Clinical and Ultrastructural Effects of Acitretin in Darier's Disease

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Thirteen patients with Darier's disease with a mean extent of the lesions of 29.4±10% of the total skin area were treated with acitretin (the main metabolite of etretinate) for 16 weeks. The dose was 30 mg/day during the initial 8 weeks and was later adjusted individually to 10–30 mg/day in order to achieve optimal results. Three patients cleared completely, 7 patients showed marked improvement and 3 patients became slightly better during treatment. The mean extent of the lesions after the treatment was 7.3±8% of the skin area. Despite good clinical clearing, the improvement at the ultrastructural level was incomplete in the 3 patients studied by electron microscopy. Normal stratification did not develop and the size and number of desmosomes remained reduced. The main side effects during treatment were pruritus in 5 patients, diffuse alopecia in 2 patients and marked elevation in serum triglycerides in 4 patients. On the basis of this study, acitretin would seem to be a useful alternative to etretinate for the treatment of Darier's disease. *Key words: Retinoids; Genodermatosis; Dyskeratosis; Acantholysis; Desmosomes.* (Received April 12, 1988.)

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Several studies have shown that etretinate is effective in the treatment of Darier's disease (1–4). In clinical practice, etretinate is useful especially in widespread and hyperkeratotic forms of the disease; these patients need intermittent treatment courses or occasionally even continuous treatment (3). At the ultrastructural level, etretinate is able to normalize at least to some degree the faulty keratinization in the epidermis but despite the clinical clearing after treatment, some ultrastructural signs of the disease still persist (3). Localized and mild cases of Darier's disease are preferably treated with topical methods, since the side effects may be more bothersome than the disease. Furthermore, the teratogenic potential of etretinate is problematic in women of childbearing age, especially since the long elimination time of the drug from the body requires contraception for 2 years after stopping treatment.

Acitretin is the main metabolite of etretinate with clinical effects quite close to those of etretinate. After oral administration, acitretin is not stored in the fatty tissues as etretinate is (5), but is rapidly eliminated; patients treated for 2 months with doses of 25–50 mg/day showed a short elimination half-life of 2–4 days (6).

Acitretin has already been shown to have an antipsoriatic effect at doses of 25–75 mg/day (7, 8). The primary purpose of this open, noncomparative study with acitretin was to evaluate the clinical response of patients with Darier's disease and to establish the best dosage with respect to efficacy and tolerability. The second purpose was to study the effect of acitretin on the faulty keratinization in Darier's disease at the ultrastructural level.

PATIENTS AND METHODS

This was an open, noncomparative, intra-individual dose-finding study. Included in the study were patients (age 18–70 years) with recalcitrant Darier's disease, confirmed by histological examination.

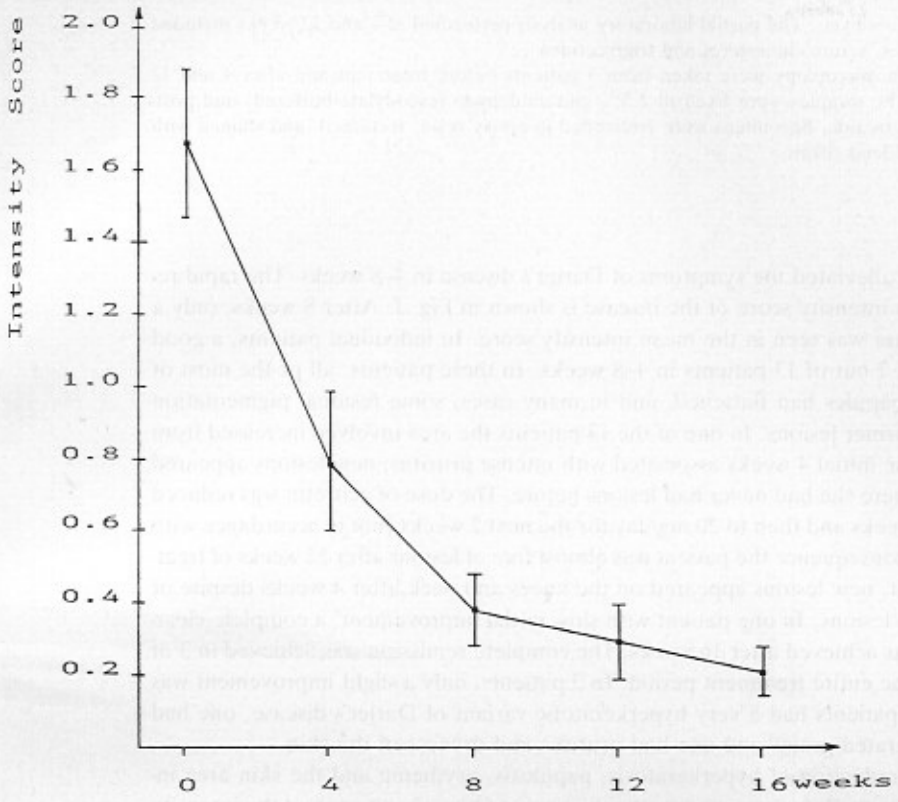

Fig. 1. The mean intensity score, i.e. (papulosis score + hyperkeratosis score + erythema score) × area percentage before and during treatment with acitretin (mean ± SE).

Excluded from participating in the study were patients with severely impaired renal or hepatic function, or with severe cardiovascular or neurological diseases. Females of childbearing potential were admitted only if they agreed to use adequate contraception. Patients who had received systemic or topical corticosteroids, etretinate or other active treatment within the last 4 weeks prior to the trial were excluded.

Thirteen patients were recruited to participate in this study. There were 6 females and 7 males ranging in age from 19 to 69 years (mean ± SD: 40.5±13.2 years). The mean weight of the patients was 68.8±13.0 (range 42–83) kg. The duration of the disease varied from 11 to 41 years (mean ± SD: 25.5±11 years). The current episode had lasted from as little as 3 months to as long as several years. Nine of the patients had previously received etretinate, with good or moderate treatment results. Four of the 6 female patients were sterilized, one of them used contraceptive pills and one had passed the menopause.

Capsules of 10 mg acitretin were used. They were taken once daily during the main meal. The patients were treated with 30 mg/day for 8 weeks. After this initial phase, dosing was individualized (10–50 mg/day) for each patient to produce optimal improvement while minimizing the side effects. There were two deviations from the protocol: the dose of one patient had to be reduced to 10 mg after 4 weeks and later to 20 mg/day because of dryness and pruritus of the skin and the dose of another patient (weight only 42 kg) was lowered to 10 mg/day because of the dramatic clinical improvement after 4 weeks.

Before treatment and at different control visits (every second week) the intensity of papulosis, hyperkeratosis and erythema (scale: 3 severe, 2 moderate, 1 mild, 0 absent) and the proportion of involvement of the whole body area were recorded. The intensity score of the disease was calculated as follows: (papulosis score + hyperkeratosis score + erythema score) × lesional area percentage (Fig. 1). Colour photographs of the patients were taken at every visit. The adverse effects were monitored at each visit using the scale: mild, moderate, severe.

The complete laboratory analysis performed before treatment and at 8 and 16 weeks of treatment included hemoglobin, erythrocyte count, leukocytes with differential count, platelet count, total bilirubin, creatinine, blood sugar, alkaline phosphatase, liver transaminases (S-alat, S-asat), serum cholesterol

and triglycerides and urinalysis. The partial laboratory analysis performed at 4 and 12 weeks included only liver transaminases, serum cholesterol and triglycerides.

Biopsies for electron microscopy were taken from 3 patients before treatment and after 4 and 12 weeks of treatment. The samples were fixed in 2.5% glutaraldehyde (cacodylate-buffered) and post-fixed in 1% osmium tetroxide. Specimens were embedded in epoxy resin, sectioned, and stained with 5% uranyl acetate and lead citrate.

RESULTS

Acitretin effectively alleviated the symptoms of Darier's disease in 4–8 weeks. The rapid reduction in the mean intensity score of the disease is shown in Fig. 1. After 8 weeks, only a slight further decrease was seen in the mean intensity score. In individual patients, a good clearing was seen in 7 out of 13 patients in 4–8 weeks. In these patients, all or the most of the hyperkeratotic papules had flattened, and in many cases, some residual pigmentation was left at sites of former lesions. In one of the 13 patients the area involved increased from 40 to 50% during the initial 4 weeks associated with intense pruritus; new lesions appeared on the lower legs where she had never had lesions before. The dose of acitretin was reduced to 10 mg/day for 2 weeks and then to 20 mg/day for the next 2 weeks (not in accordance with the protocol). As a consequence the patient was almost free of lesions after 12 weeks of treatment. In one patient, new lesions appeared on the knees and neck after 4 weeks despite of good clearing of old lesions. In one patient with slow initial improvement, a complete clearing of the lesions was achieved after 16 weeks. The complete remission was achieved in 3 of 13 patients during the entire treatment period. In 3 patients, only a slight improvement was seen. One of these patients had a very hyperkeratotic variant of Darier's disease, one had problems with macerated groins and one had pruritus and dryness of the skin.

Fig. 2 shows the reduction of hyperkeratosis, papulosis, erythema and the skin area involved during treatment. Before treatment, the thickness of hyperkeratosis and the intensity of papulosis were mainly graded as moderate or severe. Eleven of the 13 patients had at least 30% of their skin affected before treatment. The mean area was 29.4±10%. After treatment, only one patient still had such a widespread disease. The mean area for all patients was 7.3±8%.

The clinically adverse effects were numerous but usually well tolerated. All the patients had mildly or moderately dry lips at least during the initial 8-week period. Pruritus was observed in 5 patients and in 2 of them it was very intense during the initial weeks of the treatment. Pruritus was usually associated with dry skin and was controlled to some degree with emollients. Moderate diffuse alopecia was seen in 2 patients during the later phase of the treatment but it did not necessitate cessation of the treatment and it was completely reversible after stopping treatment.

In laboratory tests, elevation of serum triglycerides was seen in 5 of 13 patients. The highest value (4.7 mmol/l) was observed in a female patient with a slightly elevated pretreatment value. In 12 patients with normal pretreatment values, marked elevation (>2.7 mmol/l) was seen in 3 patients and slight elevation in one patient. Cholesterol levels above 7.2 mmol/l (upper normal limit in Finnish patients) were seen in only one female patient with a moderately increased pretreatment level (8.7 mmol/l). Of the serum transaminases, S-alat was elevated above normal (>40 IU/l) in only one patient after 12 weeks (51 IU/l), but it returned to normal despite treatment after 16 weeks. All other laboratory parameters remained within normal values during treatment.

The dosage of 30 mg/day was used for all but 2 patients (see Patients and Methods) during the initial 8 weeks of treatment. Later the optimal dose proved to be 10 to 30 mg/day; the dose most commonly used was 20 mg/day (8/13 patients) and no patient received higher doses than 30 mg/day.

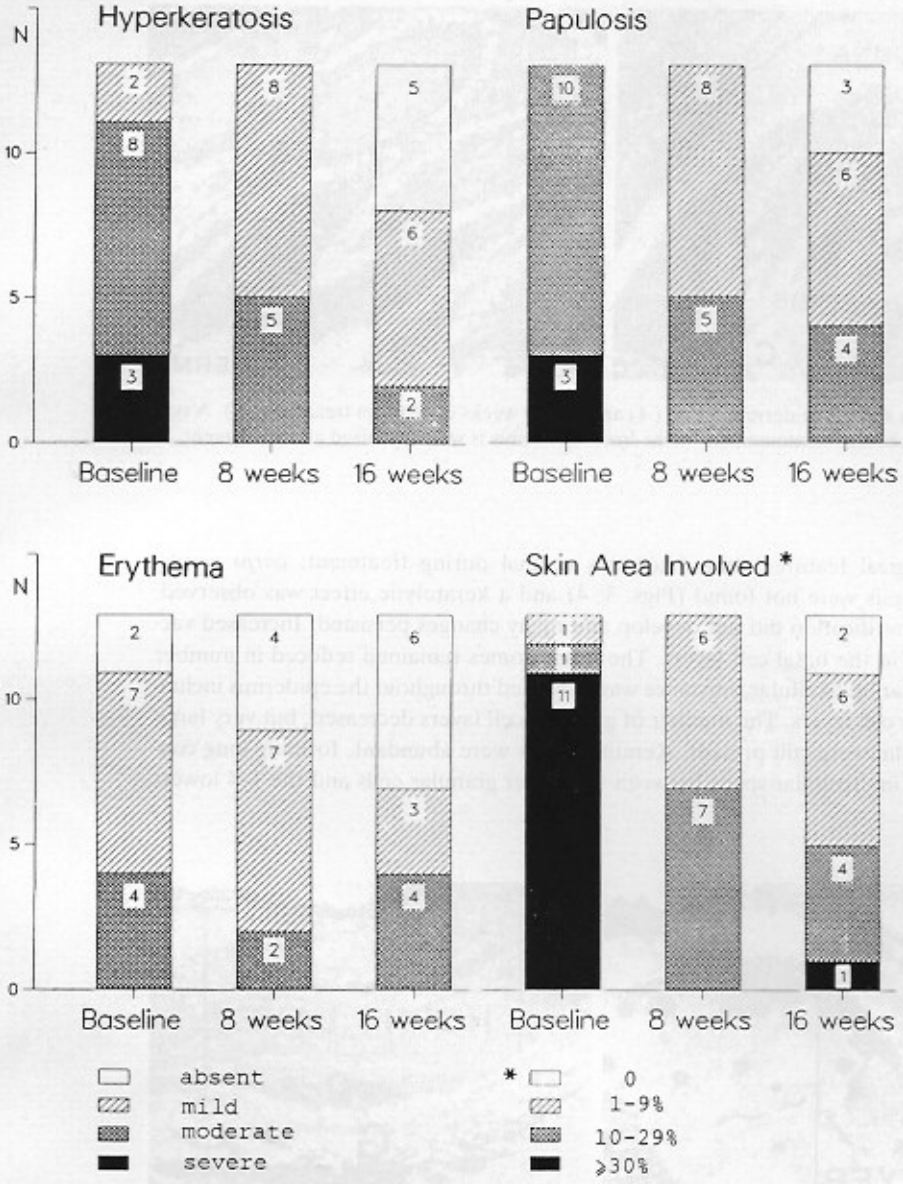

Fig. 2. The intensity of cutaneous signs and extent of lesion before and after 8 and 16 weeks of treatment. (N = number of patients; total 13.)

Ultrastructural findings

Before treatment the histopathology of the epidermis was characterized by abnormal stratification, *corps ronds*, grains, suprabasal acantholysis with suprabasal clefts and lacunae (Fig. 3), papillomatosis, acanthosis and hyperkeratosis. The desmosomes were clearly reduced in the basal and suprabasal cell layers. High to very high numbers of keratinosomes with normal lamellae were observed. The keratohyalin granules were abnormally large and the number of granular cell layers was increased. Lipid droplets were observed in the horny cells and upper granular cells.

In electron microscopic samples taken from 3 patients with good clinical clearing, the

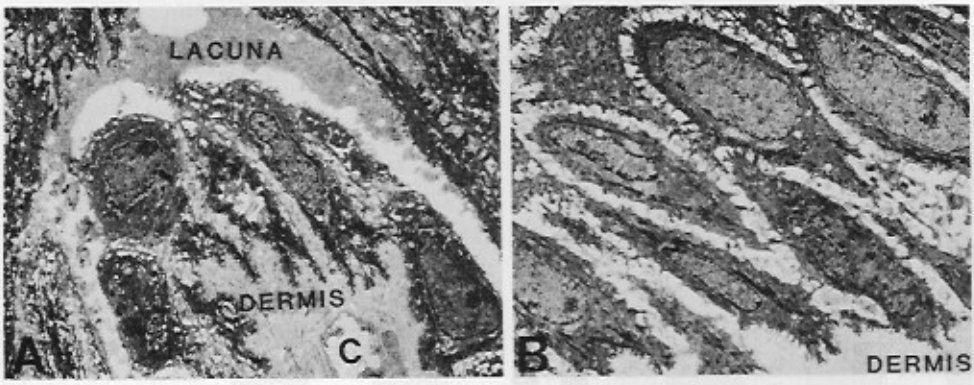

Fig. 3. Basal epidermis and upper dermis before (*A*) and after 4 weeks of acitretin treatment (*B*). A typical lacuna is observed before treatment, while the basal epidermis is well organized after treatment. *c*, capillary. ×4 500.

major histopathological features altered towards normal during treatment: *corps ronds*, grains and acantholysis were not found (Figs. 3, 4) and a keratolytic effect was observed. However, normal stratification did not develop and many changes persisted. Increased vacuolization was seen in the basal cell layers. The desmosomes remained reduced in number and size. The granular intercellular substance was increased throughout the epidermis including the lowest horny cell layers. The number of granular cell layers decreased, but very large bodies of keratohyalin were still present. Keratinosomes were abundant, forming long continuous rows in the intercellular space between the upper granular cells and the 1–4 lowest

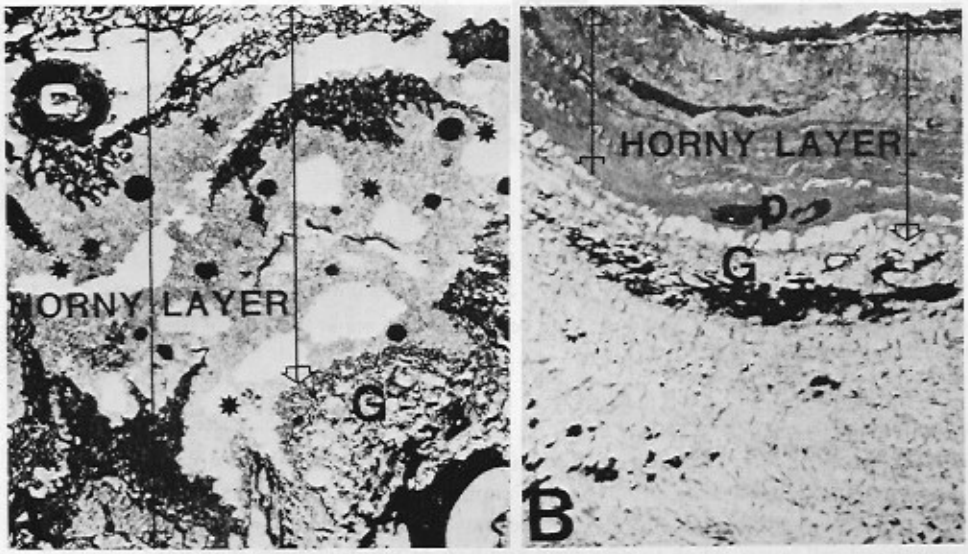

Fig. 4. Horny layer–granular layer interface before treatment (*A*) and after 4 weeks of acitretin treatment (*B*). The horny layer is disorganized before treatment. Containing large amounts of granular intercellular substance (asterisk), a *corps rond* like structure is observed (*C*). After treatment the horny layer is compact and well organized, but a parakeratotic cell is observed (*p*). *G*, uppermost granular cell. ×4 500.

horny cells. Lipid was observed in all the epidermal cell types, i.e. keratinocytes, melanocytes, Langerhans' cells and Merkel cells.

DISCUSSION

This study has shown that acitretin effectively alleviates the symptoms of Darier's disease in the majority of patients. The results are comparable with those achieved with etretinate (1, 2, 3, 4) but the doses of acitretin needed seemed to be rather smaller than those with etretinate. The retinoid dose needed and the treatment response depend of course on the type of the disease and on the condition of the skin; for instance, secondary infection, maceration or dryness and pruritic tendency of the skin may cause extra problems. Three of our 13 patients with moderate to severe skin symptoms were only slightly better after the 16-week treatment period. One of them was a very hyperkeratotic variant of Darier's disease with only a partial response to etretinate as well, one of them had problems with macerated groins and one patient had dryness and pruritus as a side effect. On the other hand, three of the 13 patients were completely free of lesions after the treatment period and 7 patients were markedly better with significantly reduced lesional areas.

The initial dose of 30 mg/day seemed to be effective enough in clearing the lesions in most patients. However, it produced pruritus in 5 patients, which was severe in 2, leading to lowering of the dose in one patient. Pruritus has been a problem in some patients treated with etretinate as well (2, 3). In our patients, only emollients could be used as topical therapy; they gave some relief. Usually some mild corticosteroid cream or sometimes oral antibiotics, especially in secondarily infected cases, can be used to control pruritic conditions. In patients with pruritic lesions, a lower initial dose of 20 or even 10 mg/day may be better tolerated and produce a better result. Higher doses than 30 mg/day seldom seem to be necessary. Such a higher dose might be needed in very hyperkeratotic forms of the disease. If the treatment has to be continued for longer than 8 weeks, the dose of 20 mg/day seems to be optimal in the majority of patients.

No intolerable side effects were seen during the 4-month treatment courses with acitretin. However, 2 cases of moderate hair loss during the later phase of the study and 4 cases of marked elevation of serum triglycerides show that during long treatment periods, increased number of unwanted effects has to be faced. No marked further improvement after 12 weeks was observed in our patients. Therefore it seems recommendable to limit the duration of a treatment period to 2–3 months in most cases. Subsequently, a satisfactory remission period may last for several months after which the patient can be treated again. In some difficult cases, continuous treatment may be necessary.

Even in cases with complete remission, the disease always recurs sooner or later since, despite the treatment, several pathological features remain in the epidermis, as revealed by electron microscopy. Although no acantholysis was found in clinically cleared lesions, the desmosomes remained reduced in number and size. Furthermore, vacuolization was still observed in the basal cell layer. There were no *corps ronds* or grains, but normal stratification did not develop. Continuous low-dose maintenance treatment might be able to maintain the improved state but because of problems in long-term retinoid treatment, this should not be done routinely.

The present study indicated that acantholysis in Darier's disease develops not only from the loss of intercellular contact layer within desmosomes (9, 10) or from separation of tonofilaments from the attachment plaques (11), but from a genetic defect resulting in the formation of decreased numbers of desmosomes that are rudimentary and without normal strength. Acitretin had a keratolytic effect and it partially normalized the faulty differentiation, but fine structural abnormalities including rudimentary desmosomes persisted.

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