F．研究発表

本研究に関しては未発表である。

H．知的財産権の出願・登録状況

最終版の完成後に出願予定

表３　成人版尺度の項目と因子構造

1．ものすごく 2．かなり 3．すこし 4．まったくない からあてはまるものを選択 質問項目	因子 （内的整合性α）	因子負荷量
1．症状による意欲低下	生活活動への影響	0.818
2．睡眠障害による日常生活への影響	(0.772)	0.617
3．掃除や寝具の手入れ洗濯などの負担		0.589
4．外用療法の大変さ	服薬の負担	0.824
5．外用療法への嫌悪感	(0.843)	0.817
6．痒みへの困惑	痒みによる障害	0.821
7．掻爬への困惑	(0.865)	0.756
8．治癒可能性への不安	将来への不安	0.828
9．皮膚状態の増悪を繰り返すことへの不安	(0.789)	0.684

アトピー性皮膚炎の瘙痒に対する治療薬の有効性

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研究要旨
アトピー性皮膚炎は強い痒みを生じる慢性再発性皮膚炎であり、そう痒のコントロールが治療において重要である。抗ヒスタミン薬の有効性を検討するために通院した AD 患者の一年間の内服薬、外用薬の使用量を検討した。抗ヒスタミン内服薬の使用量は、重症群が、中等症、軽症、軽微に比較して有意に多く、軽微群の使用量は、軽症、中等症と比較して有意に少量であった。AD の日常診療において抗ヒスタミン薬が多く使用されている現状が把握できた。また抗ヒスタミン薬を使用して一年後に明らかに症状が軽快したと判断された割合は、軽微群、軽症、中等症、重症群の順に高く、軽微群で軽快率が高い傾向を示した。以上の結果より中等症、軽症、軽微群では、比較的少量の内服薬で掻痒のコントロールが可能であり、重症になるにつれてより多くの内服薬を必要とする現状が示唆された。

A．研究目的

A目的：アトピー性皮膚炎はアレルギー性皮膚炎として強い炎症症状を有し、激しい痒みを生じる炎症性皮膚疾患である。AD の標準治療では悪化因子の除去、スキンケア、薬物療法が必要であり、そう痒を改善するための薬物療法が補助療法として有効である。止痒作用を有する抗ヒスタミン薬などを使用することによって、そう痒・掻破のサイクルを改善し、皮膚炎のコントロールが期待できる。抗ヒスタミン薬の止痒効果については、外用療法と抗ヒスタミン薬の併用によって、外用薬の使用量を軽減できること、外用薬と抗ヒスタミン薬の併用によって外用薬による副作用を軽減できることが報告されている。また、これまで炎症局所から産生されるケモカインやサイトカインなどの免疫担当細胞由来の因子が皮膚炎の増悪に関与していることを報告している。本年度の研究では、AD の標準治療におけるステロイド外用量と抗ヒスタミン薬の使用量の実態を検討した。

B．研究方法

①2004 年 12 月 31 日以前に当科外来にて AD と診断され 2006 年 1 月 1 日以降に受診歴のある患者のうち、2005 年 1 月より 2005 年 12 月までに当科外来を受診した AD 患者 96 名を対象とした。治療期間内に使用した副腎皮質ステロイド外用薬、保湿薬、その他の外用薬の総使用量、抗ヒスタミン薬の内服量について、重症度別、季節別（1 年を 3 ヶ月毎に分けて）検討した。AD の重症度は、日本皮膚科学会アトピー性皮膚炎診断基準（2004 年改訂版）に準じた。Retrospective に解析し、Anova 検定で有意差を検定した。総外用量の解析において、抗生物質を単独に含有する軟膏、抗ウイルス含有外用薬などは今回の外用薬量の調査より除外して解析した。

（倫理面への配慮）
データの解析にあたっては AD 患者のプライバシーを遵守するように努めた。

C．研究結果

①内訳は、男性 59 名（平均 23.3 歳）、女性 37 名（平均 27.7 歳）であった。3 ヶ月毎のステロイド外用量については、各季節毎の集計で重症群では 144.6g～217.3g/3 ヶ月、中等症群では 83.0g～103.6g/3 ヶ月であった。重症度別には一年間のステロイド使用量は重症群＞軽微、軽症、中等症群($p<0.05$)であり重症群で多く、また軽微群＜軽症、中等症群($p<0.05$)であり軽微群で少ないことが認められた(表 1)。各々の群において季節毎のステロイド使用量には有意差は認めなかった。プロトピック軟膏の使用量に関しては、季節毎の集計で軽症群で 2.1g～9.4g であり、いずれの群間においても有意差は認めなかった。また季節毎の使用量の有意差は認めなかった。保湿薬に関しては、軽微群＜軽症、中等症、重症群($p<0.05$)であった（表２）。ステロイド外用薬、プロトピック軟膏を含めた総使用量に関しては、1 年間で軽微群＜軽症、中等症、重症群($p<0.05$)であり、軽微群で軽症、中等症、重症群に比較して有意に少量であった。また重症群では、軽症、中等症に比べて有意に高値($p<0.05$)であった（表 3)。一年間の抗ヒスタミン薬の内服量（錠）に関しては、重症群で中等症、軽症、軽微と比較して多く、軽微群では、軽症、中等症と比較して少量であった($p<0.05$)。季節（3 ヵ月）毎の内服量は、重症群で 118.7 錠～154.9 錠/3 ヶ月、中等症で 60.2 錠～73.6 錠/3 ヶ月であった(表 4)。解析可能であった症例のなかで、抗ヒスタミン薬を内服し、一年後に明らかに皮膚症状・掻痒が改善した症例の割合は、重症群 16.6%、中等症 41.1%、

軽症 56.3%、軽微群 100%であり、有意差は認めなかったが、軽微群でその頻度が高く、重症群で比較的低い傾向を認めた（表 5)。

D．考察

ADは掻痒の強い慢性に反復する炎症性皮膚疾患であり、ADの標準治療は薬物療法、原因悪化の検索・除去、スキンケアである。薬物治療において、強い炎症を抑えるためには副腎皮質ホルモン薬を中心とした外用療法が必要であり、抗ヒスタミン薬は必要に応じて使用することが勧められている。ADではそう痒・掻破のサイクルによって皮疹の増悪を認めるため、抗ヒスタミン薬の内服によってそう痒を抑えることが治療上有効である。抗ヒスタミン内服によって皮疹の改善につながることが最近の内外の報告でも示されつつある。このような抗ヒスタミン薬の有効性を解析する上で、使用量を検討、解析することは有意義であると考えられる。今回の検討では、重症群における抗ヒスタミン薬の使用量が、中等症、軽症、軽微群に比べて有意に高値である現状が把握できた。すなわち重症群ではステロイド外用量が多いと同時に、ヒスタミン内服薬の使用量も多く、そう痒・掻破が重症化の重要な因子である可能性が示唆された。また、重症度別に検討した皮疹の有効性に関する割合で軽症群での有効率が高く、重症群で有効率が低いことが示された。このことから、抗ヒスタミン薬の有効性は軽症例ではより発揮されやすいことが示唆された。いっぽう重症群では多くの抗ヒスタミン薬を必要としており、有効率も比較的低値であることから、重症群では内服薬によっても掻痒が改善しにくい群が存在するとも捉えることができる。これまでの報告によればADの重症群のなかでステロイド外用薬など既存治療に抵抗性の難治群が全患者数の数%存在することが明らかにされており、今回の使用量の調査研究は、重症群では内服薬を増量しても効果が認められない症例が含まれる可能性を示している。抗ヒスタミン薬の有効性に関してはさらに症例を増やして、検討する必要があると考えられる。またADの重症群、とくに難治群の治療においても、内服薬の有効性、服用状況、期間などに関する検討が必要であると思われる。

E．結論

ADの治療において、重症度からみてすべての症状において抗ヒスタミン薬がしばしば使用されている現状が把握された。重症群では軽症、軽微群に比べて、多く使用されていることが明らかになった。重症AD患者における抗ヒスタミン薬の有効性に関しては今後症例を増やして検討することが必要であると考えられた。

F．研究発表

1．論文発表

なし

2．学会発表

なし

H. 知的財産権の出願・登録状況

なし

1. 特許取得

なし

2. 実用新案登録

なし

3.その他

なし

表1. 一年間におけるステロイド外用使用量（重症度別）（1年を3ヶ月毎に分類）

ステロイド外用総使用量(g)	1-3月	4-6月	7-9月	10-12月
重症	144.6	157.9	217.3	185.0
中等症	102.6	103.6	87.1	83.0
軽症	83.3	81.1	100.6	72.3
軽微	20.5	12.0	8.5	21.5

表2. 一年間における保湿薬使用量（重症度別）

保湿薬(g)	1-3月	4-6月	7-9月	10-12月
重症	71.3	125.0	112.1	114.2
中等症	120.7	117.2	95.1	108.8
軽症	117.6	112.7	100.3	122.4
軽微	30.0	28.5	56.0	73.5

表3. 一年間における外用薬の総使用量（重症度別）

保湿薬(g)	1-3月	4-6月	7-9月	10-12月
重症	287.5	360.0	459.8	367.1
中等症	231.0	235.9	191.3	203.3
軽症	222.3	221.7	241.7	226.4
軽微	63.0	41.5	68.0	96.0

表4. 一年間における抗ヒスタミン薬使用量(重症度別)

抗ヒスタミン薬(錠)	1-3月	4-6月	7-9月	10-12月
重症	143.5	154.9	118.7	120.3
中等症	58.0	73.6	72.6	60.2
軽症	44.3	60.1	50.1	53.6
軽微	23.8	25.2	14.0	5.6

表5. 抗ヒスタミン薬を使用し皮膚症状の改善した割合
(解析症例 57名)

	改善	不変	悪化	不明
重症 (12名)	2(16.6%)	5(41.7%)	5(41.7%)	0(0%)
中等症 (31)	7(22.3%)	8(25.8%)	2(6.5%)	14(45.2%)
軽症 (22)	9(45.5%)	5(16.1%)	2(9.1%)	6(27.3%)
軽微 (2)	2(100%)	0(0%)	0(0%)	0(0%)

さらにAD患者の末梢血より採取した単核球のサイトカイン産生に対する抗ヒスタミン薬の影響について明らかにすることを目的とし解析した。

・同意の得られたAD患者に抗ヒスタミン薬を4週間服用し、その内服前後において、末梢血を採取した。末梢血より単核球を採取し、培養単核球 (3、5日間) の産生するサイトカイン(IL-12、IL-18、IFN-γ)、ケモカイン(CCL17、CCL22)値について検討した。

・末梢血単治療前後で、培養単核球の CCL17, CCL22, IFN-γ産生に有意な減少を認めた。5日間培養で治療前後の CCL17 産生は 1780.5pg/ml より 889.4pg/ml に減少し、IFN-γ産生は 143.2pg/ml より 51.6pg/ml に減少した。

・抗ヒスタミン薬4週間内服による治療前後での SCOARD 値、末梢血好酸球数値、血清サイトカイン、ケモカイン値の推移。(*p<0.05, **p<0.01)

各種モデルマウスを用いた掻き行動・表皮内神経伸長に対するCX659S（MEK1/2 阻害薬）の抑制効果に関する研究

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研究要旨

(研究目的) CX659（旧名：K-412）はMAPK/ERK kinase1/2 (MEK1/2)阻害薬のひとつで、新しい抗炎症作用薬である。その機序の一つとしてケラチノサイトからの GM-CSF 産生を抑制し、間接的にランゲルハンス細胞の機能を減弱させて作用することが当教室のこれまでの研究で明らかにされている。慢性の痒みを伴う皮膚病変では、表皮内へと神経が伸長し、その執拗な痒みとの関連が指摘されているが、いくつかの他のMEK1/2阻害薬においては in vitro において神経の伸長に抑制的に作用することが明らかにされている。そこで我々はCX659Sがinvivoにて痒みを伴う慢性皮膚病変部にみられる表皮内神経の伸長を抑制し、痒み・掻破行動を抑制するのではないかとの仮説を立て、①アトピー性皮膚炎のモデルマウスである NC/Nga マウスや②ハプテン反復塗布による表皮内神経伸張マウス皮膚炎モデルを用いてこれを検証した。**(方法)** ①conventional な環境下で飼育し皮膚炎を自然発症した NC/Nga マウスの皮疹部に CX659S またはアトピー性皮膚炎治療薬 FK506 を連日塗布し、マウスの掻破行動の抑制効果を検討した。②C57BL/6 マウスの耳介・背部皮膚に隔日でピクリルクロライド(PiCl)を外用し、CX659S、FK506 またはベタメサゾンを同部に連日塗布して1週間後に組織学的に抗炎症作用や表皮内の神経伸長の差異を比較・検討した。**(結果)** ①CX659S、FK506 ともに NC/Nga マウスの掻破行動を有意に抑制した。②CX659S、FK506、ベタメサゾンの3種類の薬剤はいずれも表皮内への総神経線維伸張を抑制する効果を認めた。しかし、サスブスタンスP陽性知覚神経の伸長を有意に抑制したのは、CX659S のみであった。また、CX659S は有意差は認められなかったものの、CGRP陽性神経の伸長抑制傾向も示した。また、いずれの薬剤もPiCl外用により誘発される耳介皮膚腫脹、局所の肥満細胞数を有意に抑制させた。しかしCX659Sによる抗炎症作用は他の2剤に比べてやや弱く、トータルの炎症細胞浸潤の抑制傾向は認めるものの、有意差は認めなかった。 **(考察、結論)** MEK1/2 抑制作用を持つCX659Sは既存の免疫抑制剤FK506とともにNC/Ngaマウスにおいて掻破動作の抑制作用を示した。また、CX659S は（他の2剤と比較するとやや弱くはあるが）PiCl 外用により誘発される皮膚腫脹、局所の肥満細胞の増加やトータルの炎症細胞浸潤を有意に抑制あるいは抑制傾向を示した。興味深いことに、その比較的弱い抗炎症作用にもかかわらずCX659SのみがPiCl外用誘発による表皮内の総神経長のみならずサスブスタンスP陽性知覚神経の伸長を有意に抑制した。表皮内に伸びる知覚神経は様々な皮膚疾患の執拗な痒みと関連していると考えられており、CX659SはおそらくFK506やベタメサゾンとは異なったメカニズムで作用する、有用な痒み抑制剤となる可能性が示された。

A.研究目的

我々はこれまでに CX659S（旧名：K-412）は、1）外用によりハプテン（ピクリルクロライド：PiCl）による接触皮膚炎を in vivo で抑制すること、2）MAPK /ERK kinase1/2（MEK1/2）のリン酸化を抑制してケラチノサイトからの GM-CSF 産生を抑制すること、3）それによって間接的にランゲルハンス細胞の機能を減弱させることを明らかにしてきた。一方、MEK1/2 阻害薬は、in vitro で神経細胞の伸長に抑制的に働くことも報告されている。執拗な痒みを伴う慢性湿疹、痒疹などの慢性皮膚病変部においては、通常みられない表皮内への知覚神経侵入・伸長が確認されておりその執拗な痒みとの関連が指摘されている。そこで、慢性皮膚炎において CX659S が表皮内神経線維の伸長を抑制し痒み・掻破行動を抑制するのではないかとの仮説を立て、アトピー性皮膚炎モデルマウスである NC/Nga マウスや PiCl 反復塗布による表皮内神経伸張マウス皮膚炎モデルを用いてこれらを検証した。

B.方法

①アトピー性皮膚炎のモデルマウスである NC/Nga マウスを conventional な環境下で飼育し皮膚炎を自然発症したマウスを用いて、CX659S のマウスの掻破行動の抑制効果を検討した。自然発症した皮疹部に CX659S、FK506 を連日外用し、18 日後に掻破動作を測定した。掻破動作については Noveltec の自動掻破測定機 SCLABA を用い、マウスの後肢と薬剤投与部位である肩甲骨間に異なった2色でペイントし、一定条件を満たしたものを掻破行動として、コンピューターにより自動的にかつ客観的に定量化した。

②C57BL/6 マウスの耳介・背部皮膚に隔日で PiCl を外用し、CX659S、FK506 またはベタメザゾンを連日と付して1週間後に耳介皮膚の腫脹、組織像（HE 染色、トルイジンブルー染色）、表皮内の総神経伸長（PGP9.5 染色）、知覚神経伸長（サスブスタンス P または CGRP 染色）を、1）基剤外用群、2）FK506 外用群、3）ベタメサゾン外用群、4）CX659S 外用群で比較検討した。

（倫理への配慮）

本研究内容は、九州大学医学研究院動物実験委員会の承認を得ている。

C.結果

①掻破行動：コントロールの無処置の経過観察群に比較して、CX659S と FK506 外用群ではともに有意にマウスの掻破動作が抑制された。

②耳介皮膚の腫脹：CX659S、FK506、ベタメサゾンの3種類の薬剤塗布群ではいずれも有意に PiCl 誘発による耳介の腫脹が抑制された。

組織像（HE 染色、トルイジンブルー染色）：PiCl 単独塗布群では、溶媒のアセトン塗布群と比べ著明な表皮・真皮の肥厚と炎症細胞浸潤を認めた。CX659S、FK506、ベタメサゾンのいずれの薬剤併用群でも、PiCl 塗布誘発による局所肥満細胞数増加の抑制を認めた。しかし、CX659S による抗炎症作用は他の2剤に比べてやや弱く、トータルの炎症細胞浸潤においては抑制傾向は認めるものの、有意差は認めなかった。

表皮内神経伸長（PGP9.5、サブスタンス P、CGRP 染色）：いずれの薬剤も表皮内への全（PGP9.5 陽性）神経線維の伸張を抑制する効果を認めた。しかし、サスブスタンス P 陽性知覚神経の伸長を有意に抑制したのは、CX659S のみであった。また、CX659S は有意差は認められなかったものの、CGRP 陽性神経の伸長抑制傾向も示した。

D.考察

CX659SはMEK1/2阻害薬のひとつで新しい抗炎症作用薬であり、その機序のひとつとしてケラチノサイトからのGM-CSF産生を抑制し、間接的にランゲルハンス細胞の機能を減弱させて作用することがわかっている。MEK1/2 阻害薬と神経の伸長の関係についてはこれまでにいくつか興味深い報告がなされているが、MEK1/2 阻害薬は、In vitroで神経の伸長に抑制的に働くと報告されている。しかし、in vivoでの皮膚炎と皮膚での末梢知覚神経伸長に対して詳細な検討を加えた報告はいまだなされていない。

われわれのデータでは、MEK1/2 抑制剤であるCX659S は NC/Nga マウスの掻き動作や PiCl 外用により誘発される皮膚腫脹、局所の肥満細胞の増加（他の2剤と比較するとやや弱くはあるが）有意に抑制あるいは抑制傾向を示した。興味深いことに、その比較的弱い抗炎症作用にもかかわらずK412のみがPiCl外用誘発による表皮内の総神経伸長のみならず、サスブスタンスP陽性知覚神経線維の伸長を有意に抑制した。表皮内に伸びる知覚神経は様々な皮膚疾患の執拗な痒みと関連していると考えられており、CX659SはFK506とは異なったメカニズムで作用する、有用な皮膚炎における痒みの抑制剤となる可能性が示された。

E.結論

CX659Sは単なる抗炎症薬としてだけでなく、FK506 やベタメサゾンとは異なったメカニズムで作用する、皮膚炎における有用な痒みの抑制剤となる可能性が示された。

F.研究発表

学会発表

第16回 国際痒みシンポジウム 2006年11月18日

K412, a MEK1/2 inhibitor, diminishes epidermal nerve elongation in chronic dermatitis.

M. Kido, S. Hayashida, S. Takeuchi, Furue (Department of Dermatology, Kyushu University), J. Matsumoto (Kowa Co., Ltd.)

I.知的財産権の出願・登録状況

1.特許取得（出願中）

【発明の名称】 痒みの抑制剤 (CX659S)

知覚神経の伸長を抑制することによる痒みの抑制剤、特にアトピー性皮膚炎における痒みの抑制剤。

研究成果の刊行に関する一覧表

「みんなで考えましょう、アトピー性皮膚炎とのおつきあい(市民公開講座)」
http://www.kyudai-derm.org/atopy/openlec/index.html

「アトピー性皮膚炎についていっしょに考えましょう」
http://www.kyudai-derm.org/atopy/

「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」
http://www.kyudai-derm.org/atopy_ebm/index.html

雑誌

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Topical tacrolimus in the management of atopic dermatitis in Japan

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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. Topical calcineurin inhibitors, such as tacrolimus, not only complement existing treatment options but also overcome some of the drawbacks of topical steroid therapy and fulfill the long-term needs of patients in preventing disease progression. Short- and long-term efficacy and safety of topical tacrolimus has been widely recognized and it is also accepted as a first-line treatment for the inflammation of AD. In order to reduce the possible long-term adverse effects, it is important to monitor the clinical dose in daily clinics.

KEYWORDS: adverse effects, Atopic dermatitis, dose, topical steroids, topical tacrolimus

Introduction

Atopic dermatitis (AD) is a common, chronic, or chronically relapsing, severely pruritic, eczematous skin disease. 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). The incidence in Japanese elementary school students was around 3% in 1981–1983 but increased to around 6–7% in the 1990s (3). In 2000–2002, the research team of Japanese Ministry of Health, Labor and Welfare (chief researcher; Dr S. Yamamoto) performed physical examinations of 48,072 children living in Asahikawa, Iwate, Tokyo, Gifu, Osaka, Hiroshima, Kochi, and Fukuoka (5). They reported that national average prevalence rate of AD was 12.8% in 4-month-old, 9.8% in 18-month-old, 13.2% in 3-year-old, 11.8% in 6- to 7-year-old, 10.6% in 12- to 13-year-old, and 8.2% in 18-year-old children. Although topical steroids, emollients, and oral antihistamines are used as the first-line therapy for AD, long-term application, even in intermittent use, induces local and unavoidable adverse effects such as skin atrophy and teleangiectasia in a substantial percentage of patients. These adverse effects and emotional fear of long-term use of topical steroids have induced topical steroid phobia in many patients throughout the world (6). Moreover, a certain population of patients with AD has 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 the 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). The purpose of this article is to overview

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the clinical impact of topical tacrolimus on the treatment of AD in Japan.

Topical steroid therapy for AD in daily clinic

Before the topical tacrolimus was commercially available in Japan, the present authors collected clinical data on 1271 AD patients who had been followed for at least 6 months in the outpatient clinics (10). The check sheet for each patient included the following items: age; gender; duration of AD; global severity before treatment; global severity after 6 months of conventional topical steroid therapy; evaluation of clinical improvement; total dose of each rank of topical steroids per 6 months' therapy on the face, scalp, trunk, and extremities; association of herpes simplex infection and/or Kaposi varicelliform eruption; association of molluscum contagiosum; and adverse effects of topical steroids (telangiectasia on cheeks, skin atrophy of antecubital fossae, skin atrophy of popliteal fossae, acne and folliculitis, hypertrichosis, bacterial infection, dermatomycosis, rosacea-like dermatitis, contact dermatitis caused by topical steroids, and steroid-induced striae atrophicae). Global clinical severity was classified as "very severe," "severe," "moderate," and "mild." The ranks of topical steroids were classified as "strongest," "very strong," "strong," "mild," and "weak" in Japan.

The 1271 patients with AD were divided into three groups according to age, 210 infantile (0–1 years old) AD cases, 546 ($2 \leq < 3$ years old) childhood AD cases, and 515 adolescent and adult ($13 \leq$ years old) AD cases. All of the patients were treated with topical steroids and moisturizing emollients. The clinical severity of AD in the majority of patients improved or was unchanged after 6 months of conventional therapy ("controlled" group). However, 7% of infantile AD, 10% of childhood AD and 19% of adolescent and adult AD patients remained in a very severe or severe state or experienced exacerbation ("uncontrolled" group) (Table 1) (10). These data suggested 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. Concordantly, Brunsting pointed out that the recurrent lesions of adolescent and adult AD were resistant to treatment by local measures in 1936 (11). These uncontrolled patients were so-called "intractable" patients, and such patients are given much attention as a social problem in Japan.

Table 1. Change of clinical severity pre- and post-treatment –6 months' treatment with topical steroids – infantile (< 2 y)

	Pretreatment			
	Very severe	Severe	Moderate	Mild
Post-treatment				
Very severe				
Severe		8[a]		1[a]
Moderate	2	9	41	6[a]
Mild		6	57	76
ND			1	
Total (207)	2	23	99	83

Adolescent and adult (13 y ≤)

	Pretreatment			
	Very severe	Severe	Moderate	Mild
Post-treatment				
Very severe	15[a]	2[a]		
Severe	6[a]	65[a]	6[a]	
Moderate	7	58	161	4[a]
Mild	2	21	92	64
ND	1	1		
Total (505)	31	147	259	68

Childhood ($2 \leq < 13$ y)

	Pretreatment			
	Very severe	Severe	Moderate	Mild
Post-treatment				
Very severe	3[a]	2[a]		
Severe	5[a]	27[a]	3[a]	
Moderate	5	44	155	11[a]
Mild	1	17	141	117
ND		1	2	6
Total (540)	14	91	301	134

[a]Uncontrolled patients during 6 months' treatment.
Infantile, 7%; childhood, 10%; adolescent and adult, 19%.
ND, not described.

Total doses of topical steroids used during the 6-month treatment period were listed in Table 2 as median, 75%ile and 90%ile doses. Ninety percent of patients with AD used less than 90, 135, and 304 g of topical steroids during 6 months on the entire body in the infantile, childhood, and adolescent/adult patients with AD, respectively. The 90%ile doses applied on the face during 6 months were 10, 15, and 35 g in infantile, childhood, and adolescent/adult AD patients, respectively. The amounts of topical steroids applied in this survey were much less than those reported by Wilson et al. and Munro et al. (12,13). The incidence of association of herpes simplex infection

Table 2. Clinical doses of topical steroids during 6 months of treatment (g)

		Infantile < 2 y	Childhood 2 ≤ < 13 y	Adolescent/adult 13 y ≤
No. of cases		210	546	515
Face	50% dose	1 (g)	0 (g)	0 (g)
	75% dose	5	5	15
	90% dose	10	15	35
Total	50% dose	25	45	95
	75% dose	43	80	180
	90% dose	90	135	304
Associated diseases during 6 months of treatment		< 2 y	2 ≤ < 13 y	13 y ≤
Herpes simplex infection		2.4%	2.5%	3.5%
Molluscum contagiosum		7%	9%	0.2%

Table 3. Dose of topical steroids between controlled and uncontrolled groups during 6 months of treatment (g)

		Controlled group	Uncontrolled group
< 2 y	No.	191	15
	50% dose	20 (g)	30 (g)
	75% dose	40	60
	90% dose	70	90
	Mann–Whitney's *U*-test	0.3002	
2 ≤ < 13 y	No.	481	51
	50% dose	40 (g)	60 (g)
	75% dose	75	120
	90% dose	120	207.8
	Mann–Whitney's *U*-test	0.0018[a]	
13 y ≤	No.	406	98
	50% dose	75 (g)	140 (g)
	75% dose	150	252.5
	90% dose	250	400.5
	Mann–Whitney's *U*-test	0.0000[a]	

and molluscum contagiosum was also listed in Table 2 (10).

The present authors next examined the topical steroid doses used in the "controlled" and "uncontrolled" groups (Table 3). The total usage of topical steroids was unexpectedly larger in the uncontrolled group than in the controlled group. The statistical difference became more obvious in the adolescent and adult group than in the childhood group (Table 3). Topical steroids are useful for treating AD, but there appears to be a subgroup of patients who remain severe despite increasing applications of topical steroids.

Impact of topical tacrolimus on topical steroids therapy for AD in daily clinics

After the topical tacrolimus was commercially available, the present authors collected the clinical data from 215 patients with adolescent/adult type AD who had been followed for at least 6 months in outpatient clinics (14). The checklist was the same as mentioned previously including the total dose of topical tacrolimus per 6 months therapy. Very interestingly, the clinical severity of AD improved remarkably in the majority of patients after 6 months of combination topical therapy. In only 6% of patients with adolescent/adult-type AD was uncontrolled (14) (Table 4).

Bacterial and viral infections are commonly associated with AD (15–17). As tacrolimus and steroids are both immunosuppressive drugs, the combination topical therapy may potentially increase the risk of cutaneous infections. The present authors compared the incidence of cutaneous infections before and during treatment. The incidence of cutaneous infections did not seem to be increased during treatment compared with pretreatment. Instead, the incidence of bacterial infection was decreased from 5.6% to 1.9% on the face and neck, probably because of the marked clinical improvement of dermatitis by the combination therapy (14) (Table 5). In contrast, the incidence of herpes simplex infection did increase from 2.8% to 4.7% on the face and neck (Table 5). In the present authors' previous data before the approval of tacrolimus for clinical use, the incidence of herpes simplex infection in adolescent/adult AD patients was 3.5% (Table 2). It is difficult to conclude that the combination topical therapy increases the risk of herpes simplex infection in AD. Further studies are necessary. Very

Table 4. Change of clinical severity pre- and post-treatment in adolescent/adult patients with AD –6 months' treatment with topical steroids and tacrolimus

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

[a]Uncontrolled patients, 6%.

Table 5. Cutaneous infections on the face and neck before and during the 6-month treatment with topical steroids and tacrolimus

		Total	Severe	Moderate	Mild
Acne and folliculitis	Pretreatment	22.8%	0.9	2.8	19.1%
	During treatment	17.3%	0	1.4	15.9%
Bacterial infection	Pretreatment	5.6%	0	1.4	4.2%
	During treatment	1.9%	0	0.9	0.9%
Fungal infection	Pretreatment	0%	0	0	0%
	During treatment	0%	0	0	0%
Herpes simplex infection	Pretreatment	2.8%	0.5	0.9	1.4%
	During treatment	4.7%	0	2.8	1.9%
Molluscum contagiosum	Pretreatment	0%	0	0	0%
	During treatment	0%	0	0	0%

Table 6. Dose of topical tacrolimus and steroids on the face and neck during the 6-month treatment period

		Tacrolimus	Steroid
Face and neck	50 percentile	29 (g)	0 (g)
	75 percentile	49	5
	90 percentile	70	15

recently, Fleischer et al. reported that tacrolimus ointment for the treatment of AD was not associated with an increase in cutaneous infections (18). The present data may support their findings.

Before the approval of tacrolimus for clinical use, the 90% dose of topical steroid was 35 g/6 months on the face (10), whereas topical tacrolimus apparently reduced the dose of steroid to 15 g/6 months (14) (Table 6). 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 the face and neck lesions (99.1% of patients), whereas it was used by only 39.5% of patients on the trunk and extremities (14). Topical steroid application induces cutaneous side effects such as hypertrichosis, telangiectasia, and skin atrophy. The possibility that a reduction of the dose of topical steroid by tacrolimus application attenuated the incidence and intensity of steroid-induced side effects has been reported (19). This was the case in the present study. During the 6-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 (14) (Table 7). Patients with unreduced side effects like telangiectasia on the cheeks used significantly larger amounts of steroid on the face (14) (Table 8). The majority of the present 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. The combination therapy is feasible to avoid the adverse effects of steroids by reducing the amounts of topical steroids of long-term application. However, it should be mentioned that there still appears to be a small subgroup 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.

Table 7. Changes in adverse effects of topical steroid pre- and post-treatment by 6 months' combination therapy with topical steroids and tacrolimus

		Total	Severe	Moderate	Mild
Telangiectasia on cheeks	Pretreatment	34.9%	1.9	6.5	26.5%
	Post-treatment	18.7%	0	1.9	16.8%
Hypertrichosis on face	Pretreatment	4.7%	0	0.5	4.2%
	Post-treatment	1.9%	0	0	1.9%

Table 8. Doses of topical steroids ("mild" and "weak" rank) on the face and neck during 6 months of treatment between "reduced" and "unreduced" group with telangiectasia on cheeks

	Reduced group (g)	Unreduced group
50 percentile	0	0
75 percentile	3	10
90 percentile	10	26
Mann–Whitney *U*-test	0.032	

Evidence-based medicine of topical tacrolimus for the treatment of AD

The systematic review of treatments for AD was open for public by the National Coordinating Center for Health Technology Assessment (http://www.ncchta.org/index.htm). It was also translated in Japanese (http://www.allergykid.jp/ad/). In 2004, the present group reviewed the recent EBM for the treatment of AD and opened the information in the internet in Japanese by the support from the Ministry of Health, Labor, and Welfare, Japan (http://www.kyudai-derm.org/atopy_ebm/index.html).

Five major randomized vehicle-controlled trials have been published until 2003 in adults including Japanese clinical trials (20–24). In two randomized, double-blind studies of a total of 632 adults with AD, Hanifin et al. reported that tacrolimus (0.1% and 0.03%) ointment-treated patients showed significantly greater improvement than vehicle-treated patients for all efficacy parameters evaluated, including the percentage body surface area affected, the total score, and individual scores for signs of AD, the patient's assessment of pruritus, and EASI score (23). The 0.1% concentration was more effective than the 0.03% concentration (23). Although tacrolimus is a very potent immunosuppressant, the clinical potency is limited because of its low transepidermal absorption. When applied for 1 week, 0.1% tacrolimus ointment was shown to be more potent than 0.1% alclomethasone dipropionate ointment (25). Both 0.03% and 0.1% tacrolimus ointments were significantly more effective than 1% hydrocortisone acetate when applied for 3 weeks (26). The efficacy of 0.1% tacrolimus ointment was similar to that of 0.1% hydrocortisone butyrate ointment (8) and 0.12% betamethasone valerate ointment (27) when applied for 3 weeks. The continuous efficacy of topical tacrolimus has been confirmed by long-term study. Marked or excellent improvement or clearance of disease was reported in 54%, 81%, and 86% of patients at week 1, month 6, and month 12, respectively (28). Adverse events such as burning sensation (47% of patients) were common but tended to occur only when initiating treatment (28). In 2-year long-term application trial, marked or excellent improvement or clearance of disease was reported in 90% and 93.1%, of patients at weeks 10 and 104, respectively (29). Adverse events such as burning sensation appeared in 79.2% (450/568) of patients within 1 year; however, the incidence of irritation side effects decreased to only 5.5% (23/418) of patients who applied more than 1 year (29). Similar short-term and long-term efficacy of topical tacrolimus was reported in childhood AD (30–34). The important point is that the efficacy of topical tacrolimus is not attenuated under the long-term continuous application for at least 2 years. The blood concentration of absorbed tacrolimus is very low and usually does not exceed 3 ng/mL (most patients are below the detection limits of 0.5 ng/mL) (Table 9).

The most common adverse events were the sensation of skin burning and pruritus, especially among patients with severe or extensive disease; however, these events were usually brief and were resolved during the first few days of treatment (35). In addition, topical tacrolimus does not cause skin atrophy (36). The systematic review for 1554 patients with AD, treated with tacrolimus ointment in five clinical trials, revealed that the 12-week adjusted incidence of all cutaneous infections in patients treated with the vehicle,

Table 9. Clinical trials in Japanese literature on topical tacrolimus

Reference number	Treatment
20	Double-blinded parallel RCT, 212 cases, more than 16 years. Vehicle; 72 cases, 0.03% tacrolimus; 70 cases, 0.1% tacrolimus; 70 cases. Three weeks application. Marked or moderate improvement or clearance, vehicle; 49.2%, 0.03% tacrolimus; 71.3%, 0.1% tacrolimus; 91.9%. Burning sensation: vehicle; 9.9%, 0.03% tacrolimus; 35.7%, 0.1% tacrolimus; 36.2%.
25	Parallel RCT, 151 cases, more than 16 y. 0.1% tacrolimus; 75 cases, 0.1% alclomethasone dipropionate ointment; 76 cases. 1 week application for face and neck lesions. Marked improvement or clearance, 0.1% tacrolimus; 86.3%, 0.1% alclomethasone dipropionate ointment; 35.7%. Burning sensation: 0.1% tacrolimus; 80%, 0.1% alclomethasone dipropionate ointment; 6.6%.
27	Parallel RCT, 181 cases, more than 16 y. 0.1% tacrolimus; 89 cases, 0.12% betamethasone valerate ointment; 92 cases. 3 weeks application for lesions on trunk and extremities. Marked or moderate improvement or clearance □ 0.1% tacrolimus; 93.6%, 0.12% betamethasone valerate ointment; 90.5%. Burning sensation: 0.1% tacrolimus; 59.1%, 0.12% betamethasone valerate ointment; 8.9%.
29	Open trial, 570 cases, more than 16 years. Less than 10 g/day application of 0.1% tacrolimus for 6 months to 2 years. Marked improvement or clearance, 10 weeks later; 90%, 104 weeks later; 93.1%. No attenuation of efficacy occurred. At the time of completion of 1-year observation (N= 568, skin irritation; 79.2%, skin infections; 20.8%, accompanying symptoms; 11.1%). Patients of more than 1 year application (N= 418, skin irritation; 5.5%, skin infections; 16.7%, accompanying symptoms; 2.2%). The mean amount of tacrolimus ointment was around 2 g/day. Blood concentration of more than 3 ng/mL was detected in 4/398 samples, max; 4.4 ng/mL.
32	Double-blinded parallel RCT, 221 cases, 2–15 years. Vehicle; 75 cases, 0.03% tacrolimus; 75 cases, 0.1% tacrolimus; 71 cases. Three weeks application. Marked improvement or clearance, vehicle; 12.7%, 0.03% tacrolimus; 66.7%, 0.1% tacrolimus; 75.7%. Blood concentration was detected in 5/134 samples (max; 0.85 ng/mL) in 0.03% group and in 20/139 samples (max; 1.78 ng/mL) in 0.1% group.
33	Open parallel RCT, 214 cases, 2–15 years. 0.03% tacrolimus; 104 cases, 0.1% tacrolimus; 110 cases. One year application. Marked or moderate improvement or clearance, after 36 weeks through 52 weeks; more than 90% in both groups. 0.03% tacrolimus: skin irritation; 50%, skin infections; 33.7%, accompanying symptoms; 5.8%. 0.1% tacrolimus: skin irritation; 62.4%, skin infections; 22%, accompanying symptoms; 8.3%. Blood concentrations of more than 3 ng/mL was detected only in two patients. The blood levels decreased with the improvement of skin symptoms without any systemic adverse reactions.
34	Extension study of refs 32 and 33; 134 cases (2–15 years) were enrolled after these two double-blinded RCTs. 0.03% tacrolimus application (only 17 patients received 0.1% tacrolimus when exacerbated). Duration of observation: mean; 792 days, max; 1060 days Marked or moderate improvement or clearance, 90% after 52 weeks and beyond. Adverse effects: skin irritation; 41%, skin infections; 41%, accompanying symptoms; 11.2%. No patients had a blood concentrations exceeding 3 ng/mL was detected (max; 2.24 ng/mL, more than 95% of patients; below 0.5 ng/mL).

0.03%, and 0.1% tacrolimus ointment, respectively, were 18.0%, 24.8%, and 17.7% for adult patients, and 20.9%, 19.6%, and 23.6% for pediatric patients (18). The incidence of any individual cutaneous infection was not significantly higher in the tacrolimus group than in the vehicle group, with the exception of folliculitis in adults. In two open-label studies, there was no evidence of an increased risk of cutaneous infections with long-term use of 0.1% tacrolimus ointment (up to 1 year), based on the incidence of adverse events, incidence by cumulative length of exposure, or hazard rates (18).

Recently, the treatment algorithm has been proposed by the International Consensus Conference on Atopic Dermatitis II (37). As mentioned previously, the topical calcineurin inhibitors, tacrolimus and pimecrolimus, not only complement existing treatment options but also overcome some of the drawbacks of topical steroid therapy

and fulfill the long-term needs of patients in preventing disease progression. Moreover, the primary mechanism of action of calcineurin inhibitors, which is distinct from topical corticosteroids, is to inhibit inflammatory cytokine transcription in activated T cells and other inflammatory cells through inhibition of calcineurin. Unlike many corticosteroids, these agents may be used on all body locations for extended periods. Skin atrophy, glaucoma, and other local risks of corticosteroids do not occur, nor do the systemic side effects such as hypothalamus/adrenal-axis suppression and growth retardation (37). Based on the long-term efficacy and safety, the conference algorism reinforces the role of topical calcineurin inhibitors as maintenance therapy for AD with corticosteroids being reserved for acute control of disease progression (37). In the "Guidelines for Therapy for Atopic Dermatitis 2004," the Japanese Dermatological Association positions topical tacrolimus, like topical steroids, as the first-line therapy for the inflammation of AD (38). In order to reduce the systemic absorption, the use of 0.1% tacrolimus ointment is limited in patients of more than 16 years old. Patients under 16 years old (2 = < 16) should use only 0.03% tacrolimus ointment in Japan (38). Moreover, topical dose of tacrolimus ointment per application is regulated up to 1, 2–4, and 5 g for patients with body weight of less than 20, 20–50, and more than 50 kg, respectively (38). As 1 g ointment application can cover at least four adult hand areas (39), the dose regulation does not practically interfere the present authors' daily clinic.

In March 2005, the Food and Drug Administration issued a public health advisory to inform healthcare professionals and patients about a potential cancer risk from use of topical calcineurin inhibitors (http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01343.html). This concern is based on information from animal studies, case reports in a small number of patients, and knowledge of how drugs in this class work. In their statement they conclude that it may take human studies of 10 years or longer to determine if use of topical calcineurin inhibitors is linked to cancer development. Although topical corticosteroids have been the standard of therapy for many years and their efficacy is not in question, there are continuing concerns about their safety. However, the new class of topical calcineurin inhibitors may fulfill this unmet need by providing a safe and effective option for the long-term control of AD. These new treatments for AD are welcomed by patients, parents of patients, and physicians including dermatologists and pediatricians, as another treatment option for AD (37). Anyhow, in order to reduce the possible long-term risk for cancer development, it is necessary to monitor the clinical dose of topical steroids and calcineurin inhibitors in daily clinics.

Combination therapy with topical steroids and tacrolimus

Topical steroids are still the mainstay of treatment for inflammation of AD. Prompt treatment of flare-ups with adequately potent topical steroids until the inflammation subsides is recommended as optimal treatment for control of relapses (40–42). 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. Because of the troublesome, chronic, and relapsing nature of AD, adverse effects are the main concern of patients who must apply steroids for a long-term (40,43). Intermittent dosing with a potent steroid is sufficient for reducing the risk of relapse in AD without increasing its side effects (44,45).

Topical tacrolimus is a potent nonsteroidal immunosuppressive agent that does not exhibit the hormonal adverse effects associated with steroid therapy (9,36). 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 (14,19). However, a substantial percentage of patients prefers to use "very strong" or "strong" steroids rather than tacrolimus because of the initial burning sensation after application and of its low potency because of 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 (14,19).

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 4 weeks of treatment (46). Only 1 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. The precedent application of topical steroids for a few days usually decreases the burning sensation of subsequent topical tacrolimus (38). The application of moisturizing lotion just prior to the topical tacrolimus may reduce the burning sensation (47).

Conclusion

The major side effect of topical tacrolimus is the transient burning sensation, which usually subsides within several days by continuous application. Topical tacrolimus has already been commercially available for 6 years. Meanwhile, there is no case report on the development of internal and cutaneous malignancies because of topical tacrolimus. At this moment, topical tacrolimus is a safe and quite beneficial drug. In conjunction with topical steroid, tacrolimus plays a major role in the management of AD. Careful follow-up and dose monitoring is essential to foster this life-changing drug.

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Incidence of atopic dermatitis in nursery school children – A follow-up study from 2001 to 2004, Kyushu University Ishigaki Atopic Dermatitis Study (KIDS)

Atopic dermatitis (AD) is a multifactorial disease that usually decreases the quality of life of affected patients. We monitored the incidence of AD and serum total IgE levels annually among nursery school children in Ishigaki Island, Okinawa, Japan, from 2001 to 2004. A total of 1731 children were enrolled. The prevalence of AD ranged from 3.7 to 11% in each year, with no significant difference between boys and girls. 869 children were examined at least twice. 71.6% (53/74) of AD patients regressed spontaneously, whereas 5.5% (44/795) of non-AD individuals developed AD during the 3-year follow-up. Increases in total IgE levels were greater and more rapid in children with long-term AD than in those who had spontaneously regressed, had newly-developed AD or did not have AD. The regression rate of AD was > 70% while new-onset AD occurred at a rate of 3.67%/person year in nursery school children of Ishigaki Island.

Key words: atopic dermatitis, epidemiology, immunoglobulin E, questionnaires

Atopic dermatitis (AD) is a common and chronic inflammatory skin disease that is characterized by relapsing itch and eczema [1]. It is a major skin disease of children that is increasing in both developed [2-4] and developing countries [5]. A similar trend has been documented in Japan, [6-8] although one study has reported that AD is no longer increasing [8]. There have been many studies of the prevalence of AD [6-15]. However, there are very few population-based epidemiological studies assessing prevalence among children aged 5 years and less. In a previous study, we established the prevalence of AD and serum total and specific IgE levels among children in Ishigaki Island, Okinawa, Japan, in 2001 [16].
In the present study, we monitored children in Ishigaki Island by means of annual physical examinations from 2001 to 2004.

Methods

Study population

We performed physical examinations of children in 15 nursery schools in Ishigaki Island, which has a population of 45,000, in Okinawa Prefecture, Japan. All the children were aged 5 years or less. Approval for the study was obtained from the Ethics Committee of Kyushu University Hospital as well as from the directors and class teachers of the schools. Informed consent to allow participation of the children was obtained from the parents and guardians. The yearly average temperature and humidity were 25.4 °C and 76% on Ishigaki Island.

The physical and laboratory examination was continued annually from 2001 to 2004. The number of children examined was 631 in 2001, 836 in 2002, 844 in 2003, and 764 in 2004 *(table 1)*. Of these, 862 were examined only once; 466 were followed for one year; 297 were followed for 2 years; and 106 were followed for 3 years. 1731 individuals were thus enrolled in total, which represented 42.1% of the 4112 kindergarten pupils in Ishigaki City. The physical and laboratory examination was completed in July and August each year (summer season, average temperature 28 °C).

Physical and laboratory examination

The medical examinations for all children were done by two dermatologists from the Department of Dermatology, Kyushu University Hospital. AD was diagnosed according to the Japanese Dermatological Association criteria *(table 2)* [17]. All children were tested for total and specific IgE antibodies. Total IgE levels were determined by a radioimmunoassay with a detection limit of 20 IU/mL (Shionoria IgE, Shionogi & Co., Ltd. Japan). A total IgE level > 230 IU/mL was considered abnormal for the purpose of statistical analysis. Specific IgE antibodies against aeroallergens such as house dust, Japanese cedar pollen, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Candida*, *Malassezia*, and food allergens, such as chicken egg white, cow's milk, rice, and soy were tested with the Pharmacia Enzyme CAP procedure (Pharmacia CAP System Specific IgE FEIA, Pharmacia Diagnostics AB, Sweden). A level of specific IgE antibodies over 0.7 UA/mL was considered abnormal.

Table 1. Prevalence of atopic dermatitis in nursery school children in Ishigaki Island

	Male		Female		Total		
	Number	AD (%)	Number	AD (%)	Number	AD (%)	Mean age ± SD
2001	342	19 (5.6)	289	20 (6.9)	631	39 (6.2)	3.0 ± 1.3
2002	446	23 (5.2)	390	30 (7.7)	836	53 (6.3)	2.9 ± 1.3
2003	455	44 (9.7)	389	49 (12.6)	844	93 (11.0)	3.2 ± 1.2
2004	412	15 (3.6)	352	13 (3.7)	764	28 (3.7)	3.0 ± 1.3

Statistical analysis

Continuous data were expressed as mean values ± standard deviation (SD) or standard error (SE) of the mean. Unpaired t-tests and Mann-Whitney U-tests were used to compare the means of samples between two groups. The chi-square test or Fisher's exact test was used for categorical variables for comparisons between two groups. The Cochran-Armitage test was used to determine the relationship between the increase or decrease in the prevalence rate of AD and the IgE abnormality rate. $P < 0.05$ was considered statistically significant.

Results

Incidence of AD

Table 1 shows the annual prevalence of AD in the study population, which ranged from 3.7 to 11% (mean, 6.8%) each year, with no significant difference between boys and girls. Of the total of 1731 children examined, 869 were followed up for 1 to 3 years, of whom 74 were diagnosed as having AD, while the remaining 795 were considered to be free of AD at the initial physical examination.

Among the 74 AD cases, 53 were confirmed to have regressed during the 3-year follow-up (71.6%); 31 cases after one year, 16 at 2 years, and the remaining 6 at 3 years *(figure 1)*. In contrast, 44 of the 795 non-AD individuals (5.5%) developed AD newly-developed within this 3-year period *(figure 2)*, indicating that the rate of new onset AD was 3.67%/person year in these nursery school children.

Table 2. Definition and diagnostic criteria for atopic dermatitis by Japanese Dermatological Association

Definition

AD is a pruritic, eczematous dermatosis, the symptoms of which fluctuate chronically with remissions and relapses. Most individuals with AD have atopic diathesis.

Atopic diathesis: (1) personal or family history (asthma, allergic rhinitis and/or conjunctivitis and AD), and/or (2) predisposition to overproduction of immunoglobulin E (IgE) antibodies.

Diagnostic criteria for atopic dermatitis

1. Pruritus

2. Typical morphology and distribution:

(1) Eczematous dermatitis

(a) acute lesions: erythema, exudation, papules, vesiculopapules, scales, crusts

(b) chronic lesions: infiltrated erythema, lichenification, prurigo, scales, crusts

(2) Distribution

(a) symmetrical: predilection sites: forehead, periorbital area, perioral area, lips, periauricular area, neck, joint areas of limbs, trunk

(b) age-related characteristics

• infantile phase: starts on the scalp and face, often spreads to the trunk and extremities

• childhood phase: neck, the flexural surfaces of the arms and legs

• adolescent and adult phase: tendency to be severe on the upper half of body (face, neck, anterior chest and back)

3 .Chronic or chronically relapsing course (usually coexistence of old and new lesions):

(1) More than 2 months in infancy

(2) More than 6 months in childhood, adolescence and adulthood

Definite diagnosis of AD requires the presence of all three features.

Total IgE levels

Total IgE levels were compared in four different groups with or without AD, namely the long-term AD group, the regressed AD group, the newly-developed AD group, and the non-AD group *(figure 3)*. Total IgE levels gradually increased with increasing age in all four groups. However, in the long-term AD group, the increase of total IgE was significantly more rapid and greater than in the other

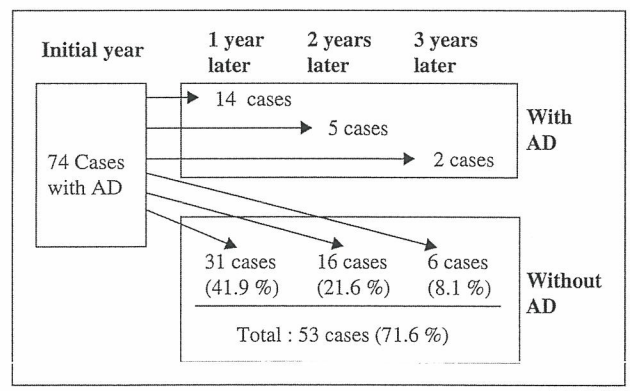

Figure 1. Rate of spontaneous regression in AD of the 74 cases with AD. 53 cases regressed during 3-year follow-up.

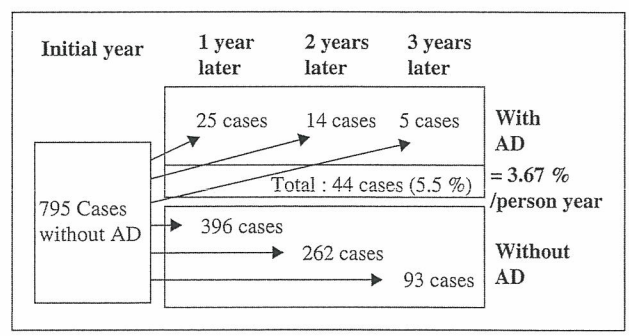

Figure 2. Rate of new-development in AD. The rate was 3.67%/person year.

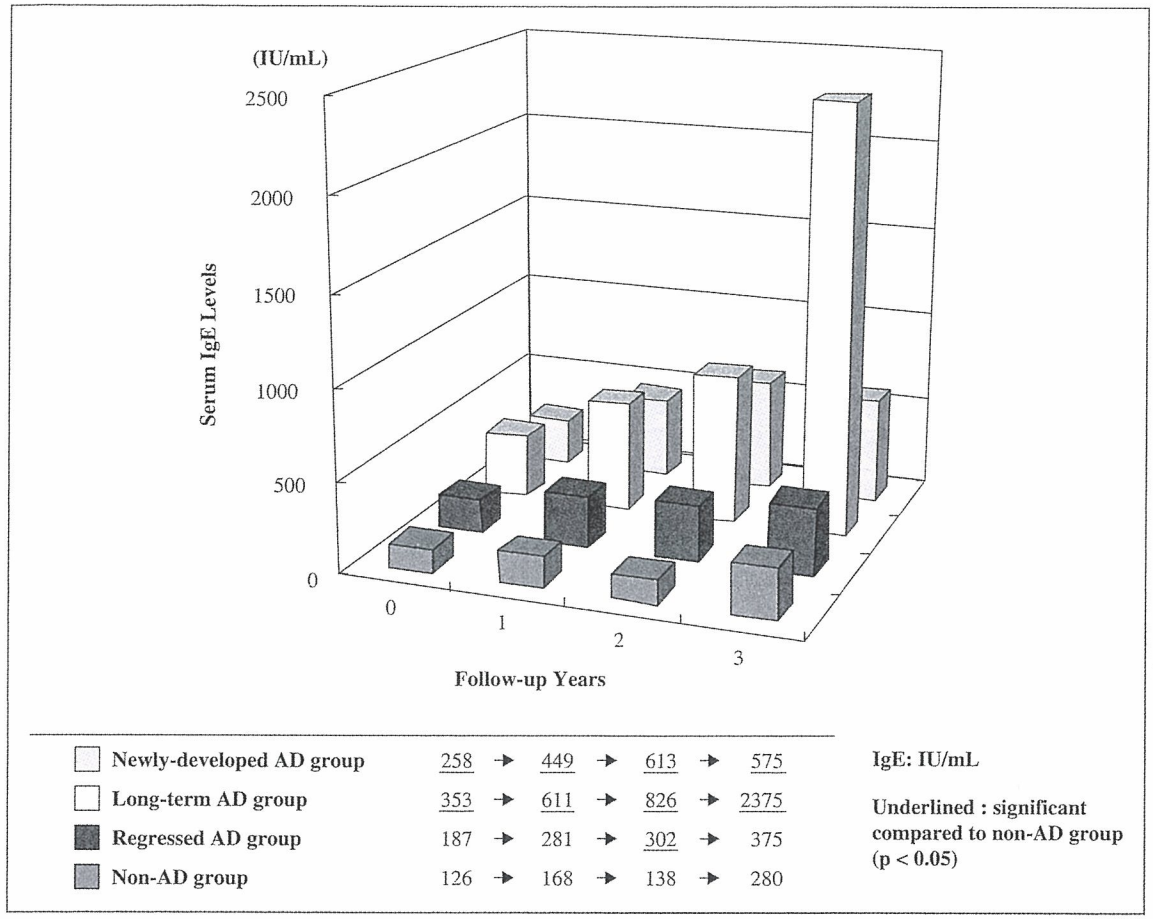

Figure 3. Changes of total IgE levels in the long-term AD group, the regressed AD group, the newly-developed AD group and the non-AD group, respectively, in nursery school children of Ishigaki Island. The increase of total IgE levels in long-term AD sufferers was significantly more marked and more rapid than in the other 3 groups during the 3-year follow-up period.

3 groups over the 3-year follow-up period *(figure 3)*. In contrast, increases in total IgE levels were very slight both in the regressed AD group and in the newly-developed AD group. However, it is interesting that IgE levels were slightly higher in the latter, and also that the IgE levels of the regressed AD group fell almost to the same levels as in children without AD.

Discussion

In the present study, we performed a follow-up study of AD in among children in Ishigaki and found that 71.6% of children with AD experienced remission during the follow-up period. Furthermore, the *de novo* occurrence of AD in these nursery school age children was estimated as 3.67%/person year.

Symptoms become apparent during the first year of life in 65% of children developing AD and in 85% during their first 5 years [18]; it is thus worthwhile to determine the incidence as accurately as possible in nursery school children. The incidence in Japanese elementary school students was around 3% in 1981 to 1983 but increased to around 6 to 7% in the 1990s [7]. In 2000 to 2002, a research team of the Japanese Ministry of Health, Labor and Welfare (chief researcher, Dr. S. Yamamoto) performed physical examinations of 48,072 children living in Asahikawa, Iwate, Tokyo, Gifu, Osaka, Hiroshima, Kochi, and Fukuoka [19, 20]. In that study, it was found that the average national prevalence of AD was 12.8% in 4-month-old children, 9.8% in 18-month-olds, 13.2% in 3-year-olds, 11.8% in 6- to 7-year-olds, 10.0% in 12- to 13-year-olds, and 8.2% in 18-year-old children in Japan. In the present study, the mean prevalence of AD in children under the age of 5 years was 6.8% in Ishigaki Island through 2001 to 2004, which was much lower than that in mainland Japan [19, 20]. Yemaneberhan *et al.* studied the prevalence of AD symptoms and the effects of potential environmental etiologies in rural and urban areas of Jimma in southwestern Ethiopia [21]. Lifetime cumulative prevalence of AD symptoms was generally low with an overall prevalence of 1.2%, but it was higher in the urban (1.5%) than in the rural areas (0.3%; odds ratio = 4.45 [95% CI 2.34-8.47]) indicating a marked urban-rural gradient [21]. In relation to industrialization and urbanization, air pollution is now believed to be undeniably involved in the increase of allergic diseases such as asthma and AD [22-25]. In a recent Spanish epidemiologic study, air pollution was associated with a higher prevalence of AD with a trend toward greater severity as well [25]. In accordance with this notion, air pollution is much lower on Ishigaki Island compared to mainland Japan.

It is generally believed from clinical experience that spontaneous regression occurs in the majority of AD patients in