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A Double-blind Comparison of Acitretin and Etretinate in the Treatment of Darier's Disease

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The objective of this double-blind study was to compare the therapeutic effects of acitretin with those of etretinate in patients with Darier's disease. Twenty-six patients (10 males and 16 females) were included in the study. Patients were treated with 30 mg daily for the first 4 weeks and with an individually adjusted dose (10–50 mg/day) for the subsequent 12 weeks. Remission or marked improvement was obtained in 10 of the 13 acitretin-treated patients and in 8 of the 11 etretinate-treated patients who completed the 16-week treatment. The usual mucocutaneous adverse reactions of retinoids were observed in all but one patient. There were no significant differences between treatment groups with regard to the incidence of these reactions. ***Key words: Efficacy; Tolerability; Oral aromatic retinoids.***

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Darier's disease shows some clinical features and histopathological changes similar to those of vitamin deficiency (1). These similarities led Peck et al. (2) in 1941 to postulate an essential role of vitamin A in the pathogenesis of Darier's disease, i.e. defective endogenous conversion of carotinoids (pro-vitamin A) into retinoids (vitamin A). Treatment of Darier's disease with large oral doses of vitamin A resulted in a remarkable improvement of the cutaneous condition (2, 3, 4). There are, however, many contradictions in the literature with regard to the relation between Darier's disease and serum vitamin A (2, 4, 5). Vitamin A and their derivatives, i.e. retinoids, seem not to act by correcting a natural deficiency (6).

Due to its toxic effects at high doses, in the last 20 years, vitamin A has been gradually replaced by different analogues for the treatment of Darier's disease. Thus, *all*-transretinoic acid (7), 13-*cis* retinoic acid (8), 9) and especially etretinate (10–15) were shown to be effective against Darier's disease. More recently, results from uncontrolled studies with acitretin, the main metabolite of etretinate, also showed this drug to be of benefit in Darier's disease (16–18). The aim of this double-blind study was to evaluate the efficacy and the tolerability of acitretin compared with etretinate.

PATIENTS AND METHODS

Patients

The inclusion period was set *a priori* at one year (June 1987 to June 1988). Based upon the investigator's estimate, the aim was to recruit 50 patients with Darier's disease, but only 26 patients were available for inclusion.

Twenty-six patients with severe Darier's disease took part in the study (Table I). The diagnosis was supported by current or previous histological examination. Verbal informed consent was obtained before starting therapy.

Patients were excluded if they had severe cardiological or neurological disease, severely impaired renal or hepatic function, as also were patients with disturbed fat metabolism.

Patients who had received etretinate or other active systemic treatment within the last 4 weeks prior to the trial were exclused. Females of childbearing age had to use an effective form of contraception during the treatment and up to 2 years after treatment cessation.

Study protocol

The study was multicentric, double-blind, and randomized centre by centre. It complied with the Declaration of Helsinki and was approved by the local medical ethics committees.

Capsules of 10 mg acitretin (Ro 10-1670/Neotigason) or 10 mg etretinate (Ro 10-9359/Tigason), identical in size and colour were used. The capsules were taken once daily with the main meal. The patients received three capsules (30 mg) daily for the first 4 weeks. After this initial phase, the dose was adjusted for each patient to produce improvement of the lesions while minimizing the adverse reactions. Maximal dose was not to exceed 50 mg daily. No other treatment was allowed except emollients and local antiseptics. The patients were followed for a total of 16 weeks in all. At intervals of 4 weeks the severity of Darier's disease was evaluated by the investigator considering the primary lesions: hyperkeratosis, papulosis and erythema. Additionally, nail- and mucous membrane involvement was recorded. In the clinical assessment of the lesions the following scale was used: 0 = none, 1 = mild, 2 = moderate, 3 = severe. The extent of the skin lesions was recorded as the proportion of body area involved. Type and severity (mild, moderate, severe) of clinical adverse events were recorded at each visit. At the end of the treatment, overall efficacy and safety were assessed by both the investigator and the patient (Table III). Complete laboratory examinations (B-erythrocytes, B-leukocytes, differential count, B-thrombocytes, S-bilirubin, S-creatinine, S-uric acid, B-glucose, S-alkaline phosphatase, S-ASAT, S-ALAT, S-cholesterol, S-triglycerides, U-protein, U-glucose, U-hemoglobin) were performed at entry, at 4 weeks and at 16 weeks. Transaminases and lipids (fasting) were also checked at weeks 8 and 12. Values were considered to be abnormal if they were outside the normal range given by the testing laboratories.

Statistical analysis

Inter-group comparability at baseline: χ^2-test was used to compare the sex distribution. The Mann-Whitney rank sum test was used to compare age, weight, severity of lesions and extent of disease.

Efficacy: the Mann-Whitney rank sum test was used to compare the severity scores and the investigators' and patients' assessments at week 16. The trial involved two factors (i.e. treatment and time). A model comprising one Mann-Whitney and two Friedmann tests to each attribute was used, corresponding to the two-way analysis of variance with repeated measures to test for direct treatment effect, improvement with time, and interaction between treatment and time.

Tolerability: the incidence of adverse events was compared by using the Fischer's exact probability test. Overall assessment of tolerability after 16 weeks was compared by using the Mann-Whitney rank sum test.

Table I. *Patient population*

	Acitretin	Etretinate
Number of patients treated	13	13
Sex distribution		
Males	6	4
Females	7	9
Age (years)		
median	33	39
range	(17–54)	(18–69)
Weight (kg)		
median	65	72
range	(48–95)	(60–95)
Duration of Darier's disease (years)		
median	18	20
range	(5–46)	(6–45)
Skin area involved (percentage)		
median	30	10
range	(5–90)	(2–75)

The level of significance was 5% for all tests (two-tailed).

RESULTS

At baseline (week 0) the two treatment groups were similar regarding distribution of demographic variables and duration of the disease, but not for the skin area involved (Table I). *Post hoc* analysis revealed that the extension of skin lesions was not correlated to the overall assessment of efficacy (Spearman's $\varrho = 0.214$; $p > 0.10$). All patients had the typical form of Darier's disease. The groups were similar regarding severity of clinical signs: hyperkeratosis, papulosis and erythema (Table II). Apart from 2 patients in the acitretin group, all patients had nail involvement. The median dosages at weeks 8, 12 and 16 were 30 mg/day (range 10–50 mg/day) for both acitretin and etretinate.

Temporarily, 2 patients also used locally chlorhexidine and 3 etretinate patients had topical corticosteroids.

In the acitretin group, all patients completed the study. Two patients from the etretinate group did not complete the study: one patient withdrew from treatment after 10 weeks because of marked improvement and the other was excluded due to adverse events (severe conjunctivitis) and lack of improvement after 11 weeks. Table II shows the improvement in the two treatments groups evaluated by the severity of clinical parameters. At the end of the study, both groups had improved significantly according to all variable. Before treatment the median extent of the lesions was 30% of the skin area in the acitretin group and 10% in the etretinate group. After 16 weeks of treatment the involved median area was reduced to 5% in both groups. No beneficial effects of the drugs were observed on nail lesions.

The overall efficacy as assessed by investigators and patients at the end of treatment did not differ between the groups (Table III). A satisfactory improvement (marked or totally cleared), as assessed by investigators, was obtained in 77% of the patients on acitretin and in 73% of the patients on etretinate. The 95% confidence limits for the +4% difference between acitretin and etretinate ranged from −30% to +38%.

Table II. *Severity of clinical signs at baseline and after 16 weeks of treatment* (n = number of patients)

	Acitretin (n = 13)		Etretinate (n = 11)	
	Week 0 n	Week 16 n	Week 0 n	Week 16 n
Hyperkeratosis				
none	0	5	0	5
mild	3	6	7	3
moderate	6	2	2	3
severe	4	0	2	0
Papulosis				
none	0	6	0	2
mild	2	5	4	4
moderate	6	2	6	3
severe	5	0	1	2
Erythema				
none	1	7	2	3
mild	5	2	4	4
moderate	5	4	3	2
severe	2	0	2	2

All patients, except one treated with acitretin, experienced adverse reactions: mainly dryness of the mucocutaneous membranes and dryness as well as scaling of the skin. Such events occurred with the same frequency in the two groups. The majority of adverse events were rated by the investigator as mild to moderate. Only one patient (in the etretinate group) withdrew from the study because of severe conjunctivitis. Three males and 2 females in the acitretin group and one male and 2 females in the etretinate group complained of hair loss, all mild except moderate for one female acitretin patient. At the end of treatment very good or good tolerability was recorded in 11 (85%) acitretin and 9 (69%) etretinate patients by both investigators and patients ($p > 0.05$; 95% confidence limits for the difference of +16% range from −16% to +48%).

With regard to laboratory findings, no statistically significant changes were found either within or between treatment

Table III. *Investigators' and patients' assessments of efficacy after 16 weeks* (n = number of patients)

	Acitretin (n = 13)	Etretinate (n = 11)
Investigator		
remission	3	3
marked improvement	7	5
mild improvement	3	2
no change	0	0
worsening	0	1
Patient		
very good	7	5
good	3	4
moderate	3	1
poor	0	1

Acitretin vs etretinate: NS.

groups. One etretinate patient had abnormal pretreatment ALAT which normalized during treatment. Five acitretin and 2 etretinate patients had minor, transitory, abnormal increases in triglycerides during treatment, whereas for 2 other etretinate patients, the triglyceride value increased to an abnormal level at week 16. These were all considered of no clinical importance by the investigators. An important change in lipids was seen in only one patient, who received acitretin and for whom triglycerides increased steadily from 3.47 at baseline to 8.99 mmol/l after 16 weeks.

DISCUSSION

In previous studies of Darier's disease, complete clearing or marked improvement after treatment with acitretin were obtained in 10 of 13 patients (16), 4 of 5 patients (17) and 4 of 4 patients (18). The results of the present study agree with these findings. This study also provides evidence that acitretin and etretinate do not differ substantially with regard to efficacy in Darier's disease.

Both drugs produced adverse reactions similar to those following other retinoids (19). There were no significant differences between treatments with regard to the incidence of these reactions.

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