平成　17年　2月　　Vol.11　No.2

調剤と情報 Rx Info

別　刷

発行：じほう

TUTORIAL

アトピー性皮膚炎の症状と治療

九州大学大学院皮膚科学　古江　増隆［*FURUE Masutaka*］

アトピー性皮膚炎とは

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る。現時点では疾患そのものを完治させ得る薬物療法がないため，対症療法を行うことが原則となる。

わが国では，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。ガイドラインでは，アトピー性皮膚炎を皮膚の生理的機能異常を伴い，複数の非特異的刺激あるいは特異的アレルゲンの関与により炎症を生じ，慢性の経過をとる湿疹としてその病態を捉える。その炎症に対してはステロイド外用療法およびタクロリムス軟膏を主に使用し，生理学的機能異常に対しては外用保湿剤などを含むスキンケアを行う。瘙痒に対しては抗ヒスタミン薬，抗アレルギー薬を補助療法として併用し，悪化因子を可能な限り除去することを治療の基本とする。本稿では，外用療法の指導法についても言及した。

情報の収集

アトピー性皮膚炎については，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委員会によるホームページも設けられている（http://web.kanazawa-u.ac.jp/~med24/atopy/therapy.html）[1~5]。また，山本昇壯らを中心とした厚生労働省研究班によって，一般臨床医を広く対象とした治療ガイドラインも作成されている。このような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。

また，患者にできるだけ平易にガイドラインの情報を解説することを目的に，筆者らは「アトピー性皮膚炎についていっしょに考えましょう」というホームページ（http://www.kyudai-derm.org/atopy/）を作成し，その普及に努めている。このサイトはおよそ400件/日と比較的多くアクセスされているが，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。

このほか，厚生労働省研究班「アトピー性皮膚炎の既存治療法のEBMによる評価と有用な治療法の普及」による研究成果を，「アトピー性皮膚炎―よりよい治療のためのEvidence-based Medicine（EBM）とデータ集―」として，インターネット上で2004年10月に公開した（http://www.kyudai-derm.org/atopy_ebm/index.html）。アトピー性皮膚炎治療のEBMに関する詳細は，このホームページを参照されたい。

ステロイド・タクロリムスの外用療法

1．日本皮膚科学会治療ガイドライン[2)]

日本皮膚科学会および厚労省研究班のステロイド外用薬のランクについては表1のように統一されている。

軟膏，クリーム，ローション，テープ剤などの剤形の選択は，病変の性状，部位などを考慮して選択する。外用回数は1日2回（朝，夕：入浴後）を原則とする。ただし，ステロイド外用薬のランクを下げる，あるいはステロイドを含まない外用薬に切り替える際には，1日1回あるいは隔日投与などの間欠投与を行いながら，再燃のないことを確認する必要がある。

(1) 用法・用量

顔面や頸部の皮疹に対してタクロリムス軟膏を用いる場合は1日1～2回を原則とし，症状の改善とともに間隔を空ける。

アトピー性皮膚炎の症状と治療

表1　主なステロイド外用薬の分類

薬　効	一般名	代表的な製品名
I群 strongest	プロピオン酸クロベタゾール 酢酸ジフロラゾン	デルモベート ジフラール，ダイアコート
II群 very strong	フランカルボン酸モメタゾン 酪酸プロピオン酸ベタメタゾン フルオシノニド ジプロピオン酸ベタメタゾン ジフルプレドナート アムシノニド 吉草酸ジフルコルトロン 酪酸プロピオン酸ヒドロコルチゾン ブデソニド	フルメタ アンテベート トプシム，シマロン リンデロンDP マイザー ビスダーム ネリゾナ，テクスメテン パンデル
III群 strong	プロピオン酸デプロドン プロピオン酸デキサメタゾン 吉草酸デキサメタゾン ハルシノニド 吉草酸ベタメタゾン プロピオン酸ベクロメタゾン フルオシノロンアセトニド	エクラー メサデルム ボアラ，ザルックス アドコルチン リンデロンV，ベトネベート プロパデルム フルコート，フルゾン
IV群 medium(Mild)	吉草酸酢酸プレドニゾロン トリアムシノロンアセトニド ピバル酸フルメタゾン プロピオン酸アルクロメタゾン 酪酸クロベタゾン 酪酸ヒドロコルチゾン	リドメックス レダコート，ケナコルトA ロコルテン アルメタ キンダベート ロコイド
V群 weak	プレドニゾロン 酢酸ヒドロコルチゾン	プレドニゾロン コルテス

ステロイド外用薬の用量については，very strongクラスの長期使用試験結果より，通常の成人患者では十分量である1日5～10g程度の初期外用量で開始し，症状に合わせて漸減する。この使用法であれば，一過性で可逆性の副腎機能抑制は生じ得るが，不可逆性の全身的副作用は3カ月間使用しても生じない。極めて例外的であるが，3カ月以上にわたって1日5～10g程度のステロイド外用薬を連用するような例では，全身への影響に対する十分な検査を定期的に行う必要があり，個々の患者に対してステロイド外用薬の減量を可能ならしめるような適切な対応が検討されるべきである。乳幼児，小児においては，より少量の初期外用量で通常開始する。体重を基に，成人での使用量から1日使用量を換算し，目安とする。

タクロリムス軟膏を用いる場合，1回塗布量が0.1％成人用では成人で5g，0.03％小児用では，2～5歳(20kg未満)で1g，6～12歳(20kg以上50kg未満)で2～4g，13歳以上(50kg以上)で5gを超えないようにする。さらに1日の使用回数は，1～2回までとする。広範囲に用いる場合，皮疹の程度に合わせてほかのステロイド外用薬を併用するなど，使用方法を工夫する。

なお，炎症症状の鎮静後にステロイド外用薬を中止する際には，急激に中止することなく，症状を見ながら漸減あるいは間欠投与を行い徐々に中止する。ただし，ステロイド外用薬による副作用が明らかな場合はこの限りではない。

(2) 顔面への使用

顔面に塗布する場合は，高い薬剤吸収率を考慮し，原則としてmediumクラス以下のステロイド外用薬を使用する。その場合でも1日2回の外用は1週間程度にとどめ，その後は間欠投与に移行し，休薬期間を設けながら使用する。近年，成人患者にしばしば見られる顔面の紅斑性病変の多くは，掻破などを含むステロイド外用薬以外の要因に起因するものではあるが，局所性副作用の発生には注意が必要な部位であり，処方に当たっては十分な診察を行う必要がある。なお，顔面はタクロリムス軟膏の高い適応がある部位であり，ガイドラインに従って積極的に使用することを考慮する。

(3) ステロイドの適正使用

ステロイド外用薬に対する誤解(ステロイド内服薬の副作用との混同や，アトピー性皮膚炎そのものの悪化とステロイド外用薬の副作用との混同が多い)から，ステロイド外用薬への恐怖感や忌避が生じ，コンプライアンス低下がしばしば見られる。誤解を解くために時間をかけて説明し，指導することが必要であり，それが治療効果を左右する。

ステロイド外用薬を適切に使用すれば，副腎不全，糖尿病，ムーンフェイスなどの内服剤で見られる全身的副作用は起こり得ない。局所性副作用のうち，ステロイドざ瘡，ステロイド潮紅，皮膚萎縮，多毛，細菌・真菌・ウイルスによる皮膚感染症などは生じ得るが，中止あるいは適切な処置により回復する。ステロイド外用薬の使用後に色素沈着が見られるこ

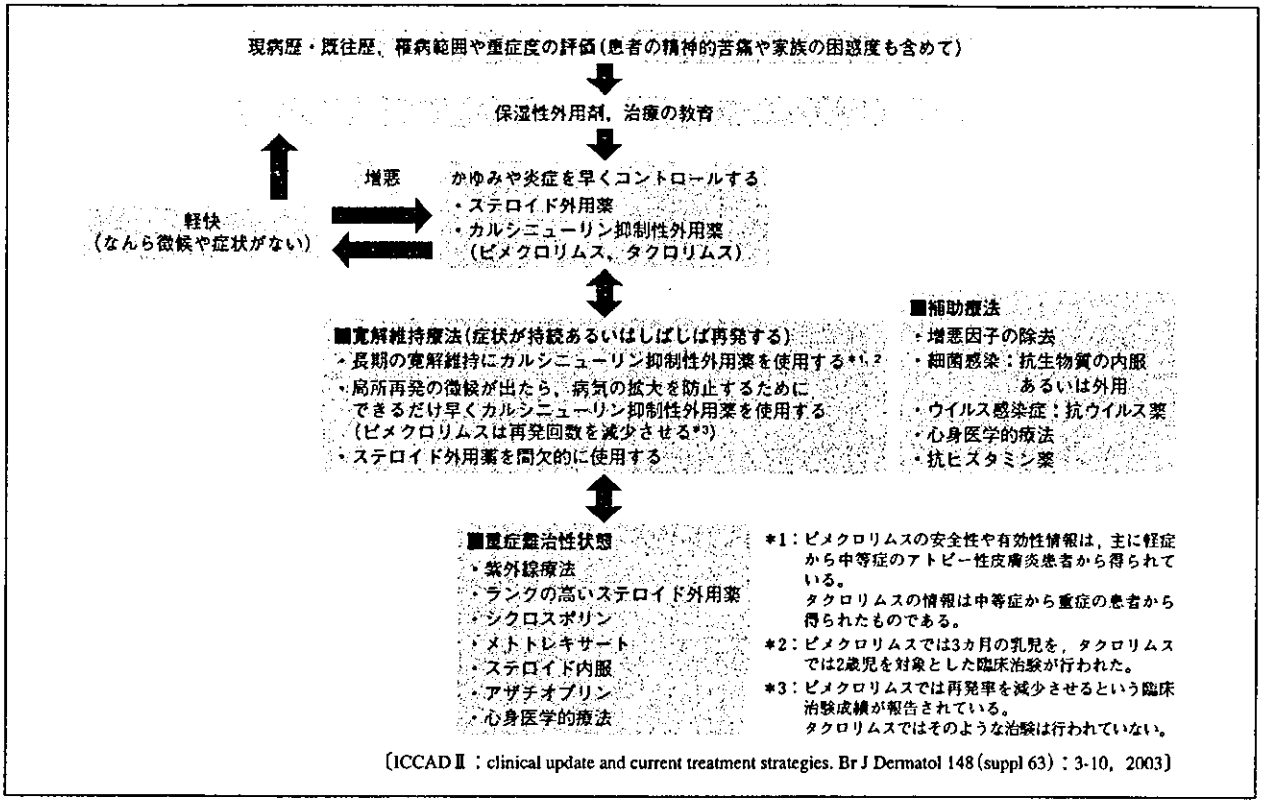


図1　アトピー性皮膚炎の治療手順

とがあるが，皮膚炎の鎮静後の色素沈着であり，ステロイド外用薬によるものではない。しかし，まれにステロイド外用薬によるアレルギー性接触皮膚炎が生じ得る。

最新のアトピー性皮膚炎治療手順

International Conference on Atopic Dermatitis Ⅱ（ICCAD Ⅱ）：Clinical update and current treatment strategieは，1999年に策定され2001年に公表されたICCAD Ⅰのリニューアル版で，アメリカ，ドイツ，イギリス，フランス，カナダ，スペイン，イタリア，メキシコ，スイスの9カ国16人の皮膚科医・小児科医が一同に会し，策定された（図1）[6]。

このICCAD Ⅱは，患者のQOLを十分に考え，患者の精神的苦痛や家族の困惑度も十分に考慮して重症度を評価すべきであるとした点[2]と，寛解維持療法にカルシニューリン抑制性外用薬（タクロリムス軟膏）の使用を強く推奨している点に特徴がある。日本皮膚科学会の治療ガイドラインに比べ，長期の維持療法におけるタクロリムス軟膏の使用を積極的に支持している。

ステロイド外用療法の適量について

日本皮膚科学会のアトピー性皮膚炎治療ガイドラインの骨子は前述の通りだが，患者への説明にはより具体的な内容のものが要求される。実際，患者相談会では「ステロイド軟膏をどのくらい塗ったらいいのか」などという質問が最も多い。

目安としては，第2指の先端から第1関節部まで5gチューブから軟膏を出すと大体0.5gとなる。この量が成人の手2個分，すなわち体表面積のおよそ2％に対する外用適量である（図2）[7, 8]。

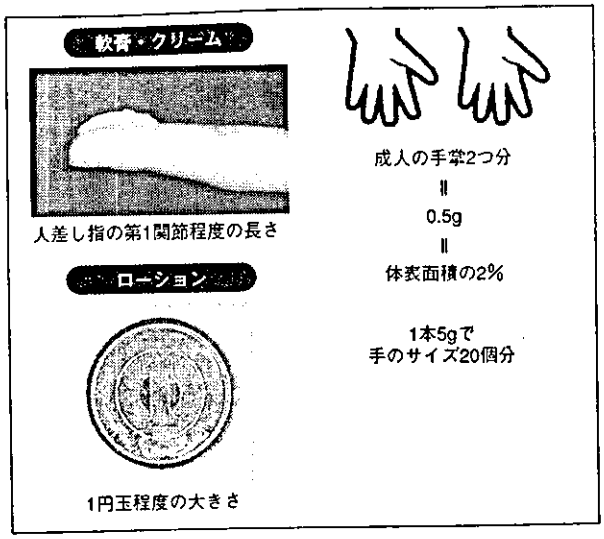


図2 Finger-tip unit

Long CC. Finlay AY. Averill RW：The rule of hand. Archives of Dermatology, 128：1129-1130, 1992
Long CC. Finlay AY：The finger-tip unit--a new practical measure. Clinical & Experimental Dermatology, 16：444-447, 1991
Long CC. Finlay AY：Area of skin disease can be used to indicate amount of treatment needed. [comment]. BMJ, 313(7058)：690, 1996
Long CC. Mills CM. Finlay AY：A practical guide to topical therapy in children. British Journal of Dermatology, 138：293-296, 1998
斉藤隆三：スペシャリストとしての外用薬の使い方. 皮膚科診療プラクティス, 12：32, 2002
松永佳世子：大人のにきび肌：マルホ株式会社

患者にわかりやすい言い方をすると，5gチューブ1本で手のサイズ20個分である。例えば，アトピー性皮膚炎の子どもで悩んでいる保護者に，次のように説明すると十分な理解が得られるだろう。

「お母さんの手で5個分の皮膚症状がお子さんにある場合，1日1回塗るとして4日間で1本使用してください。塗り始めて3～4日で赤みや痒みは治まります。赤みがとれても，指でつまんでまだ硬いところは，柔らかくなるまで10日から2週間くらいは続けてください。2週間すると，塗る量はずいぶん少なくなります。例えばお母さんの手で2個分くらいに塗る場所が狭くなってくると，10日間で1本くらいになります」。

もちろん，軟膏の使用量は個人差が大きく，べとべと感を極端に嫌う患者は軟膏をほとんど外用しない。このような場合には，クリームやローション剤を組み合わせる必要がある。このように，医師は外用薬の効果と使用量をモニターしながら治療経過を

表2 6カ月間のステロイド外用薬使用量

		2歳未満	2歳以上13歳未満	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

フォローしていく中で，個々の患者に適した外用指導を見つけていく。一度は前述のような説明を受けないと，適量の概念がなかなか患者には伝わらない。ちなみに全身にくまなく塗ると，乳児では2本，幼小児では3本，思春期・成人では5本必要である。

日常診療におけるステロイド外用薬使用量

一方，日常診療におけるステロイド外用薬使用量はどの程度なのだろうか。われわれの調査によると，アトピー性皮膚炎患者の6カ月間のステロイド外用薬総使用量における90%値(90%の患者がこの使用量以下)は，2歳未満で90g，2歳以上13歳未満で130g，13歳以上で304gであった(表2)[9]。

本調査をもとに，各年齢層における平均体重を設定して体重当たりのおよその目安を計算してみると，どの年齢層も体重10kg当たり1カ月に10g未満の使用量であった(表3)。この使用量ではステロイド外用薬による全身性の副作用は起こらない。一方，局所性副作用の発現は，ステロイド外用薬の累積使用頻度が増加するために，年齢が上昇するにつれ増加するが，すべての患者に発現するわけではなく，また2歳未満の患者では発現頻度は極めて少ない(表4)。

1999年にタクロリムス軟膏が登場したことによって，アトピー性皮膚炎の治療効果は著しく向上した[10]。さらにタクロリムス軟膏の使用によってステロイド外用薬の使用量は減少し，ステロイド外用に伴う局

TUTORIAL

表3　日常診療における6カ月間のステロイド使用量の90%値

	2歳未満（体重10kgとする）	2歳以上13歳未満（体重25kgとする）	13歳以上（体重50kgとする）
6カ月間の使用量	90g未満	130g未満	304g未満
体重10kg当たりの1カ月間使用量	15g未満	9g未満	10g未満

表4　合併症ならびにステロイド外用薬の局所性副作用

アトピー性皮膚炎に伴う合併症

	2歳未満	2歳以上13歳未満	13歳以上
ヘルペス感染症・カポジ水痘様発疹症	2.4%	2.5%	3.5%
伝染性軟属腫	7%	9%	0.2%

ステロイド外用薬の局所性副作用

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%

所性副作用も明らかに軽減した[10]。表5に示す通り，ステロイド外用薬の使用量減少とともに，局所性副作用は6カ月間でおよそ半分に減少する（皮膚線条のみは不可逆性）[10]。タクロリムス軟膏の外用量を体重10kg当たり1g以内にとどめれば，血中濃度が長期にわたって検出されることはないため，発がんなどの全身性副作用は発生しないと現時点では考えられている。ステロイド外用薬も免疫抑制剤であり，1952年以降世界的に使用され，すでに50年以上経過しているが，外用による発がん性の危惧は報告されていない。

保湿剤の使い方

アトピー性皮膚炎相談会などで保護者に聞くと，子どもの外用治療時間に30分近くかかるのでつらいという悩みが意外と多い。理由を聞いてみると，保湿剤の外用をしっかりしているが，指先で全身に

表5　ステロイド外用薬使用量の減量に伴うステロイド外用薬の局所性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
顔部の血管拡張	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

塗っているため時間がかかるという。

保湿剤はステロイド外用薬やタクロリムス軟膏と異なり，手のひらにとって全体的に塗るように指導する。こうすれば外用時間も短くてすむ。保湿の仕方については，広島大学皮膚科の秀道広教授と患者向けパンフレットを作成（マルホ提供）している。患者に対しては，次のように説明してはどうだろうか。

(1) 皮膚炎の激しいときの保湿外用剤の使用法

・炎症を抑える

皮膚が赤くただれたりブツブツとした膨らみがある時期には，保湿外用剤のみでは症状を改善させることはできない。まずは適切なランク（強さ）のステロイド外用薬を選択して炎症を抑えることが必要である。

・ステロイドは1日1回の使用で十分

保湿外用剤を追加して1日に1～2回塗る。皮膚炎を抑えるためには，ステロイド外用薬は1日1回塗るだけで十分効果が現れる。しかしこの時期には落屑（皮膚表面のボロボロした脱落）が多く，皮膚の保湿機能も大きく損なわれているため，夜入浴後に塗り薬を塗っても，翌日には皮膚が乾燥してがさがさになってしまう。このような場合には，朝または昼間にも塗り薬を塗り足すことが必要であり，このために使う外用薬は保湿外用剤だけでも構わない。

・保湿外用剤は広い範囲に塗る

ステロイド外用薬は皮膚炎の明らかな範囲を中心に塗る。患部以外の正常に見える皮膚でも，多くはドライスキンの状態にあるため，できるだけ広い範囲に保湿外用剤を塗っておく。

・しわに沿って，まんべんなく

保湿外用剤は少し多めに取り，手のひらを使って皮膚表面にまんべんなく塗りのばす。皮膚のしわは概ね体軸に対して横方向に走っているため，できるだけしわに沿って薬を塗りのばすように指導する。背中など自分で塗りにくい部位には，誰かに手伝ってもらうように伝える。

・ステロイド，タクロリムス，保湿剤を組み合わせる

近年，アトピー性皮膚炎の治療には「タクロリムス軟膏」という，ステロイドとは異なる仕組みで皮膚の炎症を静める外用薬が用いられるようになってきた。明らかな炎症を抑えるための手段としては，ステロイド外用薬以外にタクロリムス軟膏が用いられることもあるが，保湿剤の使い方に変わりはない。

(2) 保湿外用剤の使用方法

・保湿剤で良い皮膚の状態を維持

ステロイド外用薬またはタクロリムス軟膏の使用によって皮膚炎が落ち着いても，多くの場合では皮膚が乾燥した状態が続いている。皮膚炎がないからといって外用剤の塗布を止めてしまうと，どうしても皮膚は乾燥しがちとなり，さまざまな刺激に敏感に反応して容易に皮膚炎を再発してしまうため，1日1回は必ず保湿外用剤を塗る。1日のうちでは入浴後が最も適切である。

・皮膚炎が再燃したら迷わずステロイド

一時期皮膚炎が治まっていても，皮膚炎を起こしやすい体質そのものはなかなか変わらない。明らかに皮膚炎が再燃してきた場合には，保湿外用剤のみに頼ることなく，迷わず適切なランクのステロイド外用薬またはタクロリムス軟膏を塗って，皮膚炎を抑える。

・自分に合った剤形を探す

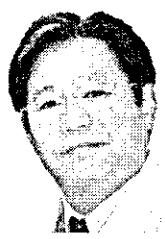
夏に保湿剤を塗るとベタついて気持ち悪い感じがする場合がある。クリームやローションといった，比較的ベタつきにくい剤形の保湿外用剤もあるので，季節，また個人の好みに合わせてそれらを試してみるのが良いだろう。

【参考文献】

1) 川島 眞，濱川雅浩，中川秀己，古江増隆，飯島正文，飯塚 一，伊藤雅章，塩原哲夫，竹原和彦，玉置邦彦，宮地良樹，橋本公二，吉川邦彦，日本皮膚科学会編「アトピー性皮膚炎治療ガイドライン」日本皮膚科学会雑誌，110：1099-1104，2000
2) 日本皮膚科学会アトピー性皮膚炎治療ガイドライン2004改訂版，古江増隆，古川福美，秀 道広，竹原和彦，日本皮膚科学会雑誌，114：135-142，2004
3) 日本皮膚科学会：アトピー性皮膚炎の定義・診断基準．日本皮膚科学会雑誌，104：1326，1994
4) 吉田彦太郎：アトピー性皮膚炎重症度分類検討委員会からの中間報告．日本皮膚科学会雑誌，108：1491-1496，1988
5) 青木敏之：アトピー性皮膚炎重症度分類検討委員会第2次報告書．日本皮膚科学会雑誌，111：2023-2033，2001
6) Ellis C, Luger T：ICCAD Ⅱ Faculty. International Consensus Conference on Atopic Dermatitis Ⅱ (ICCAD Ⅱ). clinical update and current treatment strategies. Br J Dermatol, 148 (63)：3-10, 2003
6) Furue M, Terao H, Rikihisa W, Urabe K, Kinukawa N, Nose Y, Koga T：Clinical dose and adverse effects of topical steroids in daily management of atopic dermatitis. Br J Dermatol, 148：128-133, 2003.
7) Long CC, Finlay AY.：The finger-tip unit--a new practical measure. Clinical & Experimental Dermatology, 16：444-447, 1991
8) Long CC, Finlay AY, Averill RW.：The rule of hand (4) hand areas＝2 FTU＝1g. Archives of Dermatology, 128：1129-1130, 1992
9) Furue M, Terao H, Moroi Y, Koga T, Kubota Y, Nakayama J, Furukawa F, Tanaka Y, Katayama I, Kinukawa N, Nose Y, Urabe K：Dosage and adverse effects of topical tacrolimus and steroids in daily management of atopic dermatitis.：J Dermatol in press.
10) Furue M, Terao H, Moroi Y, Koga T, Kubota Y, Nakayama J, Furukawa F, Tanaka Y, Katayama I, Kinukawa N, Nose Y, Urabe K：Dosage and adverse effects of topical tacrolimus and steroids in daily management of atopic dermatitis. J Dermatol, 31：277-283, 2004

PROFILE

古江 増隆 氏



1980年 東京大学医学部卒業
同 年 東京大学皮膚科入局
1986年 アメリカ National Institutes of Health の皮膚科部門に留学
1988年 東京大学皮膚科講師
1992年 山梨医科大学皮膚科助教授
1995年 東京大学皮膚科助教授
1997年 九州大学皮膚科教授
2002～2004年 九州大学病院副病院長

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

Masutaka Furue, Hiroshi Terao, Yoichi Moroi, Tetsuya Koga, Yumiko Kubota, Juichiro Nakayama, Fukumi Furukawa, Yoichi Tanaka, Ichiro Katayama, Naoko Kinukawa, Yoshiaki Nose and Kazunori Urabe

Reprinted from the Journal of Dermatology
Vol. 31, No. 4 pp. 277–283, April 2004

The Journal of Dermatology
Vol. 31: 277–283, 2004

Original articles

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

Masutaka Furue[1], Hiroshi Terao[1], Yoichi Moroi[1], Tetsuya Koga[1], Yumiko Kubota[2], Juichiro Nakayama[2], Fukumi Furukawa[3], Yoichi Tanaka[4], Ichiro Katayama[4], Naoko Kinukawa[5], Yoshiaki Nose[5] and Kazunori Urabe[1]

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

Received November 6, 2003; accepted for publication December 16, 2003.

This work was supported by grants from the Ministry of Health, Labor and Welfare.

[1] Department of Dermatology, Kyushu University, Fukuoka, Japan

[2] Department of Dermatology, Fukuoka University, Fukuoka, Japan.

[3] Department of Dermatology, Wakayama Medical University, Wakayama, Japan.

[4] Department of Dermatology, Nagasaki University, Nagasaki, Japan.

[5] Department of Medical Information Science, Kyushu University, Fukuoka, Japan.

Reprint requests to: Masutaka Furue M.D., Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan.

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.

References

1) Williams HC: Is the prevalence of atopic dermatitis increasing? *Clin Exp Dermatol*, **17**: 385–391, 1992.
2) Williams HC, Robertson C, Stewart A: Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood, *J Allergy Clin Immunol*, **103**: 125–138, 1999.
3) Takeuchi M, Ueda H: Increase of atopic dermatitis (AD) in recent Japan, *Envir Dermatol*, **7**: 133–136, 2000.
4) Sugiura H, Umemoto N, Deguchi H, et al: Prevalence of childhood and adolescent atopic dermatitis in a Japanese population: Comparison with the disease frequency examined 20 years ago, *Acta Dermato-Venereologica*, **78**: 293–294, 1998.
5) Brunsting LA: Atopic dermatitis (disseminated neurodermatitis) of young adults, *Arch Derm Syph*, **34**: 935–957, 1936.
6) Furue M, Terao H, Rikihisa W, et al: Clinical dose and adverse effects of topical steroids in daily management of atopic dermatitis, *Br J Dermatol*, **148**: 128–133, 2003.
7) Nakagawa H, Etoh T, Ishibashi Y, et al: Tacrolimus ointment for atopic dermatitis, *Lancet*, **344**: 883, 1994.
8) Reitamo S, Rustin M, Ruzicka T, et al: Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis, *J Allergy Clin Immunol*, **109**: 547–555, 2002.
9) Lazarous MC, Kerdel FA: Topical tacrolimus protopic, *Drugs Today*, **38**: 7–15, 2002.
10) Japanese Dermatological Association criteria for the diagnosis of atopic dermatitis, *Jap J Dermatol*, **106**: 64–65, 1996.
11) Japanese FK-506 ointment study group: Long-term study of FK-506 (Tacrolimus) ointment in patients with atopic dermatitis —Analysis at the time of 1-year observation—, *Rinsho Iyaku*, **14**: 2405–2432, 1998. (in Japanese)
12) Charman CR, Morris AD, Williams HC: Topical corticosteroid phobia in patients with atopic eczema, *Br J Dermatol*, **142**: 931–936, 2000.
13) David TJ, Cambridge GC: Bacterial infection in atopic eczema, *Arch Dis Child*, **81**: 20–23, 1986.
14) Bonifazi E, Garofalo L, Pisani V, Meneghini CL: Role of some infectious agents in atopic dermatitis, *Acta Derm Venereol (Stockh)*, **114**: 98–100, 1985.
15) Gianetti A: Viral skin diseases in atopic dermatitis, in Happle R, Grosshans E (eds): *Pediatric Dermatology*, Springer-Verlag, Berlin, 1987, p 110.
16) David TJ, Longson M: Herpes simplex infection in atopic eczema, *Arch Dis Child*, **60**: 338–343, 1985.
17) Fleischer AB, Ling M, Eichenfield L, et al: Tacrolimus ointment for the treatment of atopic dermatitis is not associated with an increase in cutaneous infections, *J Am Acad Dermatol*, **47**: 562–570, 2002.
18) Griffiths WAD, Wilkinson JD: Topical therapy, in Champion RH, Burton JL, Burns DA, Breathnach SM (eds): *Textbook of Dermatology*, 6th ed, Blackwell Scientific Pub, Oxford, 1998, p 3519.

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

Takeshi Nakahara, Tetsuya Koga, Shuji Fukagawa, Hiroshi Uchi and Masutaka Furue

Reprinted from the Journal of Dermatology
Vol. 31, No. 7 pp. 524–528, July 2004

The Journal of Dermatology
Vol. 31: 524–528, 2004

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

Takeshi Nakahara, Tetsuya Koga, Shuji Fukagawa, Hiroshi Uchi and Masutaka Furue

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

Received January 15, 2004; accepted for publication March 9, 2004.

This work was supported by grants from the Ministry of Health, Labor and Welfare.

Department of Dermatology, Kyushu University, Fukuoka, Japan.

Reprint requests to: Masutaka Furue M.D., Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan.

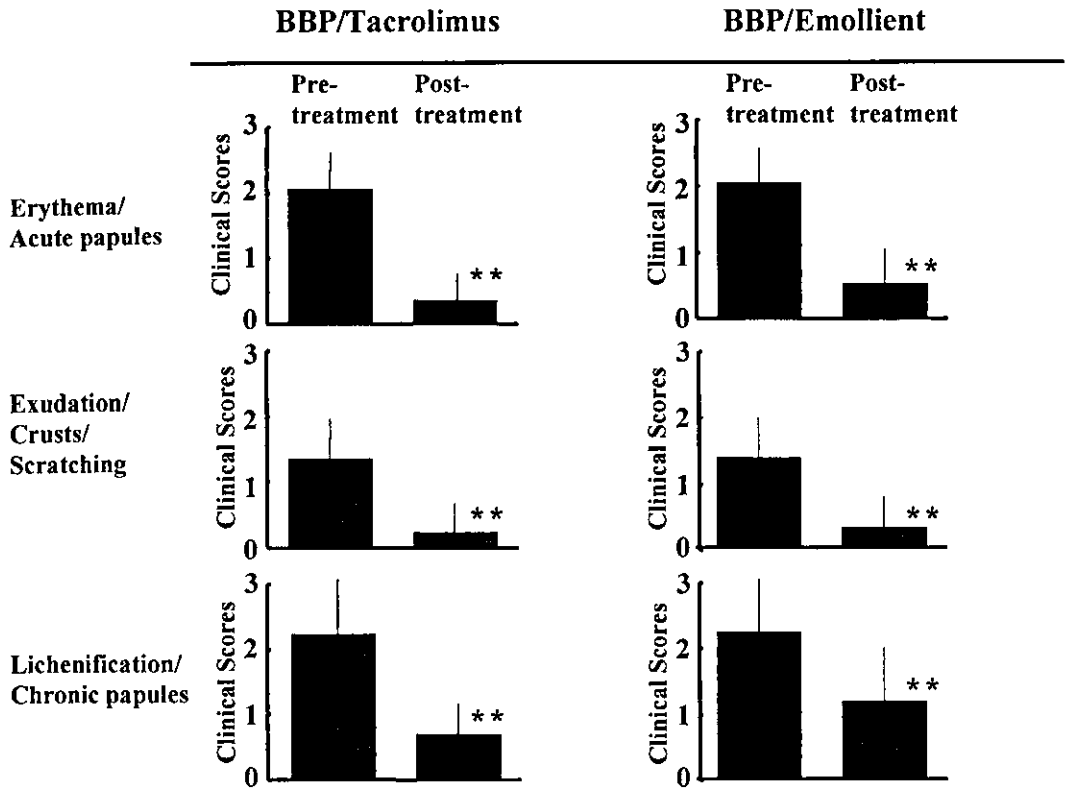


Fig. 1. Clinical effects of intermittent topical betamethasone butyrate propionate (BBP)/tacrolimus, and BBP/emollient sequential treatment. The eruption scores (mean ± SD) were evaluated at pre-treatment and post-treatment after four weeks of treatment. ** indicates $p<0.01$.

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.

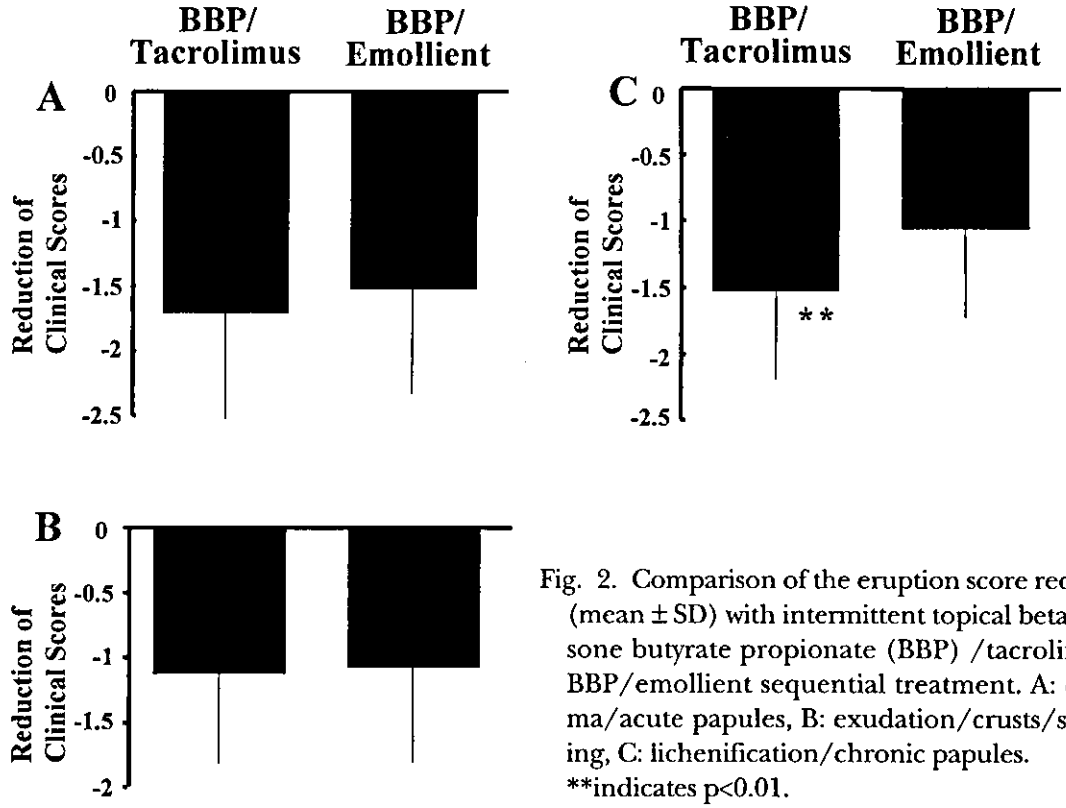


Fig. 2. Comparison of the eruption score reduction (mean ± SD) with intermittent topical betamethasone butyrate propionate (BBP) /tacrolimus or BBP/emollient sequential treatment. A: erythema/acute papules, B: exudation/crusts/scratching, C: lichenification/chronic papules.
**indicates $p<0.01$.

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.

References

1) Williams HC: Is the prevalence of atopic dermatitis increasing?, *Clin Exp Dermatol*, **17**: 385–391, 1992.
2) Williams HC, Robertson C, Stewart A, et al: Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood, *J Allergy Clin Immunol*, **103**: 125–138, 1999.
3) Takeuchi M, Ueda H: Increase of atopic dermatitis (AD) in recent Japan, *Envir Dermatol*, **7**: 133–136, 2000.
4) Brunsting LA: Atopic dermatitis (Disseminated neurodermatitis) of young adults, *Arch Derm Syph*, **34**: 935–957, 1936.
5) Furue M, Terao H, Rikihisa W, et al: Clinical