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Original articles

Dosage and Adverse Effects of Topical Tacrolimus and Steroids in Daily Management of Atopic Dermatitis

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Abstract

Since 1999, combination therapy with tacrolimus and topical steroids has been widely used for the treatment of adolescent/adult-type atopic dermatitis. In order to determine the clinical doses of topical tacrolimus and steroids for daily treatment of atopic dermatitis and to elucidate their beneficial and adverse effects, we analyzed the clinical data from 215 patients with atopic dermatitis who were more than 16 years old. Less than 70g of tacrolimus and less than 15 g of steroids were applied to 90% of the patients on the face and neck, and less than 75.8 g of tacrolimus and less than 322 g of steroids were applied to 90% of the patients on the trunk and extremities during the six-month treatment period. Topical tacrolimus is much more frequently used on face and neck lesions (99.1%); in only 39.5% of cases was it used on the trunk and extremities. The majority of patients improved after six months of the combination topical therapy; however, atopic dermatitis was not controlled in 6% of the patients. The combination therapy did not seem to increase the risk of cutaneous infections; however, the incidence of herpes simplex infection on the face and neck was 2.8% at pre-treatment and slightly increased to 4.7% during the therapy. The incidence of all steroid-induced adverse effects was reduced both in frequency and intensity with a decrease in the dose of topical steroids through simultaneous tacrolimus application. Combination therapy with topical tacrolimus and steroids is useful for treating atopic dermatitis, but a small percentage of the patients still cannot be satisfactorily treated. For such patients, adjustments of the dose and rank of topical steroids and tacrolimus and other therapeutic adjuncts are necessary.

Abbreviation: AD: atopic dermatitis

Key words: atopic dermatitis; topical tacrolimus; topical steroids; dose, adverse effects

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Introduction

Atopic dermatitis (AD) is a common, chronic or chronically relapsing, severely pruritic, eczematous skin disease mostly associated with hyperimmunoglobulinemia E and eosinophilia. Although any area can be affected, the eczematous lesions have a predilection for the face, neck, and flexure sites. The incidence of AD is generally considered to be increasing worldwide (1, 2). The percentage of adolescent- and adult-type AD has also been increasing (3, 4). In 1936, Brunsting pointed out that the recurrent lesions of adolescent and adult AD

Table 1. Changes of clinical severity pre- and post-treatment

		Pre-treatment state				Total (215)
		Very severe	Severe	Moderate	Mild	
Post-treatment state	Very severe					0
	Severe	5	5			10 (5%)
	Moderate	5	30	31	3	69 (32%)
	Mild	5	20	79	32	136 (63%)
	Total (215)	15 (7%)	55 (26%)	110 (51%)	35 (16%)	

: Uncontrolled patients, 6%

were resistant to treatment by local measures (5). In accordance with this notion, our previous study, which evaluated the clinical dose of topical steroids, revealed that the incidence of very severe and severe AD was significantly higher in the adolescent and adult AD group than in the infantile and childhood groups (6). Moreover, the clinical manifestations were more unresponsive to the anti-inflammatory effects of topical steroids in adolescent and adult AD than in infantile and childhood AD (6).

A substantial percentage of AD patients have intractable facial dermatitis, which is usually called atopic red face. Nakagawa et al. first pointed out that topical tacrolimus (FK-506) is very effective, especially on face and neck lesions of AD (7). It has been widely used in Japan since 1999 in combination with topical steroids for the treatment of AD and, more recently, worldwide (8, 9). However, there is little information about the clinical dosage and adverse effects of topical combination therapy with tacrolimus and steroids in outpatient clinics. In order to clarify these points and to further assess the clinical impact of tacrolimus on the former topical therapy, we analyzed clinical data from 215 patients with AD.

Materials and Methods

Subjects and patient information

We collected clinical data from 215 AD patients (mean age, 29.5 ± 9.5 years; males, 111; females, 99; sex not noted, 5). All fulfilled the Japanese Dermatological Association criteria for the diagnosis of AD (10) and had been followed for at least six months in outpatient clinics. The chart for each patient included the following: age; gender; duration of AD; global severity before treatment; global severity after six months of topical therapy; total dose of topical tacrolimus per six months' therapy on the face and neck, and trunk and extremities, respectively; total dose of each rank of topical steroids per six months' therapy on the face and neck, and trunk and extremities, respectively; total dose of moisturizing emollients per six months' therapy; association of herpes simplex infection; association of molluscum contagiosum; and adverse effects. Global clinical severity was classified as "very severe", "severe", "moderate", or "mild." A "very severe" case was defined as inflamed skin lesions covering more than 30% of the body surface, a "severe" case was defined as inflamed skin lesions covering more than 10% but less than 30% of the body surface, a "moderate" case was defined as inflamed skin lesions covering less than 10% of the body surface, and a "mild" case was defined as lesions being mostly mild, such as dry skin, scaling and faint erythema (6). Topical steroids were ranked as "strongest", "very strong", "strong", "mild", and "weak".

Statistical analysis

The dosage of drugs within groups were compared by the Mann-Whitney's U-test.

Results

Clinical severity and total dosage of topi-

Table 2. Total clinical dose of topical tacrolimus and steroid during the 6-month treatment period

		Tacrolimus	Steroid
Face & Neck	Median	29 (g)	0 (g)
	75 percentile	49	5
	90 percentile	70	15
Trunk & Extremities	Median	0	75
	75 percentile	10	175
	90 percentile	75.8	322
Moisturizing emollients	Median	130	
	75 percentile	315	
	90 percentile	600	

Table 3. Cutaneous infections before and during the 6-month treatment period

		Total (severe, moderate, mild)
Face & Neck		
Acne & folliculitis	Pre-treatment	22.8% (0.9 2.8 19.1) %
	During treatment	17.3% (0 1.4 15.9) %
Bacterial infection	Pre-treatment	5.6% (0 1.4 4.2) %
	During treatment	1.9% (0 0.9 0.9) %
Fungal infection	Pre-treatment	0% (0 0 0) %
	During treatment	0% (0 0 0) %
Herpes simplex infection	Pre-treatment	2.8% (0.5 0.9 1.4) %
	During treatment	4.7% (0 2.8 1.9) %
Molluscum contagiosum	Pre-treatment	0% (0 0 0) %
	During treatment	0% (0 0 0) %
Trunk & Extremities		
Acne & folliculitis	Pre-treatment	5.6% (0 0.9 4.7) %
	During treatment	4.2% (0 0.5 3.7) %
Bacterial infection	Pre-treatment	2.8% (0 0.5 2.3) %
	During treatment	2.3% (0 0.9 1.4) %
Fungal infection	Pre-treatment	0% (0 0.5 0) %
	During treatment	1.4% (0 0 1.4) %
Herpes simplex infection	Pre-treatment	0.9% (0.5 0 0.5) %
	During treatment	0.9% (0 0.5 0.5) %
Molluscum contagiosum	Pre-treatment	0 % (0 0 0) %
	During treatment	0.5% (0 0 0.5) %

cal tacrolimus and steroids

Pre- and post-treatment severity grades are summarized in Table 1. The clinical severity of AD in the majority of patients improved or was unchanged after six months of combination topical therapy. In only 6% (13/215) of patients was AD uncontrolled, that is, it remained very severe or severe or was exacerbated (Table 1).

Total doses of topical tacrolimus and steroids used during the six-month treatment period are presented in Table 2 as me-

Table 4. Changes in adverse effects of topical steroid pre- and post-treatment

		Total (severe, moderate, mild)
Telangiectasia on cheeks	Pre-treatment	34.9% (1.9 6.5 26.5) %
	Post-treatment	18.7% (0 1.9 16.8) %
Hypertrichosis on face	Pre-treatment	4.7% (0 0.5 4.2) %
	Post-treatment	1.9% (0 0 1.9) %
Skin atrophy of antecubital fossae	Pre-treatment	19.1% (0 2.3 16.7) %
	Post-treatment	13.6% (0 0.5 13.1) %
Skin atrophy of popliteai fossae	Pre-treatment	18.1% (0 1.9 16.3) %
	Post-treatment	10.8% (0 0.5 10.3) %

Table 5. Doses of topical tacrolimus and steroid on the face & neck during 6 months of treatment between "Reduced" and "Unreduced" groups with telangiectasia on cheeks

	Tacrolimus		Steroids					
			Total doses		"Strongest+very strong+strong" rank doses		"Mild+weak" rank doses	
	R	U	R	U	R	U	R	U
Median	27 (g)	30	0 (g)	0	0 (g)	0	0 (g)	0
75 percentile	45	71	5	10	0	0	3	10
90 percentile	65.2	113	10.6	26	0	0	10	26
Mann-Whitney's U-test	0.3006		0.0671		0.2746		0.032*	

R: "Reduced" group U: "Unreduced" group

dian, 75 percentile, and 90 percentile doses applied to the face and neck, and trunk and extremities, respectively. Fifty percent of the patients applied less than 29 g, 75% of the patients applied less than 49 g, and 90% of the patients applied less than 70 g of tacrolimus on the face and neck, while less than 15 g of steroids were applied by 90% of the patients to the face and neck during the six-month treatment period (Table 2). Less than 75.8 g of tacrolimus and less than 322 g of steroids were applied by 90% of the patients to the trunk and extremities during the six-month treatment period. The 90 percentile dose of moisturizing emollients was 600 g during the six-month treatment period. Because of the better clinical effects of tacrolimus on the face and neck area than on other areas, topical tacrolimus was much more frequently used on face and neck lesions (99.1%, 213/215); it was used by only 39.5% of patients (85/215) on the trunk and extremities.

Cutaneous infections before and during combination topical therapy

Bacterial and viral infections are commonly associated with AD (10). Because tacrolimus is an immunosuppressive drug and may increase the risk of cutaneous infections, we next compared the incidence of cutaneous infections before and during treatment. As shown in Table 3, acne and folliculitis were frequently observed on the face and neck; however, most manifestations were mild. The pre-treatment incidence of acne and folliculitis on the face and neck was 22.8% and during therapy was 17.3%. Bacterial infection on the face and neck was found before treatment in 5.6% of patients,

Table 6. Doses of topical tacrolimus and steroid on the trunk & extremities during 6 months of treatment between "Reduced" and "Unreduced" groups with skin atrophy of antecubital fossae

	Tacrolimus		Steroids					
			Total doses		"Strongest+very strong+strong" rank doses		"Mild+weak" rank doses	
	R	U	R	U	R	U	R	U
Median	0 (g)	0	72.5 (g)	137	69 (g)	137	0 (g)	0
75 percentile	7.5	30.3	163.8	228.8	150	185	0	0
90 percentile	73.7	96.4	315.5	405	300	344.5	0	59
Mann-Whitney's U-test	0.2152		0.1792		0.1493		0.5558	

R: "Reduced" group, U: "Unreduced" group

Table 7. Doses of topical tacrolimus and steroid on the trunk & extremities during 6 months of treatment between "Reduced" and "Unreduced" groups with skin atrophy of popliteal fossae

	Tacrolimus		Steroids					
			Total doses		"Strongest+very strong+strong" rank doses		"Mild+weak" rank doses	
	R	U	R	U	R	U	R	U
Median	0 (g)	0	75 (g)	100	70 (g)	100	0 (g)	0
75 percentile	9	30.8	172.5	220.3	157.5	195	0	0
90 percentile	77.2	76.5	309	435	292	383.5	0	45
Mann-Whitney's U-test	0.3832		0.3211		0.2757		0.8111	

R: "Reduced" group, U: "Unreduced" group

and its incidence was decreased (1.9%) during the combination therapy. The pre-treatment incidence of herpes simplex infection on the face and neck was 2.8% and increased slightly to 4.7% during therapy. The incidence of other adverse effects such as fungal and molluscum infections was very low (0 to 1.4%).

Beneficial effects of topical tacrolimus on steroid-induced adverse effects

In previous clinical trials of topical tacrolimus, it has been observed that the steroid-induced adverse effects gradually disappeared upon reducing the dose of steroid during the tacrolimus treatment (11). We therefore compared the pre- and post-treatment incidence of four major steroid-induced adverse effects in patients with AD, such as telangiectasia of the cheeks, hypertrichosis on the face, skin atrophy of antecubital fossae, and skin atrophy of popliteal fossae. As expected, the incidence of all steroid-induced adverse effects was reduced in both frequency and intensity (Table 4). We next analyzed the dosages of topical steroids and tacrolimus between patients who had "reduced" incidence of

steroid-induced adverse effects with those in the "unreduced" group. When we focused on the telangiectasia of cheeks, although both groups almost exclusively used "mild" or "weak" ranked steroids on the face, the "unreduced" group had used significantly greater amounts of steroids ("mild + weak" rank) than had the "reduced" group (Table 5). In patients with steroid-induced skin atrophy of the antecubital fossae or popliteal fossae, the "unreduced" group had also used greater amounts of topical steroids than had the "reduced" group, but the difference was not statistically significant (Tables 6, 7).

Discussion

Topical tacrolimus has been commercially available for the treatment of AD patients older than age 16 years in Japan since 1999. Before topical tacrolimus was approved for clinical use, we examined the clinical dose and beneficial and adverse effects of topical steroids in a series of 1,271 patients with AD (6). We reported that AD was well controlled in the majority of patients; however, 7% of infantile, 10% of childhood, and 19% of adolescent and adult patients remained in a very severe or severe state or experienced exacerbation even though they applied larger amounts of topical steroids than did the controlled patients (6). These were so-called "intractable" patients, and such patients are given much attention as a social problem in Japan. These patients often fear long-term use of topical steroids and may be included among persons with serious topical steroid phobia (12). In the present study we intended to elucidate the impact of topical tacrolimus on daily treatments for AD in combination with topical steroids and emollients. The majority of our AD patients were effectively treated by a combination of topical tacrolimus and steroids, resulting in a marked decrease of "uncontrolled" patients with adolescent/adult type AD in comparison with previous data (19% to 6%) (6). Before the approval of tacrolimus for clinical use, the 90% dose of topical steroid was 35g/6 months on the face as reported previously (6), whereas topical tacrolimus apparently reduced the dose of steroid to 15g/6 months.

AD is known to be frequently associated with bacterial and viral infections. Bacterial infection has been reported to occur in 40% of patients with AD, with 15% of the patients requiring hospitalization (13). Viral infections associated with AD include herpes simplex, which has a reported incidence of 6% to 10% (14–16), and molluscum contagiosum at 4% (14). As tacrolimus and steroids are both immunosuppressive drugs, the combination topical therapy may potentially increase the risk of cutaneous infections. In the present study, however, the incidence of cutaneous infections did not seem to be increased during treatment compared with pre-treatment. Instead, the incidence of bacterial infection was decreased from 5.6% to 1.9% on the face and neck, probably due to the marked clinical improvement of dermatitis by the combination therapy. In contrast, the incidence of herpes simplex infection did increase from 2.8% to 4.7% on the face and neck. In our previous data before the approval of tacrolimus for clinical use, the incidence of herpes simplex infection in adolescent/adult AD patients was 3.5% (6). It is difficult to conclude that the combination topical therapy increases the risk of herpes simplex infection in AD. Further studies are necessary. Very recently, Fleischer et al. reported that tacrolimus ointment for the treatment of AD was not associated with an increase in cutaneous infections (17). Our data may support their findings.

Topical steroid application induces mild and reversible cutaneous side effects such as hypertrichosis, telangiectasia and skin atrophy (18). The possibility that a reduction of the dose of topical steroid by tacrolimus application clearly attenuated the incidence and intensity of steroid-induced side effects has been reported (11). This was the case in the present study. During the six-month treatment period, both the incidence and intensity of steroid-induced adverse effects

such as telangiectasia on the cheeks and hypertrichosis on the face decreased by almost half. Patients with unreduced side effects like teleangiectasia on the cheeks used significantly larger amounts of steroid on the face.

Combination therapy using topical steroids and tacrolimus dramatically decreased the number of patients with intractable AD, attenuating steroid-induced adverse effects. However, it should be mentioned that there still appears to be a small sub-group of patients whose AD remains severe despite increasing applications of topical steroids and tacrolimus. For such patients, adjustments of dose and rank of topical steroids seem to be necessary in combination with other therapies such as ultraviolet irradiation, education about treatment, and psychological counseling.

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Intermittent Topical Corticosteroid/Tacrolimus Sequential Therapy Improves Lichenification and Chronic Papules More Efficiently than Intermittent Topical Corticosteroid/Emollient Sequential Therapy in Patients with Atopic Dermatitis

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Abstract

Atopic dermatitis (AD) is a common, chronic, relapsing, severely pruritic, eczematous skin disease. Topical steroids are the mainstay of treatment. However, the adverse effects of steroids on hormonal function are the major obstacle for their use as long-term topical therapy. Intermittent dosing with potent topical steroids and/or combination therapy with steroid and tacrolimus have been frequently used in the daily management of AD to overcome the problems accompanying the long term use of steroids. We compared the clinical effects of topical steroid/tacrolimus and steroid/emollient combination treatments in 17 patients with AD. An intermittent topical betamethasone butyrate propionate/tacrolimus sequential therapy improved lichenification and chronic papules of patients with AD more efficiently than an intermittent topical betamethasone butyrate propionate/emollient sequential therapy after four weeks of treatment. Only one out of 17 patients complained of a mild, but temporary, burning sensation after tacrolimus application. The intermittent topical steroid/tacrolimus sequential therapy may be a useful adjunctive treatment for AD.

Abbreviation: AD: atopic dermatitis

Key words: atopic dermatitis; topical tacrolimus; topical betamethasone butyrate propionate; sequential therapy

Introduction

Atopic dermatitis (AD) is a common, chronic, relapsing, severely pruritic, eczematous skin disease that is frequently associated with hyperimmunoglobulinemia E and eosinophilia. Although any area can be affected, the eczematous lesions have a predilection for the face, neck, and flexure sites. The incidence of AD is increasing worldwide and affects approximately 5% to 20% of all children by 11 years of age (1, 2). The incidence of adolescent- and adult-type AD has also been increasing (3). In 1936, Brunsting pointed out that the recurrent lesions of adolescent and adult AD were resistant to treatment by local measures (4). Our previous study, which evaluated the efficacy and clinical doses of topical steroids, also showed that the incidence of severe to very severe AD was significantly higher in the adolescent and adult AD group than in the infantile and childhood groups (5). Moreover, 7% of infantile, 10% of childhood, and

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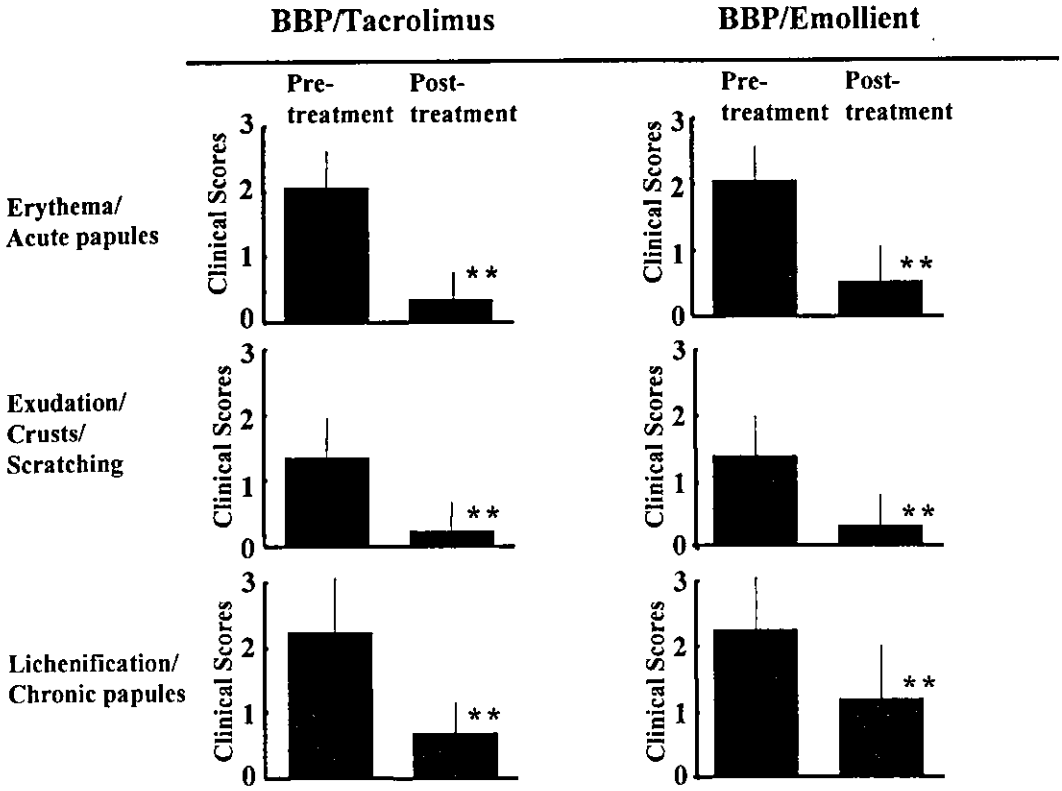

Fig. 1. Clinical effects of intermittent topical betamethasone butyrate propionate (BBP)/tacrolimus, and BBP/emollient sequential treatment. The eruption scores (mean ± SD) were evaluated at pre-treatment and post-treatment after four weeks of treatment. ** indicates $p<0.01$.

19% of adolescent and adult patients remained in a severe to very severe state or experienced exacerbation despite the application of higher amounts of topical steroids when compared to well-controlled patients (5). Such failures to respond to high doses of topical steroids suggests that the clinical manifestations of AD in adolescent and adult patients are less responsive to the anti-inflammatory effects of topical steroids than are patients with infantile and childhood AD.

Nakagawa et al. first pointed out that topical tacrolimus (FK-506) is very effective, especially on face and neck lesions of AD (6). It has been widely used in Japan since 1999 in combination with topical steroids, and, more recently worldwide (7, 8) for the treatment of AD. Topical steroids are classified in Japan as "strongest", "very strong", "strong", "mild" and "weak". Topical tacrolimus has been shown to be as effective as "strong" rank steroids on lesions of the trunk and extremities (7). Patients prefer to use "very strong" or "strong" steroids other than tacrolimus because of the initial burning sensation after application and of its low potency due to poor skin penetration. However, the reduction of the dose of topical steroid when tacrolimus is used clearly attenuates both the incidence and intensity of steroid-induced side effects (9).

The purpose of this study was to determine whether topical betamethasone butyrate propionate/tacrolimus sequential therapy is more effective than topical betamethasone butyrate propionate/emollient sequential therapy in the treatment of AD.

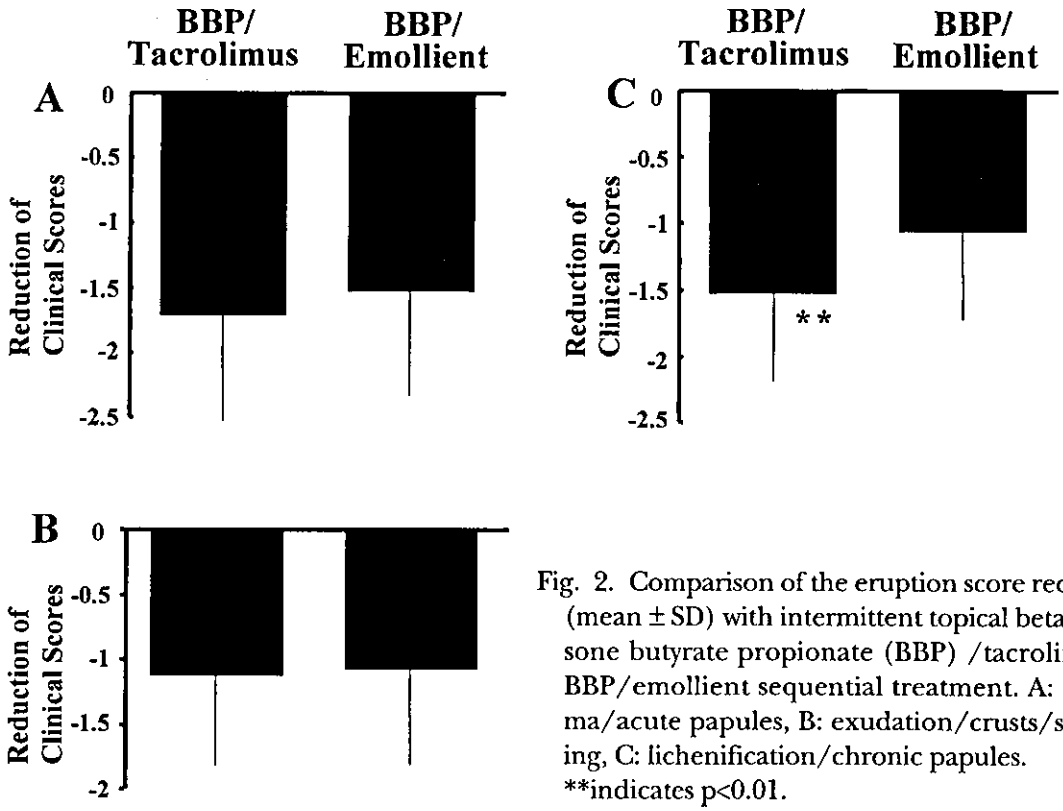

Fig. 2. Comparison of the eruption score reduction (mean ± SD) with intermittent topical betamethasone butyrate propionate (BBP) /tacrolimus or BBP/emollient sequential treatment. A: erythema/acute papules, B: exudation/crusts/scratching, C: lichenification/chronic papules.
**indicates $p<0.01$.

Materials and Methods

Subjects and Treatment Protocol

Seventeen patients (mean age, 30.2 ± 14.2 years; males, 8; females, 9) were enrolled with informed consent. All of the patients fulfilled the Japanese Dermatological Association criteria for the diagnosis of atopic dermatitis (10). All the AD patients were classified as having moderate severity with a chronic clinical course and had been treated with occasional topical corticosteroids. Before beginning the study treatment, an evaluation area was selected where the lesions were of similar severity and symmetrically (right/left) distributed. On the right side of the body, each patient applied 0.05% betamethasone butyrate propionate ointment twice daily for four days followed by the application of 0.1% tacrolimus ointment twice daily for the following three days. On the left side of the body, patients applied 0.05% betamethasone butyrate propionate ointment twice daily for four days followed by the regular application of white Vaseline emollient twice daily for the following three days. These intermittent sequential treatments were repeated for four weeks. The potency of 0.05% betamethasone butyrate propionate ointment is classified as "very strong". No oral antihistamines or other emollients were administered during the treatment period. The eruption scores at the evaluation site were evaluated by the three major symptoms of erythema/acute papules, exudation/crusts/scratching, and lichenification/chronic papules as recommended by the Japanese Dermatological Association (11). Each symptom was scored from 0 to 3, and the pre- and post-treatment scores were compared. The patient preference for either betamethasone butyrate propionate/tacrolimus or betamethasone butyrate propionate/emollient treatment was also determined by interview.

Statistical analysis

Data were compared by the chi-square and Student's t tests. A p value less than 0.05 was statistically significant.

Results

For each symptom, we assessed the pre-treatment score and post-treatment score after four weeks of treatment with betamethasone butyrate propionate/tacrolimus or betamethasone butyrate propionate/emollient. Both treatments significantly improved all three pre-treatment symptoms of erythema/acute papules, exudation/crusts/scratching, and lichenification/chronic papules (Fig. 1). We compared the potency of both treatments by evaluating the reductions in scores of clinical lesions. After four weeks, both treatments gave similar improvements in the scores for erythema/acute papules (Fig. 2A) and exudation/crusts/scratching (Fig. 2B). However, the betamethasone butyrate propionate/tacrolimus treatment reduced the score of lichenification/chronic papules more dramatically than the betamethasone butyrate propionate/emollient treatment (Fig. 2C). One out of 17 patients complained of a mild burning sensation with tacrolimus application during the first week of therapy, but the patient completed the four week treatment course with no additional side effects. The betamethasone butyrate propionate produced no adverse effects during the treatment period. Ten patients preferred the betamethasone butyrate propionate/tacrolimus treatment over the betamethasone butyrate propionate/emollient treatment. The remaining 7 patients stated that both treatments were equally effective. The patient preference for betamethasone butyrate propionate/tacrolimus treatment over betamethasone butyrate propionate/emollient treatment was statistically significant ($p<0.01$).

Discussion

Topical steroids are the mainstay of treatment for AD (12, 13). Prompt treatment of flare-ups with adequately potent topical steroids until the inflammation subsides is recommended as optimal treatment for control of relapses (14–16). Once the AD lesions are stabilized, the frequency and dosage of steroid application can be decreased, and long-term management with daily emollients or low potency topical steroids can be used (12, 15). Because of the troublesome, chronic, relapsing nature of AD, adverse effects are the main concern of patients who must apply steroids for a long term (14, 17). Intermittent dosing with a potent steroid is sufficient for reducing the risk of relapse in AD without increasing its side effects (18, 19).

Topical tacrolimus is a potent non-steroidal immunosuppressive agent that does not exhibit the hormonal adverse effects associated with steroid therapy (7–9). Previous reports show that the incidence and intensity of steroid-induced side effects can be reduced when the topical steroid is applied in conjunction with tacrolimus (9, 20). The present study shows that intermittent sequential treatments with both potent steroid/tacrolimus and potent steroid/emollients were effective and useful for management of AD. In addition, the inclusion of tacrolimus in the regimen significantly reduced the score of lichenification/chronic papules when compared to the regimen that did not include tacrolimus. The data support the approach of using topical combination therapy with steroid and tacrolimus as a useful adjunct for the treatment of AD.

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ステロイド軟膏適正使用ガイドライン

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ステロイド軟膏適正使用ガイドライン

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アトピー性皮膚炎は遺伝的素因も含んだ多病因性の疾患であり，疾患そのものを完治させうる薬物療法は現時点ではない。よって対症療法を行うことが原則となる。本邦ではアトピー性皮膚炎治療ガイドラインが作成され，日常診療に寄与している。アトピー性皮膚炎の炎症に対してはステロイド軟膏ならびにタクロリムス軟膏による外用療法が主として用いられている。本稿ではステロイド軟膏の適正使用について私見を述べたい。

アトピー性皮膚炎/治療ガイドライン/ステロイド軟膏/タクロリムス軟膏/外用量

はじめに

アトピー性皮膚炎に対しては，日本皮膚科学会を中心に診断基準，重症度分類，治療ガイドラインが作成され，アトピー性皮膚炎治療問題検討委員会による相談窓口も設けられている(http://web.kanazawa-u.ac.jp/~med24/atopy/therapy.html)[1)~5)]。また一般臨床医を広く対象とした治療ガイドラインは，山本昇壯らを中心として厚生労働省研究班によっても作成されている。このような活動の過程で本症の病態と治療に対する医師間のコンセンサスは得られつつある。著者らは，ガイドラインの情報を患者にできるだけ平易に解説する目的で，「アトピー性皮膚炎について一緒に考えましょう」(http://www.kyudai-derm.org/atopy/)というホームページを作成し，その普及に努めている。このサイトはおよそ300件/日と比較的多くのアクセスを得ているが，患者の治療への不安や不満が払拭されたとはとても言いがたい状況である。本稿では，患者の関心が最も高いステロイド軟膏の適正使用に関する考察を述べたい。

Ⅰ．日常臨床におけるステロイド外用薬の使用量調査

日本皮膚科学会による治療ガイドラインに示されているように，外用療法の選択は「個々の皮疹の重症度」によってなされるべきである(表1)。長期治療が必要な本症においては，特に高い専門性が要求される。

表1　皮疹の重症度と外用薬の選択

	皮疹の重症度	外用薬の選択
重症	高度の腫脹/浮腫/浸潤ないし苔癬化を伴う紅斑，丘疹の多発，高度の鱗屑，痂皮の付着，小水疱，びらん，多数の掻破痕，痒疹結節などを主体とする。	必要かつ充分な効果を有するベリーストロングないしストロングクラスのステロイド外用薬を第一選択とする。痒疹結節でベリーストロングクラスでも充分な効果が得られない場合は，その部位に限定してストロングストクラスを選択して使用することもある。
中等症	中等度までの紅斑，鱗屑，少数の丘疹，掻破痕などを主体とする。	ストロングないしミディアムクラスのステロイド外用薬を第一選択とする。
軽症	乾燥および軽度の紅斑，鱗屑などを主体とする。	ミディアムクラス以下のステロイド外用薬を第一選択とする。
軽微	炎症症状に乏しく乾燥症状主体。	ステロイドを含まない外用薬を選択する。

（文献1より引用）

表2　6カ月間のステロイド外用薬使用量（g）

		2歳未満	2歳以上 13歳未満	2歳以上 13歳以上
患者数		210	546	515
顔面	50%値	1	0	0
	75%値	5	5	15
	90%値	10	15	35
頭部	50%値	0	0	0
	75%値	0	0	0
	90%値	10	10	65
躯幹・四肢	50%値	21	45	80
	75%値	40	80	160
	90%値	74.5	130	280
総外用量	50%値	25	45	95
	75%値	43	80	180
	90%値	90	130	304

しかし日常診療上ステロイド外用薬がどの程度使用されているのかについての具体的な報告は極めて少ない。表2は1999年（タクロリムス軟膏発売前）福岡県臨床皮膚科医会を中心に行った使用量調査の一例であるが，乳児期，幼小児期，思春期・成人期の6カ月間のステロイド外用薬使用量の50%値，75%値，90%値（全患者の50%，75%，90%が使用している外用量）が外用部位ごとに示されている。6カ月間の総使用量をみると，患者の90%は2歳未満で90g以内，2歳以上13歳未満で130g以

内，13歳以上で304 g以内を使用していた[1]。顔面ではmild/weakのステロイド外用薬が頻用され，年齢別では13歳以上になるとstrong以上の外用薬が頻用される傾向が明らかであった。

このような外用量でほとんどの患者は軽快あるいは中等症以下に留まっていたが，コントロール不良の患者（ステロイド外用量はコントロール群に比べ多かった）が2歳未満で7％，2歳以上13歳未満で10%，13歳以上で19%にみられた（表3）。このことは①アトピー性皮膚炎が年長になるにつれ難治性になること，②ステロイド外用だけではうまくコントロールできない症例があり，このような難治の患者が診療する側の大きな悩みであったこと，③難治の症例では治療に対する教育や生活指導，精神的なカウンセリング，外用療法の見直しや紫外線療法などの他治療法の活用などが必要であることを示していた。

ステロイド外用薬による副作用（表4）は，乳児期にはきわめて低頻度であった。頬部の血管拡張や肘窩・膝窩の皮膚萎縮は思春期・成人期では10%～15%に認められ，予想よりも低頻度であった。皮膚線条は思春期・成人期の1％に認められた。頬部の血管拡張と性別，年齢，罹病期間，ステロイド（strongest＋very strong＋strong）使用量，ステロイド（mild＋weak）使用量，総ステロイド使用量とを組み合わせたlogistic regression analysisを行ったところ，頬部の血管拡張は①罹病期間が6年未満までは1年に約1.8倍ずつ起こりやすくなるが，6年以上はほぼ横ばいとなる，②乳児期，幼小児期，思春期・成人期となるにつれて起こりやすい，③顔面への総ステロイド使用量が6カ月間で20 g以上になると徐々に起こりやすくなることが明らかとなった。同様の解析の結果，肘窩の皮膚萎縮は，①乳児期，幼小児期，思春期・成人期となるにつれて起こりやすい，②罹病期間が9年未満までは1年に約1.2倍ずつ起こりやすくなるが，9年以上は起こりにくくなる，③女性よりも男性の方が起こしやすい，④ステロイド(strongest＋very strong＋strong)使用量が6カ月間で500 g以上になると徐々に起こりやすくなることが分かった。またヘルペス感染症と伝染性軟属腫の合併は乳児期で2.4%と7％に，幼小児期で2.5%と9％に，思春期・成人期で3.5%と0.2%にそれぞれ認められた。

Ⅱ．タクロリムス軟膏によるステロイド外用療法へのインパクト

その後，タクロリムス外用薬*注1の登場後に行われた同様の使用量調査（215例，2001年調査）では，タクロリムス軟膏が顔面には99.1%に，躯幹には39.5%に使用されていることがわかった（表5）[7]。顔面へのタクロリムスとステロイドの外用量の90%値はそれぞれ70 g/6カ月，15 g/6カ月で(表5)，表1と比較するとタクロリムス軟膏の使用によってステロイド外用量が減少していることが窺える。興味深いことは，タクロリムス外用薬の登場によって思春期・成人期のコントロール不良群は6カ月間で6％に激減していた(表6)。ステロイド外用薬による局所性副作用は可逆性で使用量が少なくなると回復することが知ら

＊注1
免疫抑制薬であるFK506（タクロリムス）を含有する外用薬。成人用と小児用がある。

表3　治療前後の重症度の変化

乳児期

治療後＼治療前	最重症	重症	中等症	軽症
最重症				
重症		8		1
中等症	2	9	41	6
軽症		6	57	76
総計 (206)	2	23	98	83

思春期・成人期

治療後＼治療前	最重症	重症	中等症	軽症
最重症	15	2		
重症	6	65	6	
中等症	7	58	161	4
軽症	2	21	92	64
総計 (503)	30	146	259	68

幼小児期

治療後＼治療前	最重症	重症	中等症	軽症
最重症	3	2		
重症	5	27	3	
中等症	5	44	155	11
軽症	1	17	141	117
総計 (531)	14	90	299	128

6カ月間でコントロール不良の患者（　内）が，2歳未満で7％ (15/206)，2歳以上13歳未満で10% (51/531)，13歳以上で19% (98/503)
有意差あり

表4　ステロイド外用薬の局所性副作用

	2歳未満	2歳以上 13歳未満	13歳以上
顔部の血管拡張	0%	2.3%	13.3%
肘窩の皮膚萎縮	1.5%	5.2%	15.8%
膝窩の皮膚萎縮	1.9%	4.1%	9.8%
ざ瘡・毛嚢炎	0%	1.3%	8.2%
多毛	0.5%	1%	2.7%
細菌感染症	1.4%	2.1%	2.5%
真菌感染症	1.9%	0.6%	1.2%
酒さ様皮膚炎	0%	0.4%	3.1%
接触皮膚炎	0%	0.4%	0.8%
皮膚線条	0%	0%	1%

れている。実際にタクロリムス外用薬の使用によりステロイド外用量が減少すると，ステロイドによる局所性副作用は6カ月間でかなり軽快・消失することが日常診療の場でも観察される(表7)。免疫抑制作用を有するタクロリムス軟膏とステロイドの併

表5　6カ月間のタクロリムスおよびステロイド外用量

		タクロリムス	ステロイド	使用頻度
顔面・頸部	50%値	29 (g)	0 (g)	
	75%値	49	5	(99.1%, 213/215)
	90%値	70	15	
躯幹・四肢	50%値	0	75	
	75%値	10	175	(39.5%, 85/215)
	90%値	75.8	322	
保湿性外用薬	50%値	130		
	75%値	315		
	90%値	600		

表6　タクロリムス軟膏市販後の治療前および治療6カ月後の重症度の推移

		治療前				
		最重症	重症	中等症	軽症	Total (215)
治療後	最重症					0
	重症	5	5			10 (5%)
	中等症	5	30	31	3	69 (32%)
	軽症	5	20	79	32	136 (63%)
	Total (215)	15 (7%)	55 (26%)	110 (51%)	35 (16%)	

：コントロール不良群，6%

表7　ステロイド外用による副作用の治療前および治療6カ月後の推移

		計 (重度,	中等度,	軽度)
頬部の血管拡張	治療前	34.9% (1.9	6.5	26.5) %
	治療後	18.7% (0	1.9	16.8) %
顔面の多毛	治療前	4.7% (0	0.5	4.2) %
	治療後	1.9% (0	0	1.9) %
肘窩の皮膚萎縮	治療前	19.1% (0	2.3	16.7) %
	治療後	13.6% (0	0.5	13.1) %
膝窩の皮膚萎縮	治療前	18.1% (0	1.9	16.3) %
	治療後	10.8% (0	0.5	10.3) %

用外用療法によって皮膚感染症が増加することがとても危惧されたが，治療前後の皮膚感染症の頻度を見てみると(表8)，皮膚感染症を増加させている明らかな証拠は今のところ見出せていない。ただし，顔面・頸部の単純疱疹ウイルス感染症[*注2]が治療

＊注2
アトピー性皮膚炎では単純疱疹ウイルス感染症を合併しやすい。重症例はカポジ水痘様発疹症とよばれている。