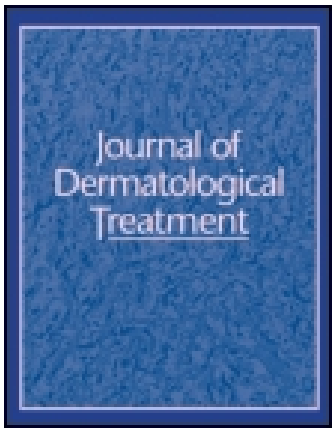

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A controlled study of comparative efficacy of oral retinoids and topical betamethasone/salicylic acid for chronic hyperkeratotic palmoplantar dermatitis

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A controlled study of comparative efficacy of oral retinoids and topical betamethasone/salicylic acid for chronic hyperkeratotic palmoplantar dermatitis

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BACKGROUND: Chronic hyperkeratotic dermatitis of the palms and soles represents a severe multi-etiological problem, too often faced with ineffective or tedious topical remedies.
METHODS: A single-blind, matched-sample design investigation was carried out of 42 patients with chronic hyperkeratotic palmoplantar dermatitis, who were administered acitretin 25–50 mg/day for 1 month, which was controlled versus a conventional topical treatment (betamethasone/salicylic acid ointment). Therapeutic improvement was expressed with the reduction of severity score (expressed on a 0–10 scale).
RESULTS: Acitretin was significantly better than the conventional treatment after 30 days (two sided $p<0.0001$). Moreover, improvement significantly persisted 5 months after suspension of acitretin ($p<0.0001$), while this was not the case after suspension of the control treatment ($p=0.3019$). Lesions improved more rapidly with acitretin than with the control treatment ($p<0.0002$). Some cases of loss of sensitization in patch-test-positive patients were observed. Side effects were minimal or absent, and patients expressed overtly their preference for acitretin treatment.
CONCLUSION: After evaluating the former literature, the risks and the benefits, as well as the overt superiority of retinoid treatment, the authors conclude that acitretin should be considered a first choice treatment for this fastidious condition. (*J Dermatol Treat* (2004) **15:** 88–93)

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Introduction

Hand and/or foot dermatitis (HFD) represents a common, troubling, clinical problem, the cause of which is often unknown.[1,2] HFD can depend either on exogenous factors (irritants, allergens, infections) or on endogenous ones, including atopic dermatitis, pompholyx, and psoriasis, which can assume peculiar eczematous or pompholyx-like ('dyshidrosiform') aspects, with deep-set tiny blisters in these districts.[3] A critical point is that HFD does not correspond to a single etiology: rather, it is to be regarded as a collection of heterogeneous disorders.[1] Such different disturbances can overlap and influence the course of each other. Thus, it is not uncommon for the clinical appearance to change with time, altering the disorder's diagnostic label.[1,3] Indeed, it is classically recognized that the differential between 'hand eczema' and 'hand psoriasis' is often a clinical opinion to be disputed.[4] Moreover, even in a given fixed clinical context (e.g. atopy), the morphology of the eruption can vary widely.[5] Accordingly, some students regard HFD as an autonomous nosographical entity,[1,2] and, on the grounds of our experience, we agree completely with them.

Most cases of HFD are exasperatingly chronic-relapsing ones, and typically present with a distressing

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hyperkeratotic-fissured pattern, often with intermingled dyshidrosiform aspects and recurrent eczematous flare-ups. Their treatment represents a major problem. Even in those cases in which an offending agent is discovered, not always can patients avoid the allergens or irritants or koebnerizing factors involved in their disease. It should be underscored that hand psoriasis can be as occupational as contact dermatitis (concept of occupational contact psoriasis[6]). From an 'operational' viewpoint, the practical clinician needs something that is more active than routinely prescribed topical treatments. Here we present a controlled study on the use of the well-known oral retinoid acitretin (etretin) in chronic HFD.

Patients and methods

History and selection of subjects: baseline assessment

Candidates for enrollment were patients with chronic moderate-to-severe HFD presenting with hyperkeratotic lesions ('eczema keratoticum manuum et pedum') and intermingled dyshidrosiform aspects. Their disease had proven resistant to topical treatments, and was particularly disturbing and disabling. It was carefully explained to them that the aim of the study would be to compare two different oral treatments coupled with ordinary topical measures for their disorder. Accordingly, 42 out of 156 consecutive such patients seen in the period December 1998 to August 2002 gave their informed consent and accepted recruitment to the study (Table I).

All of them had previously undergone topical treatments such as corticosteroids of various strengths, salicylates, urea, glycolic acid, ammonium lactate, tretinoin, tazarotene, vitamin D_3 derivatives, sodium fusidate/fusidic acid, mupirocin, barrier creams, local antiseptics and wet dressings. None had undergone systemic treatments, except oral anti-H_1 antihistamines and, in four cases, short courses of oral corticosteroids. One subject had undergone outpatient PUVA therapy, but had to give it up because such a treatment was too time-demanding. Dermatomycoses, hereditary and rare secondary (pityriasis rubra pilaris, lichen planus, HPV, syphilis, mycosis fungoides,[1,7] keratoderma climactericum) keratodermata, as well as secondary pompholyx-like (bullous pemphigoid) dermatitides were excluded by means of proper evaluations (careful dermatologic examination of the whole integument and adnexa, histology, immunohistochemistry and direct immunofluorescence in selected cases, KOH scrapings, laboratory examinations and pedigree analysis: HLA typing).

At the recruitment visit, nine patients were found to be atopic (six oculo-respiratory syndrome, one typical dermatitis, two both); eight presented subtle psoriatic genucubital and/or scalp aspects; two presented features of both atopy (oculorespiratory syndrome plus dermatitis) and of minimal genucubital or scalp psoriasis. None of the patients with minimal psoriasis presented HLA haplotypes characteristic of palmoplantar pustular psoriasis. All of the atopic patients were <40 years old; four of them had total serum IgE levels exceeding 200 IU/ml. All of the patients >50 years old were or had been engaged in manual jobs for at least 2 consecutive years. All of the patients were patch-tested on days 1, 180, and 360 (Table I) (same patch test kits [Chemotechnique, Malmö, Sweden] and same observer).

Study design

This study was planned and conducted as a single-blind, matched sample design investigation, controlled versus a conventional topical treatment. In the first phase ('Treatment 1'), patients were administered a placebo capsule and applied a commercially available ointment containing betamethasone (0.05%) and salicylic acid (3%) twice a day for 1 month. Afterwards, the administration of the oral placebo was suspended and the patients applied only an inert placebo gel for an additional 5 months. Then, during the second phase ('Treatment 2'), they were shifted to the oral administration of acitretin (Neotigason®, 25 or 50 mg/day, according to body weight) and the application of white petrolatum (comparable with the control treatment in aspect) for 1 month, followed by the application of the placebo gel alone for a further 5 months. Routine laboratory examinations were performed at recruitment, after 1 week of either Treatment 1 or 2, and then monthly. Results were communicated by telephone, fax, or e-mail to the investigators.

The degree of clinical severity was evaluated at days 1, 30, 180, 210 and 360 on a visual analogue scale from 0 (=no evidence of disease) to 10 (=extremely severe frank dermatitis) by each investigator and the patient him/herself in order to introduce a factor of self-evaluation and to include the information linked with the subjective perception of the disease into the evaluation. The mean value of the ranks (four attributed by the investigators, plus one attributed by the patient) was approximated to the nearest integer, then definitely assigned. Patients were considered 'responsive' when the reduction of the severity visual score was >4 points at day 30 and day 210 as compared with day 1 and 180, respectively. The minimum entry score after preliminary recruitment was 5 (arbitrarily defined as the cut-off between mild and moderate-to-severe HFD), and none of the 42 patients willing to take part in the study displayed a day 1 score<5. The improvement induced by each 30-day treatment, the time (in days) needed to reach the maximum improvement (TMI) since the beginning of each treatment (as testified by the

Number of patients	42
Males	32
(mean age [years] ±SD; range)	(42.5±16.7; 17–70)
Females	10
(mean age [years] ±SD; range)	(39.8±17.3; 18–77)
Mean approximate duration [years] of symptoms at the first visit (range):	
males	6.9 (0.5–30)
females	5.6 (0.5–10)
Main positivities of patch tests[a]	
Total	15
$NiSO_4$	13
$K_2Cr_2O_7$	4
$CoCl_2$	3
Parabens	2
Dermatophagoides	2
Thiuram mix	2
Occupations and significant leisure activities in the last 10 years[b]: employees (14), shop assistants (8), housewifes (6), bricklayers (4), barmen and barmaids (4), school teachers (3), engineers (2), gas station operators (2), raincoat waxing operator (1), steel worker (1), cook (1), butcher (1); stitching and needlework (6), gardening (5), carpentry and do-it-yourself (2), pottery decoration (2), modelling (1).	
Concomitant declared medications for other-than-dermatologic indications[c]: ACE-inhibitors (5), thiazide diuretics (1), calcium channel inhibitors (3), losartan (1), oral contraceptives (3), oestradiol valerate-ciproterone acetate (1), alendronate (1), oral anti-H_1 antihistamines (12), sodium cromoglicate (1), montelukast (1), benzodiazepines (11), zolpidem (1), tolazamide (1), omeprazole (1), lansoprazole (1), nizatidine (1), ranitidine (1), inhaled salbutamol (2), inhaled budesonide (2).	

[a]Some patients displayed more than one definite ($\geqslant ++$) patch test positivity.
[b]Cumulative value exceeding the total number of subjects because some patients had changed their occupations. In case of retired people, the quotation refers to the last declared occupation.
[c]Some patients were polymedicated.

Table I

Demographic characteristics of enrolled patients

patients, who were asked to keep a diary of their current conditions) and the persistence of the therapeutic result at day 180 and 360 after suspension of each oral treatment were evaluated. The response was considered persistent when, in the occurrence of a worsening, the increase of the severity score did not exceed 4 points at day 180 and 360 as compared with day 1 and 180, respectively. When the treatment was followed by no improvement, or even by worsening, the TMI was assigned the conventional value 30 (i.e. the maximum time available for improvement) for the purpose of statistical calculations. Concomitant treatments for diseases other than hand and foot dermatitis are listed in Table I. The study was not sponsored. To the best of our knowledge patients were unrelated and had no occasion to communicate between themselves.

Statistical methods

An inferential analysis was carried out with the McNemar paired test with Yates' correction, the Wilcoxon signed rank test, and the Mann–Whitney test, as required (Tables II and III). All tests were two-tailed, and a significance level of 0.05 was chosen. Owing to the dimensions of the studied sample and to other relevant parameters (SD), type II error [β] was kept <0.1 for all comparisons. Statistical calculations were performed by means of the Instat2 software package (v 2.04, 1990–1993; GraphPad Software, San Diego, CA, USA) run on a PC-compatible computer.

Results

Results are summarized in Tables II and III. Moreover, at recruitment, 15 patients were definitely positive ($\geqslant ++$) for one or more contact allergens (Table I). Nine out of 15 patients that were positive for $NiSO_4$ ($\geqslant ++$) at days 1 and 180 turned out to be $NiSO_4$-negative at day 360. One of them who was also $K_2Cr_2O_7$-positive had his positivity reduced (from $+++$ to $+$) at day 360. There were no dropouts, but two patients missed the control visit at day 30, and at day 180, respectively (in these cases, the last observation carried forward (LOCF) method for substitution of missing data was applied). Patients who were still completely disease-free at a 3-month follow-up had been able to attend their usual occupations without breakdown. No case of acute rebound of HFD was observed after suspension of Treatment 2. Side effects other than slight exfoliative cheilitis or dryness were absent. In particular, a close monitoring of metabolic indexes showed no alterations of the lipidogram. Only four patients presented slight alterations of hepatic

	Day 1	Day 30	Day 180	Day 210	Day 360
Median	7.50	6.00	8.00	2.00	4.00
Mean	7.52	5.45	7.71	1.98	3.52
SD	1.55	2.12	1.73	1.51	1.68
Range	5–10	2–10	5–10	0–6	0–7

Significant improvement if reduction of the severity score was $\geqslant 4$ over the considered periods:
Comparison – Treatment 1 versus Treatment 2 (period 0–30 days versus period 180–210 days):
McNemar paired test with Yates' correction: extremely significant difference (two-sided $p<0.0001$)
Comparison – Treatment 1: Persistence of clinical result at day 180 compared with clinical presentation at day 1:
Wilcoxon signed rank test: difference not significant (two-sided $p=0.3019$).
Comparison – Treatment 2: Persistence of clinical result at day 360 compared with clinical presentation at day 180:
Wilcoxon signed rank test: extremely significant difference (two-sided $p<0.0001$).

Table II

Results (I): clinical severity scores

function tests (three during Treatment 2, one during Treatment 1), which, however, did not prevent continuation of their participation in the study. Qualitative evaluation of patients' diaries pointed out a clear-cut predilection for Treatment 2.

Discussion

It is difficult to design a blinded placebo-controlled trial of drugs that have recognizable side effects.[8] We chose to administer supplementary oral or topical placebos to help maintain the blind element.[9] This measure is inexpensive and helps avoid placebo effect bias. According to their diaries, patients were able to recognize the 'active treatment' from placebo, but this was due to effectiveness more than from adverse effects. Every patient underwent topical treatment first, then oral retinoid because, given the long half-life of acitretin, an impractically long wash-out period would have been required for those patients receiving acitretin first. This does leave open the possibility of a temporal trend bias; however, this is less important given the chronic nature of HPD.

The term 'hand and/or foot dermatitis' refers to the clinical merging node of a collection of heterogeneous diseases, which can overlap, and not uncommonly change their appearance with time, altering the disorder's diagnostic label.[1–5] In common they have the following features:

1. they are exceedingly hyperkeratotic and fissured to a disabling extent; spongiosis is usually present;
2. whether on allergic or irritant or mechanic basis, they are often related to a condition of hypersensitiveness of the skin to the environment;
3. a definitive diagnosis cannot often be reached, but patients are suffering and need help.

Indeed, 20 years after the statement by Reimann,[10] 'eczema keratoticum', i.e. hyperkeratotic HFD, still seems little known, as its treatment as well. Some textbooks[11,12] refer to systemic retinoids as probably the most effective treatment choice for such patients, but it is astonishing to discover that this statement leans on the reiterated quotation[11–13] of only two original sources,[10,14] one of which is a chapter in a non-English book. Moreover, no textbook says anything about effectiveness of oral retinoids in the pompholyx-like form of the disease, except for the cases in which this clinical feature is an evident manifestation of an underlying psoriasis. Many dermatologists are afraid of the possible severe adverse effects ensuing from

	Treatment 1	Treatment 2
Median	25.00	16.50
Mean	22.71	17.05
SD	7.29	6.28
Range	4–30[a]	5–30[a]

Comparison – TMI with Treatment 1 versus TMI with Treatment 2
Mann – Whitney test: extremely significant difference (two-sided $p<0.0002$)

[a]When the treatment was followed by no improvement, or even by worsening, TMI (time to maximum improvement) was assigned the conventional value 30, i.e. the maximum time available for improvement, for the purpose of statistical calculations: this was the case for seven patients after Treatment 1. This applies also to the subject who missed the after-Treatment 1 control visit at day 30. This was one of the two cases to which the last observation carried forward (LOCF) method for substitution of missing data was applied (see text).

Table III

Results (II): time needed to reach the maximum improvement (TIMI) since the beginning of each treatment (days)

systemic retinoid administration. Thus, it is not surprising that very few clinicians are confident about prescribing these drugs in HFD, giving their defensive preference to local treatments and environmental changes. However, attempts at environmental prophylaxis of contact factors (either allergic or irritative, or generically koebnerizing) is usually disappointing. This fact poses a major problem when the disease is chronic, relapsing and disabling,[15] and unresponsive to messy topical remedies. The main causes of unavoidable exposition to environmental offending agents are their ubiquitousness, an unbreakable job-related contact, or simply an exquisite cutaneous vulnerability.[15] These unlucky patients would be compelled to choose between the alternatives of having their life wrecked by job loss or tormenting skin lesions which prevent effective performance in any case.

Acitretin was long-lastingly effective on hyperkeratosis and painful fissuring. Treatment with acitretin reduced hospitalization required for elaborate topical and physical treatments (inpatient PUVA, occlusive dressings), an event previously experienced by eight out of the 156 candidates, and by three out of the 42 studied patients. Indeed, we underscore a uniformly favourable, persistent effect of acitretin even on the pompholyx-like component of the clinical picture. Moreover, a quite unexpected result was the persistent reduction of some type IV sensitizations in nine patients. It is not known whether retinoids could influence allergic delayed reactions.[16] Alternatively, this phenomenon could be unrelated to retinoid therapy, and represent the expression of simple loss of contact sensitization, although nickel and chromate allergies are not prone to rapid spontaneous disappearance.[17]

The administration of systemic retinoids is generally better tolerated and less hazardous than treatment with low-dose corticosteroids coupled with azathioprine, or with cyclosporine A.[7,15] Acitretin is a practical treatment for palmoplantar keratoderma due to pityriasis rubra pilaris, and similarly appears to be a good choice for chronic moderate-to-severe HFD. Acitretin improves the quality of life of such patients, including their ability to cope with work and family exigencies, and to give up messy, expensive, and often ineffective topical treatments; this was clearly stated by most studied patients in their diaries (in seven cases with the significant term 'liberation'). Because of its lack of significant drug interactions, acitretin can be used in combination with other topical or systemic treatments when needed.[7,12]

By providing evidence of the effectiveness of acitretin for HFD, we hope to give physicians greater confidence in the 'off-label' choice of this agent.[18,19] We find that even compared with active topical treatment, the effectiveness and safety of systemic retinoids make it a good first choice in these clinical settings.

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