Long-term Safety and Efficacy of Tacrolimus Ointment for the Treatment of Atopic Dermatitis in Children

Anita Remitz, MD, Department of Dermatology, Helsinki University Central Hospital, Helsinki, Finland, John Harper, MD, Royal Free Hospital, London, UK, Malcolm Rustin, MD, Academic Medical Centre, University of Amsterdam, The Netherlands, Wouter M. Goldschmidt, MD, University Central Hospital Oulu, Oulu, Finland, Graham Sharpe, MD, Alder Hey Children’s Hospital, Liverpool, UK, Catherine Smith, MD, Skin Therapy Research Unit, St John’s Institute of Dermatology, St Thomas’ Hospital, London, UK, C. H. Smith, MD, University of Szeged, Szeged, Hungary, kristiina Turjanmaa, MD, Tampere University Hospital, Tampere, Finland

Tacrolimus ointment is a topical calcineurin inhibitor for the treatment of atopic dermatitis. The primary objective of this open-label study was to assess the long-term safety of tacrolimus ointment. The primary end-point was the incidence of adverse events. Secondary end-points included the Eczema Area and Severity Index and a modified version of this index. A total of 466 children with atopic dermatitis, aged 2–15 years, applied 0.03% or 0.1% tacrolimus ointment twice daily for up to 29.5 months. Skin burning and pruritus were the most common application site events; their prevalence decreased over time. There was no increase in viral infections or other adverse events over time. Laboratory profiles were consistent with those reported in atopic populations. Substantial improvement in all efficacy end-points was observed by week 2 and maintained throughout the study. Long-term treatment with tacrolimus ointment is safe and effective in these patients with atopic dermatitis. Key words: atopic dermatitis; tacrolimus ointment; long-term; safety.

(Received June 13, 2006.)


Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease characterized by episodes of pruritus and excessive scratching that affects approximately 15% of children in developed countries (1, 2). The exact aetiology is unknown, but the disease is driven by the local release of pro-inflammatory mediators and cytokines (3).

Topical corticosteroids have been the mainstay of treatment; although in general they are safe when used according to guidelines, clinical response is not always satisfactory and long-term treatment carries the risk of local side-effects, such as skin atrophy and glaucoma (4, 5), and rare, systemic side-effects, such as abnormal adrenocortical function and growth retardation (6, 7).

In addition, tachyphylaxis may develop, making alternative approaches to treatment advisable (8).

Tacrolimus ointment is a macrolide calcineurin inhibitor which down-regulates cutaneous T-cell activation. Tacrolimus was initially developed for the prevention of allograft rejection after organ transplantation (9, 10). The topical formulation was specifically developed for the treatment of AD.

The short- and long-term safety and efficacy of tacrolimus ointment in patients with AD have been demonstrated in numerous studies; clinical trials including more than 17,000 patients have been conducted worldwide (Astellas Pharma Europe Ltd, data on file). These trials have shown that both the 0.1% and 0.03% formulations are efficacious and well tolerated by adult and paediatric patients alike (11–20). The most common side-effects are skin burning and pruritus, which are mainly mild to moderate and decrease after the first days of treatment. Tacrolimus ointment does not cause thinning of the skin (21) and can be used safely on the more vulnerable regions of the skin, such as the face and neck. Systemic absorption of the ointment is minimal (22).

A US 12-month study previously investigated the long-term safety of 0.1% tacrolimus ointment twice daily in children with AD aged 2–15 years (17). The present study is the first European long-term tacrolimus ointment study in children. As AD is chronic or recurrent in most patients, treatment periods of up to 29.5 months were covered.

MATERIALS AND METHODS

Study design

The primary aim of this long-term, open-label, non-comparative, phase IIIb study was to assess the long-term safety of 0.03% and 0.1% tacrolimus ointment in children with AD aged 2–15 years. The study was conducted at 39 centres in 11 European countries between October 2000 and April 2003. The ethics committee from each centre reviewed the protocol and granted approval prior to the start of the study. Informed consent was provided by parents and guardians, and by the children themselves if they were considered mature enough.
The originally planned duration of study was 12 months. An extension period was added defining the end of study as the next scheduled visit following the launch of tacrolimus ointment in the patient’s country of residence (but not later than April 2003 in countries without launch).

The study consisted of visits at baseline (day 1), at weeks 2 and 4, months 3, 6, 9 and 12 and, if applicable, every 3 months thereafter until the end of study.

Patient selection
Male and female patients with AD, aged 2–15 years, were enrolled in the study. All participants had previously taken part in a 3-week comparative trial with a treatment regimen of 0.03% tacrolimus ointment once or twice daily or 1% hydrocortisone acetate ointment twice daily (20). In this precursor study, all patients were diagnosed with AD based on the criteria of Hanifin & Rajka (23). At baseline, approximately 50% of patients had moderate and 50% had severe AD following the severity grading of Rajka & Langeland (24). The interim period between the end of the precursor study and the beginning of the present study was at least one week.

Treatment plan
A thin coat of tacrolimus ointment was applied twice daily to affected areas during episodes of active disease. Patients were initially treated with 0.03% tacrolimus ointment for 2 weeks or until clearance of lesions, whichever occurred first. If one or more of the treated lesions did not respond satisfactorily within 2 weeks of treatment, the patient was provided with 0.1% tacrolimus ointment. The respective lesions were then treated with 0.1% tacrolimus ointment for 2 weeks or until clearance of lesions, whichever occurred first. If any of the lesions treated with 0.1% tacrolimus ointment did not respond satisfactorily within 2 weeks of treatment, the patient could be excluded from the study at the investigator’s discretion.

Prohibited therapies included topical and systemic corticosteroids for the treatment of AD, other investigational drugs, UV light therapy and non-steroidal immunosuppressants. The washout phase for these therapies ranged from a minimum of 5 days (for topical and systemic corticosteroids) to a maximum of 6 weeks (for UV light therapy) prior to the start of the study. The washout period for non-steroidal immunosuppressants and other investigational drugs was 2 and 4 weeks, respectively. Restricted therapies included systemic non-steroidal anti-inflammatory drugs (≤ 2 weeks of treatment within any 3-month period) and non-medicated emollients (not to be applied to the treatment area within ≤ 2 hours of study drug application; the same emollient was to be used throughout the study).

Assessments
Safety assessments during the study included monitoring of adverse events and clinical laboratory assessments. The primary end-point of the study was the incidence of adverse events, classified as application and non-application adverse events. An adverse event was defined as any undesirable experience that occurred to a patient during the study, regardless of whether it was related to the study drug. Adverse events assessed by the investigator as being causally related to the study drug were defined as all adverse events with highly probable, probable, possible or not assessable causal relationship to the study drug or adverse events where the assessment of the relationship to study drug was missing.

Secondary safety end-points were laboratory assessments, including haematology, blood chemistry profile and renal and hepatic function, and were performed at day 1, months 6 and 12, and at the end of study.

The patient’s height and weight was recorded at day 1, months 6, 12 and 18, and at the end of study.

Efficacy end-points were assessed on each visit and included changes in Eczema Area and Severity Index (EASI) (25) and modified EASI (mEASI) and their single components; the physician’s assessment of individual signs, the affected body surface area and the patient’s assessment of itch.

The EASI is a composite score comprising ratings of the severity of erythema, oedema/induration/papulation, excoriations and lichenification weighted according to the estimated percentage of affected body surface area. The mEASI is identical to the EASI except that it includes an additional assessment of itch, one of the primary symptoms of AD (24).

A physician assessed the therapeutic response of the disease to the treatment at each visit after day 1 as “satisfactory: yes/no” for each body region.

Quality of life was measured at every study visit with the Infants’ Dermatitis Quality of Life Index (26) for children aged 2–4 years and the Children’s Dermatology Life Quality Index (27) for children aged 5–15 years.

Statistical analysis
In addition to the overall analysis of the study population, patients aged 2–6 years and patients aged 7–15 years were analysed separately. The evaluable population (intent-to-treat population) comprised patients who received at least one application of tacrolimus ointment. All data were summarized by descriptive statistics and frequency counts. Adverse events were coded according to a modified COSTART (coding symbols for the thesaurus of adverse event reaction terms) dictionary. Efficacy data were analysed using the Last Observation Carried Forward principle.

RESULTS
Patient baseline information, disposition and characteristics
A total of 466 patients (233 per age group; 2–6 and 7–15 years) were enrolled. The mean baseline percentage affected body surface area as a percentage of the total body surface area (affected BSA) was 30.7% (SD 24.2). The mean EASI and mEASI scores for all patients were 15.8 (SD 12.5) and 20.5 (SD 16.1), respectively. Patient’s assessment of itch, using a 10 cm visual analogue scale (VAS), was 5.4 (SD 2.9). All patients received at least one dose of 0.03% tacrolimus ointment. The mean interval between precursor study and the present study was 6.6 months (SD 3.9). Patient disposition is shown in Table I: 138 patients (29.6%) did not complete the study; the majority of them discontinued for administrative reasons (e.g. lost to follow-up, withdrawal of consent). Thirty-eight patients (8.2%) discontinued due to lack of efficacy and 6 (3.4%) due to an adverse event. Fifty-nine patients (12.6%) discontinued before month 12, 21 patients (4.5%) did not give consent for the extension period.

There was a slight excess of female patients. Over 80% of patients were Caucasian. The younger age group had a higher baseline disease severity in all clinical efficacy parameters and quality of life scores.
The mean study duration was 16.3 months (SD 6.4) (median 17.9 months; range 1–897 days (29.5 months)). On average, patients used tacrolimus ointment on 63.7% of study days. A total of 347 patients (74.5%) used 0.1% tacrolimus ointment at least once in the study, but only a quarter of these patients used this concentration on approximately 50% or more of study days.

Safety

The most common adverse events (irrespective of causality) are shown in Table II. The most common application site adverse events overall were pruritus and skin burning. Most of these events were considered to be causally related to the study drug (Table III); their prevalence was highest during the first weeks of treatment and then decreased over time (Fig. 1). The prevalence rates of other application site adverse events, including viral infections (Fig. 2), were low and did not change substantially over time. The majority (85.6%) of these events were of mild to moderate severity. The most common non-application site events were seasonal infections, such as flu-syndrome (Table II), which were mainly considered to be unrelated to tacrolimus ointment (Table III). Their prevalence did not increase over time.

Overall, a higher percentage of younger than older patients experienced adverse events, which was mainly due to the higher incidence of cutaneous and non-cutaneous infections in the younger age group. Most events (65.1%) in the category “skin infection” (non-specific cutaneous infections not defined by an individual COSTART term) were classified by the investigator as bacterial infections.

Twenty-three patients (4.9%) suffered from herpes simplex during the study; in 16 patients (3.4%), a causal relation to tacrolimus was found. The most common non-application site adverse events were seasonal infections, such as flu-syndrome (Table II), which were mainly considered to be unrelated to tacrolimus ointment (Table III). Their prevalence did not increase over time.

Overall, a higher percentage of younger than older patients experienced adverse events, which was mainly due to the higher incidence of cutaneous and non-cutaneous infections in the younger age group. Most events (65.1%) in the category “skin infection” (non-specific cutaneous infections not defined by an individual COSTART term) were classified by the investigator as bacterial infections.

Twenty-three patients (4.9%) suffered from herpes simplex during the study; in 16 patients (3.4%), a causal relation to tacrolimus was found. The most common non-application site adverse events were seasonal infections, such as flu-syndrome (Table II), which were mainly considered to be unrelated to tacrolimus ointment (Table III). Their prevalence did not increase over time.

Overall, a higher percentage of younger than older patients experienced adverse events, which was mainly due to the higher incidence of cutaneous and non-cutaneous infections in the younger age group. Most events (65.1%) in the category “skin infection” (non-specific cutaneous infections not defined by an individual COSTART term) were classified by the investigator as bacterial infections.

Twenty-three patients (4.9%) suffered from herpes simplex during the study; in 16 patients (3.4%), a causal relation to tacrolimus was found. The most common non-application site adverse events were seasonal infections, such as flu-syndrome (Table II), which were mainly considered to be unrelated to tacrolimus ointment (Table III). Their prevalence did not increase over time.

Overall, a higher percentage of younger than older patients experienced adverse events, which was mainly due to the higher incidence of cutaneous and non-cutaneous infections in the younger age group. Most events (65.1%) in the category “skin infection” (non-specific cutaneous infections not defined by an individual COSTART term) were classified by the investigator as bacterial infections.

Twenty-three patients (4.9%) suffered from herpes simplex during the study; in 16 patients (3.4%), a causal relation to tacrolimus was found. The most common non-application site adverse events were seasonal infections, such as flu-syndrome (Table II), which were mainly considered to be unrelated to tacrolimus ointment (Table III). Their prevalence did not increase over time.
relationship to the study drug was reported. Eight patients (1.7%) had recurring episodes of herpes simplex. Four patients (0.9%) were classified by investigators as cases of eczema herpeticum, a condition typically affecting patients with AD (28). Two cases were rated as mild and 2 cases were rated as severe; a possible causal relationship to study drug was reported in 3 cases. Thirty-eight patients (8.2%) were affected by varicella infections (chickenpox or shingles) at some stage in the study; in 7 patients (1.5%) this condition was assessed as being causally related to the study drug. The majority of affected patients were younger patients who had chickenpox; 5 patients (1.1%) were diagnosed as cases of shingles. Seventeen patients (3.6%) were diagnosed with “skin neoplasm benign” (all cases were classified as warts); in 8 patients (1.7%), a causal relationship to the study drug was reported. No malignant skin neoplasms occurred.

Fourteen patients (3.0%) were diagnosed with molluscum contagiosum, a causal relationship to study drug was reported in 7 patients (1.5%).

A total of 33 patients (7.1%) experienced a serious adverse event during the study (Table IV). Eleven patients (2.4%) experienced 14 serious adverse events which were assessed by the investigator as being causally related to the study drug (10 events of skin infection, 3 events of herpes simplex and one event of herpes zoster; all but one were present on the application site). Adverse events leading to treatment discontinuation and assessed as being causally related to study drugs were reported in 15 patients (3.2%). All but one of these adverse events were application site events such as skin infection and pruritus. A 6-year-old boy had leukopaenia at month 6 (white blood cell count 3.0 × 10⁹/l) and was withdrawn from the study. There were no accompanying symptoms of illness reported and this case was not considered to be a serious adverse event. Subsequently the patient’s leukocyte count was confirmed to be normal (5.8 × 10⁹/l) by the patient’s paediatrician. Leukopaenia has rarely been reported (isolated cases only) as an adverse event in tacrolimus ointment clinical trials to date.

Table III. Incidence of most common adverse events assessed by the investigator as causally related – number of patients (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>All Patients</th>
<th>Patients 2–6 years</th>
<th>Patients 7–15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>466</td>
<td>233</td>
<td>233</td>
</tr>
<tr>
<td>Skin burning</td>
<td>124 (26.6)</td>
<td>52 (22.3)</td>
<td>72 (30.9)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>123 (26.4)</td>
<td>64 (27.5)</td>
<td>59 (25.3)</td>
</tr>
<tr>
<td>Skin infection</td>
<td>75 (16.1)</td>
<td>42 (18.0)</td>
<td>33 (14.2)</td>
</tr>
<tr>
<td>Lack of drug effect</td>
<td>40 (8.6)</td>
<td>17 (7.3)</td>
<td>23 (9.9)</td>
</tr>
<tr>
<td>Skin erythema</td>
<td>22 (4.7)</td>
<td>9 (3.9)</td>
<td>13 (5.6)</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>19 (4.1)</td>
<td>3 (1.3)</td>
<td>16 (6.9)</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>16 (3.4)</td>
<td>8 (3.4)</td>
<td>8 (3.4)</td>
</tr>
<tr>
<td>Application site reaction</td>
<td>12 (2.6)</td>
<td>4 (1.7)</td>
<td>8 (3.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>10 (2.1)</td>
<td>6 (2.6)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Skin neoplasm benign</td>
<td>8 (1.7)</td>
<td>5 (2.1)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>7 (1.5)</td>
<td>1 (0.4)</td>
<td>6 (2.6)</td>
</tr>
<tr>
<td>Pustular rash</td>
<td>7 (1.5)</td>
<td>5 (2.1)</td>
<td>2 (0.9)</td>
</tr>
</tbody>
</table>

At least 2% of patients in any age group – results refer to overall (application- and non-application site) events.

“Causally related” was assigned if the investigator assessed the event as having a highly probable, probable, possible, or not assessable relationship to the study drug or if the assessment for relationship to study drug was missing.
No cases of growth retardation or skin atrophy were reported by investigators.

Laboratory measurements showed eosinophil levels greater than the reference range in approximately 40% of the study population throughout the study. There were no marked changes of mean laboratory values over time. Except for the reported case of leukopaenia, no changes in laboratory parameters during the study suggested a safety concern.

**Efficacy**

There was similar improvement in all efficacy endpoints in both age groups. Substantial improvement in all clinical efficacy parameters was notable after 2 weeks of therapy, continued until month 6 and was maintained during the rest of the study (Fig. 3). There was no indication of a decrease in efficacy. According to the physician’s assessment of therapeutic response, a substantial proportion (73.0–77.0%) of patients experienced at least a satisfactory response to treatment by the end of study (head and neck: 77.0%; trunk: 73.0%; upper limbs: 75.8%; lower limbs: 74.0%).

The clinical efficacy data were confirmed by the quality of life measurements; a substantial improvement in quality of life was shown between day 1 and week 2, with further improvement by month 6 and maintenance of these levels throughout the study in both age groups.

**DISCUSSION**

In this long-term study with a mean duration of 16.3 months, 0.03% and 0.1% tacrolimus ointment were shown to be well tolerated and effective for the treatment of AD in children aged 2–15 years for periods up to 29.5 months. The long-term safety and efficacy profile of tacrolimus ointment was similar to that of a US 12-month paediatric study including 255 patients (17).

The majority of adverse events related to tacrolimus ointment occurred at the application site, the most common ones being skin burning and pruritus, which were transient events of mainly mild to moderate severity.

Adverse events not caused by local irritation of the skin were related mainly to seasonal infections such as flu syndrome, paediatric diseases and illnesses generally associated with AD and atopy, such as asthma. The higher incidence of adverse events in the younger age group can be explained by the increased susceptibility of this age group to infections and by their higher disease severity.

No systemic toxic effects of tacrolimus ointment were apparent. Growth retardation or skin atrophy, potential side-effects of long-term use of topical corticosteroids (5, 7), were not reported for any patient.

Although incidence rates vary between studies, patients with AD tend to show a disposition towards bacterial and viral infections (28–40).

The overall incidence of herpes simplex in this study was 4.9%. In an epidemiological survey of 2514 nursery school children, 8.3% of children with AD had recurrent cutaneous herpes simplex infection (37). In a prospective study of 179 children with AD studied over a period of 2.75 years (mean observation period: 1.5 years), herpes simplex was reported in 5.6% of patients (38).

In the present study, varicella infections were reported for 8.2% of patients, which were mainly cases of chickenpox occurring in the younger age group; 5 patients (1.1%) were diagnosed as cases of shingles. Incidence data on shingles in children with AD are scarce.
In healthy children, yearly incidence rates of 0.1% to 0.2% have been reported (39). In a survey of 955 adults with present or past AD, 7% with active disease had a history of herpes zoster (32).

In the present study, 3.6% of patients were diagnosed with warts. Epidemiological data on warts are scarce and inconsistent; rates between 1.8% and 17% in children with AD have been recorded (37, 40, 41). The above quoted survey of nursery school children reported a prevalence of warts in 13.6% of children with AD compared with 8.2% of children without AD (37). These results are contradicted by a birth cohort study of 9263 11-year-old school children; warts were observed in 1.8% of children with AD and in 4.0% of children without AD (41).

Molluscum contagiosum was diagnosed in 3.0% of the study population. There are few incidence data on this condition but it is seen as a typical complication of AD (30).

Bacterial colonization of the skin, especially with *S. aureus*, is common in AD and can exacerbate the disease (33). The carrier rate of *S. aureus* has been shown to be between 85% and nearly 100% in lesions of patients with AD (35–37). In a paediatric study of 190 patients with AD followed over a 2.5-year period (mean observation period: 13 months), 40% of patients experienced bacterial skin infections (36). In the present study, the overall incidence of skin infection (COSTART term) was 29.2%; 65.1% of cases were classified as bacterial infections.

The incidence of flu syndrome, the most common adverse event in the present study, was 31.5%. In a US survey, the prevalence of flu syndrome over a 1-year period was 34.8% for the general population and 46.3% for children from 5 to 17 years of age (42).

The incidence rates of infections in the present study were in line with reported rates in the literature, suggesting that the incidence rates in the study population reflect the epidemiology of infections in the atopic and general populations. However, one needs to acknowledge the limitations of retrospectively comparing incidence data from a non-comparative study with incidence data from studies comprising different patient populations. In addition, these populations may have been treated with topical corticosteroids (which are known to increase susceptibility to skin infections (43)) and may not be ideal comparators to assess an increased risk of infection in tacrolimus-treated patients. Furthermore, the data presented only document incidence, not extent of infection, and the theoretical risk that tacrolimus ointment may reduce skin resistance to infection leading to more extensive (not necessarily more common) infections cannot be assessed.

Only one patient (a 6-year-old boy with leukopaenia assessed as being causally related to study drug) was discontinued from the study because of abnormal laboratory values. Otherwise, no changes in laboratory parameters during the study suggested a safety concern. Laboratory profiles were consistent with those previously reported in patients with AD; eosinophilia, a known feature of AD (3), was seen in approximately 40% of patients throughout the study.

The efficacy results of this study are in line with findings from the previously quoted short- and long-term trials. Even when considering the natural course of AD, the resolution of symptoms was considerable. There was no indication of tachyphylaxis; only a few patients discontinued due to lack of efficacy, and the effectiveness of tacrolimus ointment in study completers did not decrease over time. The clinical efficacy results were confirmed by considerable improvements in the quality of life of the study population.

The population in the present study only included children over 2 years old. Pharmacokinetic trials in younger children are currently being conducted and clinical trials are planned. A recent review of 12 AD patients younger than 2 years treated with 0.03% or 0.01% tacrolimus ointment showed that all patients experienced an improvement in symptoms. No significant adverse effects were noted (44).

In conclusion, the results of the present study show that long-term treatment with 0.03% and 0.1% tacrolimus ointment for periods up to 29.5 months is a safe and effective therapy for 2–15-year-old patients with AD. Local irritation seems to be the only adverse event clearly associated with tacrolimus ointment.

ACKNOWLEDGEMENTS

Additional investigators in the European Tacrolimus Ointment Study Group: A. Alomar (Hospital Santa Creu i Santa Pau, Servicio de Dermatologia, Barcelona, Spain), C. Bieder (Hôpital Armand Trousseau, Service d’Hématologie-Immunologie, Paris, France), J. Berth-Jones (George Eliot Hospital, Dermatology Department, Coventry, UK), M. Blaszczzyk (Klinika Dermatologiczna, Warsaw, Poland), C. Bruijnzeel-Koomen (University Hospital Department of Dermatology, Utrecht, The Netherlands), F. Cambazard (Hôpital Nord, Service de Dermatologie, Saint Etienne, France), J-P. Denoeux (CHU, Groupe Hospitalier SUD, Amiens, France), K. Despotin (Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg), L. Dubertret (Hôpital Saint Louis, Policlinique de Dermatologie, Paris, France), P. Friedmann (Southampton General Hospital, Department of Dermatology, Southampton, UK), C. Gelmetti (IRCSS Ospedale Maggiore di Milano, Milan, Italy), A. Gianetti (Policlinico di Modena, Clinica Dermatologica, Modena, Italy), A. Green (Great Ormond Street Hospital for Children, London, UK), MA Gonzalez (Hospital Sant Joan de Deu, Servicio de Dermatologia, Barcelona, Spain), R. Harvima (Kuopio University Hospital, Department of Dermatology, Kuopio, Finland), K. Kalimo (Turku Allergy Centre, Turku, Finland), J-M. Lachapelle (Ecole de la Santé Publique, Dermatologie, Bruxelles, Belgium), L. Misery (Hôpital Morvan, Service de Dermatologie, Brest, France), M-A. Gonzalez (Hospital Sant Joan de Deu, Servicio de Dermatologia, Barcelona, Spain), C. Moss (Birmingham Children’s Hospital, Paediatric Dermatology Department, Birmingham, UK), AP.

Acta Derm Venereol 87
REFERENCES


33. Williams JV, Vowels BR, Honig PJ, Leyden JJ. S. aureus isolation from the lesions, the hands, and the anterior nares of pa-