Successful Treatment of Anogenital Lichen Sclerosus With Topical Tacrolimus

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**Background:** Lichen sclerosus of the anogenital area is a chronic inflammatory and fibrosclerotic disease associated with substantial morbidity. Topical ultrapotent corticosteroids are currently the treatment of choice.

**Observations:** Three prepubertal girls and 3 adults (2 men, 1 woman) were treated with 0.1% tacrolimus ointment once daily. All patients experienced complete resolution with long-lasting remission for up to 1 year. No major adverse effects were observed, and treatment was well tolerated.

**Conclusions:** Topical tacrolimus is a promising novel agent in the treatment of lichen sclerosus of the anogenital area. A major advantage over topical corticosteroids is the lack of skin atrophy. Further clinical trials are warranted to confirm our findings.

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LICHEN SCLEROSUS (also known as kraurosis vulvae in women and balanitis xerotica obliterans in men) is a chronic inflammatory fibrosclerotic skin disorder that can affect any site of the body but occurs most commonly in the anogenital area. When affecting the latter region, lichen sclerosus can lead to substantial morbidity, including itching and burning, dysuria, painful intercourse and defecation, and anal and vulval bleeding. Scarring atrophy may cause labial fusion and phimosis requiring plastic surgery in women and circumcision in men. In addition, patients with anogenital disease are at increased risk for development of squamous cell carcinoma in the affected area.

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The cause of lichen sclerosus is still unknown. An association with borreliosis has been suspected but recent studies were unable to support this theory. Ultra-potent topical corticosteroids such as clobetasol propionate have become the first-line treatment for genital lichen sclerosus in adults and children. They are applied daily for up to 3 months and afterwards at reduced frequency. Such treatment can reverse some of the histologic changes of lichen sclerosus with reduction in epidermal atrophy. However, recurrences are common and maintenance or intermittent therapy is often required. In addition, it is well established that overuse of topical corticosteroids causes skin atrophy. Since tacrolimus is not atrophogenic, we evaluated the potential of this new topical immunosuppressant in the treatment of anogenital lichen sclerosus.

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**REPORT OF CASES**

We describe 6 patients (3 prepubertal girls, aged 5, 9, and 9 years; one 46-year-old woman; and 2 men, aged 30 and 62 years) with typical lichen sclerosus of the anogenital area (Table). All patients had extensive genital pruritus. The second-9-year-old girl (patient 3) also experienced painful defecation during each toilet visit that lasted for up to 1 hour. All female patients presented with characteristic porcelain-white atrophic scarring in a figure-8 pattern around the vulva and anus and associated with hemorrhages and erosions (Figure, A). In addition, patient 3 had a perineal protrusion, an unusual manifestation of lichen sclerosus recently described. The 2 men had the disease for about 2 years, affecting the glans penis and foreskin. There were white fibrous constrictions around the penile shaft making circumcision problematic.
All patients had tried numerous therapies including emollients, antifungal agents, astringents, estrogen ointments (adult woman), and testosterone ointments (men). Potent topical corticosteroids had been used intermittently for short courses, more often and longer in the adult patients than in the prepubertal girls. Anal dilatation had been performed in patient 3 (the 9-year-old girl with perineal protrusion) without benefit. Biopsy specimens from lesional skin of the 2 men and the woman were similar and showed epidermal atrophy, hydropic degeneration of the basal keratinocytes, homogenization of the collagen in the upper dermis, and a subepidermal mononuclear infiltrate consistent with lichen sclerosus.

Since the diagnosis was obvious, biopsies from the young girls were not requested. Blood tests for Borrelia burgdorferi were negative in 5 patients but revealed a positive IgM titer in one 9-year-old girl (patient 2), whereupon amoxicillin was prescribed for 2 weeks without any benefit on the lichen sclerosus.

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Tacrolimus ointment (Protopic; Fujisawa Healthcare Inc, Deerfield, Ill) was applied once daily. We chose the 0.1% ointment because previous studies had shown that this concentration is more potent than the 0.03% ointment without increasing the frequency of adverse effects. After 1 to 2 weeks, all patients reported substantial improvement and reduction of pruritus. Complete remission occurred in the 5-year-old girl after 1 1/2 months (Figure, B), in one 9-year-old girl (patient 2) after 4 1/2 months, and in the woman within 6 1/2 months. In the second 9-year-old girl (patient 3), pain on defecation disappeared within the first 2 months, and complete resolution including the perineal protrusion occurred within 7 months. In both men, tacrolimus ointment induced complete clearing after 10 months.

After remission, treatment with tacrolimus was discontinued in all patients. During a follow-up period of 12 months in the 5-year-old and 8 months in one of the 9-year-old girls (patient 2) and in the woman, no new lesions developed. In the 2 men, there was no relapse during a follow-up period of 9 and 11 months. There was no rebound flare in any patient after discontinuation of treatment with tacrolimus ointment. In general, tacrolimus ointment was well tolerated. The 3 prepubertal girls experienced a slight burning sensation for several minutes on applying the ointment. These minor adverse effects subsided within a few days. There were no signs of atrophy at any treated site (Table).

During therapy, the whole-blood concentration of tacrolimus was measured in 2 patients. In the first girl (patient 2), the tacrolimus level was 1.6 ng/mL, while in the second girl (patient 3), it was undetectable (lower limit of detection, 1.5 ng/mL; therapeutic range in organ transplant recipients, 5-15 ng/mL).

### Clinical Data for Study Patients

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Duration of Disease</th>
<th>Previous Therapies</th>
<th>Duration of Tacrolimus Therapy, mo</th>
<th>Outcome</th>
<th>Relapse-Free Period, mo</th>
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<td>4.5</td>
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<td>8</td>
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<tr>
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<td>em, af, as, st, te</td>
<td>10</td>
<td>CR</td>
<td>9</td>
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<tr>
<td>6/M/62</td>
<td>2 y</td>
<td>em, af, as, st, te</td>
<td>10</td>
<td>CR</td>
<td>11</td>
</tr>
</tbody>
</table>

Abbreviations: ad, anal dilatation; af, antifungal agents; as, astringents; em, emollients; es, estrogen ointments; st, topical corticosteroids; te, testosterone ointments; CR, complete remission.

A, Typical lichen sclerosus with porcelain-white atrophic scarring, erosions, and hemorrhages in the genital area. B, After 6 weeks of treatment with topical 0.1% tacrolimus.
Tacrolimus (FK506) is an immunosuppressive agent used as a systemic drug for the prevention of organ rejection after allogeneic transplantation. Because of its structural and pharmacokinetic properties, tacrolimus penetrates better than cyclosporine into the skin. Multi-center randomized trials with topical formulations have shown short- and long-term therapy to be effective and safe in adults and children with moderate to severe atopic dermatitis. Tacrolimus acts by inhibiting calcineurin, a phosphatase crucially involved in gene transcription of activated T lymphocytes. Recent studies confirmed that tacrolimus neither affects keratinocyte proliferation nor interferes with collagen synthesis. This feature is of particular interest when treating atrophy-prone sites such as intertriginous areas and the face. In contrast, topical corticosteroids, which are the treatment of choice for anogenital lichen sclerosis, are well known to cause skin atrophy. We have repeatedly observed atrophy, telangiectasia, and striae distensae in patients treated for as short a period as 4 weeks with topical corticosteroids in intertriginous areas. Conversely, in our patients, treatment with topical tacrolimus did not induce atrophy and showed excellent effects on anogenital lichen sclerosis. Therapy was tolerated well, and there was no rebound flare, which occurs with corticosteroid therapy. None of the patients showed any signs of relapse.

We believe that the defective barrier in the inflamed anogenital skin and the natural occlusion in this intertriginous area largely contribute to the efficacy of topical tacrolimus. Dermal penetration studies on intact human skin have shown a relatively low percutaneous absorption of tacrolimus ointment, while penetration in damaged skin is markedly higher. Since penetration may be higher in early or erosive lesions than in fibrosclerotic skin, treatment of lichen sclerosus with tacrolimus should be initiated as soon as possible. In our patients, remission took longer to achieve the longer the patient had the disease (Table). It is possible that the advanced fibrotic stage of lichen sclerosus may take longer to resolve than the early inflammatory stage. Our encouraging findings on the efficacy of topical tacrolimus in anogenital lichen sclerosus are supported by the good results of this new immunosuppressive agent in erosive oral lichen planus where penetration can also be expected to be high.

Despite optimal conditions for penetration and resorption in the treated intertriginous sites, tacrolimus blood levels were below or at the detection limit. This may be owing to the relatively limited treatment area. Because of concern about percutaneous absorption in this area close to mucosal surfaces—especially in the children—tacrolimus ointment was applied only once a day. A twice-daily regimen may optimize and shorten the treatment. However, until more data are available regarding the percutaneous absorption of tacrolimus in the genital area, we recommend monitoring the blood level in children.

In summary, topical tacrolimus appears to be a promising novel agent in the treatment of lichen sclerosus of the anogenital area. Application is not associated with skin atrophy as is treatment with overused topical corticosteroids. As shown by this pilot study, topical tacrolimus is well tolerated even in the anogenital area. However, careful long-term follow-up is mandatory in these patients, and controlled clinical trials are warranted to confirm our findings.

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REFERENCES