions</td>
<td>None</td>
<td>Vulva</td>
<td>Positive</td>
<td>Topical corticosteroids, antifungal, topical estrogen, oral corticosteroid*</td>
</tr>
<tr>
<td>14/65/12 20</td>
<td>Vulva, including introitus</td>
<td>Pain</td>
<td>Erosions</td>
<td>Oral, gingival</td>
<td>Labia majora</td>
<td>Not done</td>
<td>Topical corticosteroids, retinoid</td>
</tr>
<tr>
<td>15/67/4 7</td>
<td>Introitus, labia</td>
<td>Pain, soreness, burning</td>
<td>Erosions, stenosis, labia destroyed</td>
<td>Oral, gingival, cutaneous</td>
<td>Vulva</td>
<td>Not done</td>
<td>Topical corticosteroids, topical estrogen</td>
</tr>
<tr>
<td>16/67/1 7</td>
<td>Introitus, labia</td>
<td>Pain</td>
<td>Erosions, stenosis, labia destroyed</td>
<td>Oral, gingival, cutaneous, otic, esophageal</td>
<td>Esophageal</td>
<td>Nondiagnostic</td>
<td>Topical estrogen</td>
</tr>
</tbody>
</table>

Abbreviation: DIF, direct immunofluorescence.

*Patient used this medication concomitantly with topical tacrolimus.
continued using topical tacrolimus because of adverse effects, including irritation, burning, and tingling. One patient discontinued therapy (therefore, stopping the therapy) because she believed that her lesions were unchanged during topical therapy. In 10 patients, the lesions recurred within 6 months after discontinuation of therapy with topical tacrolimus (median, 1 week; range, 0.3–24 weeks). The recurrent lesions, compared with lesions before therapy, were less severe or of the same severity in 9 patients. One patient believed that her lesions were unchanged during topical therapy; symptoms of burning resolved with continued therapy. The tacrolimus was well tolerated; symptoms of burning resolved with continued use of the ointment.

At present, 14 patients continue to use topical tacrolimus: 2 apply it twice daily, 7 apply it once daily, and 4 apply it weekly. Fifteen patients reported satisfaction with the treatment.

Minor adverse effects occurred in 6 patients, including irritation, burning, and tingling. One patient discontinued using topical tacrolimus because of adverse effects, but when the lesions recurred, she reapplied it and had no adverse effects. The patients who experienced adverse effects stated that they resolved with continued use of tacrolimus.

Our results are consistent with results from previous reports of recalcitrant genital lichen planus that responded to topical tacrolimus (Table 4). However, we report a larger number of patients than that previously reported, and we describe a relatively long duration of follow-up (mean, 15.7 months). We believe that our results are valid: the diagnosis of lichen planus was made in a consistent manner (diagnosed by 1 physician; confirmed in more than two thirds of the cases with oral, vulvar, or esophageal biopsy); the treatment was consistently prescribed and advised; and follow-up data were obtained by 1 physician in a consistent, standardized manner. All but 2 of the patients with vulvar lichen planus had lichen planus at multiple sites. These patients had oral, cutaneous, otic, esophageal, perianal, or perineal lichen planus in addition to genital in-
volvement. Many of the patients had the vulvovaginal-gingival variant of erosive lichen planus, which has been reported to be more recalcitrant to treatment. All patients had not had a response with other treatments.

We recognize that a retrospective review of clinical material is not optimal; however, we benefited from the consistency of 1 expert physician making the diagnosis. Follow-up data were obtained by means of a telephone survey, which has its own shortcomings because the patients are subject to recall bias and memory lapses. However, we tried to avoid creating bias in our telephone survey. The survey was the only practical means of following up our patients because many of them lived too far from our institution to conveniently return for follow-up. Yet the patients who returned for follow-up had improvement on clinical examination that was consistent with the questionnaire responses.

Genital lichen planus is well recognized as a debilitating condition for many patients. Symptoms of genital pruritus, burning, pain, and dyspareunia may have detrimental psychological effects. Erosions and ulcerations due to lichen planus may lead to scarring and adhesions that prohibit sexual intercourse.

Treatment options are limited by the lack of consistently effective and safe drugs. Surgical procedures to reconstruct the stenotic, fibrosed vaginal vault have been performed; however, scarring frequently recurs after the procedure. Tacrolimus is a macrolide immune modulator produced by Streptomyces tsukubaensis, which has been reported to be effective in treating oral lichen planus. Tacrolimus has also been reported to be effective for treatment of erosive vulvovaginal lichen planus. Although the exact mechanism of action in treating lichen planus is unknown, topical tacrolimus has been shown to inhibit T-lymphocyte activation by inhibiting the phosphatase activity of calcineurin. Without calcineurin to dephosphorylate the nuclear factor of activated T cells, gene transcription for lymphokines, interleukin 2, and γ-interferon is inhibited, leading to a decrease in numbers of these lymphocytes.

In this retrospective review of 16 consecutive female patients with vulvar lichen planus, therapy with topical tacrolimus was safe and effective in controlling the symptoms and improving lesions in most (94%) of the patients. Topical tacrolimus is a promising new treatment option for this often recalcitrant and problematic disease.

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REFERENCES

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Table 4. Previously Reported Cases of Genital Lichen Planus Responding to Therapy With Topical Tacrolimus*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vente et al29†</th>
<th>Kirtschig et al35‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59</td>
<td>54</td>
</tr>
<tr>
<td>Duration of disease, y</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Genital site</td>
<td>Vulva, including introitus</td>
<td>Vulva, vagina</td>
</tr>
<tr>
<td>Extragenital involvement</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Prior treatment</td>
<td>Topical corticosteroids, topical retinoids</td>
<td>Topical corticosteroids, topical retinoids, topical cyclosporine</td>
</tr>
<tr>
<td>Frequency of application</td>
<td>Twice daily</td>
<td>Three times weekly</td>
</tr>
<tr>
<td>Time to response</td>
<td>4 wk to complete resolution</td>
<td>3 wk to completely healed</td>
</tr>
<tr>
<td>Current use</td>
<td>Unknown</td>
<td>Once weekly</td>
</tr>
<tr>
<td>Occurrence of relapse after cessation of therapy</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Slight burning</td>
<td>Slight burning</td>
</tr>
<tr>
<td>Duration of follow-up, wk</td>
<td>7</td>
<td>24</td>
</tr>
</tbody>
</table>

*All patients were women.
†Patients received 0.1% tacrolimus (Prograf; Fujisava Healthcare, Inc, Deerfield, Ill) in a hydrophilic petrolatum ointment containing bleached beeswax, stearyl alcohol, cholesterol, and white petrolatum.
‡Patients received 0.1% tacrolimus (Prograf; Fujisava) in a paraffin ointment.


