Low-concentration Topical Tacrolimus for the Treatment of Anogenital Lichen Sclerosus in Childhood: Maintenance Treatment to Reduce Recurrence

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A B S T R A C T

Background: Lichen sclerosus (LS) is a chronic inflammatory skin disorder that is commonly found in the anogenital area, especially in females. Ultra-potent topical corticosteroids are first line for the treatment of LS, but their atrophic side effects and the recurrence of the disease restrict their use. An equally effective, safer, tolerant therapeutic option is required, especially in the treatment and preventing relapse of children.
Methods: Fourteen prepubertal girls (range of age: 4 to 11years) with anogenital lichen sclerosus were treated with 0.03% tacrolimus ointment twice daily for 16 weeks, then 9 of the 14 patients adhered to 2 times weekly for further 6 months (a total of 10 months). The therapeutic effects were evaluated according to 3 grades: complete response (>75% improvement, partial response (30%-75% improvement), or no response (<30% improvement).
Results: Clinical improvement occurred in all patients (100%). Complete response of symptoms and signs was achieved in 5 (36%), 9 (64%) and 11 (79%) patients at week 8, week 16, and month 10 respectively. During the follow-up period of 1 year, 4 patients (4/5, 80%) who treated with tacrolimus ointment for 16 weeks had a recurrence of symptoms, while only 2 of 9 (22%) patients who insisted on maintenance therapy developed recurrence of disease. No severe side effects were observed.
Conclusions: Low-concentration topical tacrolimus appears to be an effective and safe treatment for children with anogenital lichen sclerosus. Maintenance therapy (2 times a week for 6 months) can reduce the relapse of the disease.
Key Words: Anogenital, Childhood, Lichen sclerosus, Topical tacrolimus, Maintenance therapy

Introduction

Lichen sclerosus (LS) is a chronic inflammatory and relapsing skin disorder,[1–3] that occurs commonly on the skin and mucosae of the anogenital area, particularly on the vulva. It affects most commonly postmenopausal women; however, it has another peak in prepubertal girls.

Childhood LS represents 15% of total cases of the disorder, with a 10:1 ratio of females to males.[4] One review study on pediatric vulvar LS indicated a prevalence of 1:900 girls.[5,6] The disease runs a chronic course and is often characterized by severe pruritus, dysuria, and painful defecation.[7] Typical lesions of lichen sclerosus are porcelain-white papules and plaques. The skin commonly appears thinned, whitened and crinkling ("cigarette paper" appearance).[8] Although the cause of LS is still unclear, autoimmune association and genetic susceptibility are suggested.[5,9]

Topical corticosteroids (TCS) remain the primary treatment of vulvar LS[10] including in children at present. LS requires continuous topical steroid treatment because of a high recurrence rate of up to 82% after stopping steroids[11]; however, long-term super-potent TCS use can cause skin atrophy and telangiectasia, so alternative well tolerated therapies are required, especially in the treatment of childhood LS.

The nonsteroidal anti-inflammatory drug tacrolimus ointment is a topical calcineurin inhibitor (TCI)[12,13]; it is approved for the treatment of atopic dermatitis in patients above the age of 2 years.[14] This agent is an immunomodulator that blocks the proliferation of T-lymphocytes and therefore the release of inflammatory cytokines from these cells.[12] TCIs are as effective as a mid-potency steroid,[15,16] but they do not cause side effects that are known to be associated with prolonged use of topical corticosteroids. There have been many reports about other immuno-mediated skin diseases such as vitiligo,[17] psoriasis,[18] vulvar lichen planus,[19] and pruritic diseases such as generalized or localized pruritus. Prurigo nodularis[20] may be treated with topical tacrolimus ointment. Recently, some authors have reported the therapeutic effects of topical tacrolimus in the treatment of lichen sclerosus. According to these researchers, beneficial effects of topical tacrolimus on genital lichen sclerosus can be found.[21–24] Matsumoto et al[25] first reported topical low-concentration tacrolimus showing a dramatic effect in the treatment of a 5-year-old girl's vulvar lichen sclerosus.

Therefore, we expect that topical tacrolimus might also be beneficial in more childhood patients with vulvar lichen sclerosus. Considering their age and location, we chose the low concentration tacrolimus ointment (0.03%). We evaluated the efficacy and safety of 0.03% topical tacrolimus in anogenital LS.

Methods

Patients

Fourteen prepubertal girls who suffered from LS of the anogenital region were recruited from the outpatient clinic

The authors indicate no conflicts of interest.

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1083-3188/$ - see front matter
http://dxdoi.org/10.1016/j.jpag.2012.11.010

Table 1
Basic Characteristics of 14 Patients with Lichen Sclerosus

Total	N = 14
Mean age (y)	8.1 (4-11)
Mean duration of the disease (mo)	13.8 (6-30)
Involvement	
Vulva and anus (a figure of "8")	9
Vulva	5
Clinical features	
Pruritus	14
Whitish sclerotic lesions	14
Burning pain	7
Dysuria	4
Painful defecation	5
Bleeding	14
Fissuring	4
Erythema	3
Erosion	5
Ulceration	2
Crusting	4
Previous diagnosis	
Eczematous dermatitis	3
Fungal infection	2
Vitiligo	2
Previous treatment	
Topical steroids	5
Topical anti-fungals	2

at the Department of Dermatology, between May 2006 and September 2010 (Tables 1, 2). Inclusion criteria were age between 2 and 12 years, and with typical clinical vulvar lichen sclerosus. Exclusion criteria were concomitant severe chronic disease, allergy to macrolides, contraindications for tacrolimus, other dermatologic diseases, viral systemic disease. The 14 patients had a mean age of 8.1 years (range 4-11) and a mean duration of vulvar disease of 13.8 months (range 6-30). Because of the unequivocal clinical appearance and the patients' age, only 4 girls had a biopsy-proven diagnosis. All patients had extensive pruritus and characteristic whitish, sclerotic skin changes in the vulvar and perineal region; nine had additional involvement of the perianal region (figure of "8"). Patients' subjective complaints were burning pain (n = 9), dysuria (n = 7), painful defecation (n = 4), skin findings of lichen sclerosus included erythema (n = 3), erosion (n = 5), bleeding (n = 5), partly deep fissuring (n = 4), ulceration (n = 2), and crusting (n = 4), as listed in Table 1. Some patients had been misdiagnosed with eczematous dermatitis (n = 3), fungal infection (n = 2), vitiligo (n = 2); 5 patients had been treated with topical steroids and 2 patients had been treated with topical antifungal agents, but the effect was not remarkable (Table 1). All patients were asked to discontinue other treatments including topical and systemic agents for 2 weeks before the study started.

Treatment Protocol and Assessment

0.03% tacrolimus ointment (Protopic, Astellas Toyama Co, Toyama, Japan) was applied twice daily in a thin layer to the affected areas for 16 weeks, then 2 times per week for 6 months for 9 of the patients voluntarily (maintenance treatment); no other topical or systemic therapy was allowed. Clinical examination and recording of patients' symptoms was performed before, at week 4, 8, 12, and 16 of the therapy, and at month 1, 3, and 6 of maintenance treatment, then at 1, 3, and12 months in the post-therapy follow-up period. Local skin reactions such as erythema, bleeding, erosion, ulceration, and crusting were assessed visually by the doctor. The severity was graded using the following scale: 0, absent; 1, mild; 2, moderate; 3, severe. Subjective symptoms such as burning pain, dysuria, and pruritus were graded by the patients (0, absent; 1, mild; 2, moderate; 3, severe), and were recorded at every treatment visit. The response to therapy was assessed at the scheduled clinic visits, by the same 2 dermatologists who compared the clinical symptoms and photographs obtained at the initial visit and last visit. Complete response (CR) was defined as more than 75% improvement of clinical signs (erythema, erosion, fissuring, crusting, and ulceration, except sclerosis and atrophy), and subjective symptoms (burning pain, pruritus, dysuria) attributable to lichen sclerosus. Partial response (PR) was defined as 30%-75% improvement in the severity of clinical signs, and subjective symptoms attributable to lichen sclerosus. No response (NR) was assigned to less than 30% improvement in clinical signs and subjective symptoms.

We observed and compared the treatment response at 8 weeks (short-term treatment), 16 weeks (long-term treatment), and 10 months (maintenance treatment) respectively, in addition, we compared the relapse rate of LS between long-term treatment and maintenance treatment.

Table 2
Clinical Data of Each Patient Treated with Tacrolimus

Patient No./age (y)	Duration (mo)	Distribution	Initial Response (wk)	Efficacy (8 wk)	Efficacy (16 wk)	Maintenance Treatment	Efficacy (10 mo)	Relapse	Side Effects
1/8	9	"8"	4	PR	CR	Yes	CR	No	Burning
2/11	11	"8"	2	CR	CR	No	CR	No	No
3/10	18	Vulvar	2	PR	PR	Yes	CR	No	Folliculitis
4/6	6	Vulvar	4	PR	CR	Yes	CR	Yes	Burning
5/9	20	"8"	2	CR	CR	Yes	CR	No	No
6/7	10	"8"	2	PR	CR	No	CR	Yes	No
7/6	8	"8"	4	NR	PR	No	PR	Yes	Itching
8/9	12	Vulvar	3	PR	PR	Yes	PR	No	No
9/4	30	"8"	4	PR	PR	No	PR	Yes	Burning
10/8	15	"8"	2	CR	CR	No	CR	Yes	No
11/9	14	Vulvar	3	CR	CR	Yes	CR	No	Hyperpigmentation
12/10	7	Vulvar	4	NR	PR	Yes	CR	No	Itching
13/8	16	"8"	2	PR	CR	Yes	CR	No	No
14/9	18	"8"	2	CR	CR	Yes	CR	Yes	No

"8", a figure of eight; CR, complete response (>75% improvement); NR, no response (<30% improvement); PR, partial response (30%-75% improvement)