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A Double-blind Comparison of Acitretin and Etretinate in the Treatment of Severe Psoriasis

Results of a Nordic Multicentre Study

K. KRAGBALLE,[1] C. T. JANSÉN,[2] J.-M. GEIGER, [3] J. R. BJERKE,[4] E. S. FALK,[5] L. GIP,[6] N. HJORTH,[7] J. LAUHARANTA,[8] N.-J. MORK,[9] T. REUNALA,[10] K. ROSÉN,[11] H. SCHMIDT,[12†] P. O. THUNE[13] and C. VAHLQUIST[14]

[1]*Departments of Dermatology, Marselisborg Hospital, Aarhus, Denmark;* [2]*Central Hospital, Turku, Finland;* [3]*Clinical Research Dermatology, F. Hoffmann-La Roche & Co. Ltd. Basle, Switzerland;* [4]*Haukeland Hospital, Bergen, Norway;* [5]*Tromsö Hospital, Tromsö, Norway;* [6]*Sundsvalls Sjukhus, Sundsvall, Sweden;* [7]*Gentofte Hospital, Copenhagen, Denmark;* [8]*Central Hospital, Helsinki, Finland;* [9]*Rikshospitalet, Oslo, Norway;* [10]*Central Hospital, Tampere, Finland;* [11]*Sahlgrenska Hospital, Gothenburg;* [12]*Odense Sygehus, Odense, Denmark;* [13]*Ulleval Hospital, Oslo, Norway;* [14]*University Hospital, Uppsala, Sweden*

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Acitretin, the free acid of etretinate, is less lipophilic and has a much shorter terminal half-life than the parent compound. The present double-blind, randomized study compared the therapeutic effectiveness and the tolerability of acitretin (n=127) and etretinate (n=41) in psoriasis. Patients were treated with 40 mg daily for the first 4 weeks and with an individually adjusted dose for the subsequent 8 weeks. The average daily doses of acitretin (0.54 mg/kg/day) and etretinate (0.65 mg/kg/day) were similar. The PASI (Psoriasis Area and Severity Index) scores improved in parallel in the 2 treatment groups. At the completion of the study, the PASI score improvement was 75.8% for acitretin and 70.8% for etretinate. Both acitretin and etretinate resulted in mucocutaneous side effects. Assessments of tolerability by investigators and patients showed a statistically significant difference in favour of etretinate. These results demonstrate that acitretin and etretinate have similar therapeutic effectiveness in psoriasis. Although the tolerance to acitretin was lower than to etretinate, acitretin offers the important advantage of a much shorter period of potential teratogenicity and is, therefore, to be preferred in women of childbearing potential. (Accepted July 12, 1988.)

K. Kragballe, Department of Dermatology, Marselisborg Hospital, Aarhus, Denmark.

The aromatic retinoid etretinate has been proved to be effective in the symptomatic treatment of severe psoriasis (1–4). However, etretinate has the pharmacokinetic disadvantage of being extremely slowly eliminated with a reported terminal elimination half-life of up to 120 days (5, 6). Fatty tissues have been identified as the storage sites of etretinate (7). Due to the teratogenic potential of etretinate, the existence of such a deep compartment has practical consequences for women of childbearing potential who have to use an effective contraceptive not only during the treatment, but also for 2 years after discontinuation of the treatment.

It becomes, therefore, of interest that studies of etretinate metabolism have shown that this compound, which possesses an ethylester group, is hydrolysed in the gastrointestinal tract to the corresponding free acid, acitretin (5, 6). Compared to etretinate, acitretin is less lipophilic and is detectable only in negligible quantities in fatty tissue (7). Accordingly, acitretin has been shown to have a shorter terminal half-life of 2–4 days during longterm treatment (6, 8).

Because of these pharmacokinetic properties, acitretin treatment may represent an important alternative to etretinate in females of childbearing potential. From recent clinical studies it appears that acitretin is effective in the treatment of psoriasis (9–12). The aim of the present study was to evaluate both the anti-psoriatic activity and the tolerability of acitretin compared to etretinate in a larger group of patients.

PATIENTS AND METHODS

Patients

One hundred and sixty-eight patients with longstanding, severe psoriasis took part in the study (Table I), and an oral informed consent was obtained before start of therapy. Patients were excluded if they had severely impaired renal of hepatic function or severe cardiological or neurological disease. Females of childbearing potential were only admitted if they accepted to use an effective form of contraception.

Patients who had received etretinate within the 4 weeks prior to the trial and patients recalcitrant to previous treatment with etretinate were excluded. Patients who had received PUVA- or UVB-treatment, topical tar-derivatives, and topical corticosteroids within the 4 weeks prior to the trial were also excluded.

Study protocol

The study was designed as a double-blind group comparison of acitretin and etretinate. Patients were randomly allocated to two different, numerically unequal groups, group 1: acitretin and group 2: etretinate. The group sizes were selected primarily to show efficacy and safety of acitretin, using etretinate as a positive control.

Capsules of 10 mg acitretin (Ro 10-1670) or 10 mg etretinate (Ro 10-9359), identical in size and colour, were used. The capsules were taken once daily, with the main meal.

The patients received 40 mg daily for the first 4 weeks. After this initial phase, the dose was individualized for each patient to produce improvement of the lesions while minimizing the adverse reactions. The maximal dose was not to exceed 80 mg daily. No other treatment was allowed except emollients.

At biweekly intervals, the severity of psoriasis was evaluated by means of the PASI score (Psoriasis Area and Severity Index) based on the following parameters: estimated intensity of erythema, infiltration, desquamation, pustulation and extent of the lesions, as described elsewhere (2). The PASI score used in the present study was slightly modified as described by Geiger and Czarnetzki (12).

The main criterion for efficacy was the change of the PASI score at the end of treatment compared with baseline. Type and intensity of clinical adverse events were recorded at each visit. Complete laboratory examinations (blood count, serum biochemistry and urinalyses) were performed at entry and at week 12. Transaminases, gamma GT and lipids (fasting) were also checked at weeks 4 and 8.

Table I. *Patient population*

Values are medians and ranges

	Acitretin	Etretinate
Number of patients treated	127	41
Sex distribution		
Male	75 (59%)	27 (66%)
Female	52 (41%)	14 (34%)
Age (years)	44 (18-76)	48 (21–79)
Weight (kg)	75 (50–120)	75 (52–100)
Type of psoriasis		
Psoriasis vulgaris	115 (90%)	35 (86%)
Pustular psoriasis	10 (8%)	5 (12%)
Erythrodermic psoriasis	2 (2%)	1 (2%)
Duration of psoriasis (years)	15 (0–60)	16 (0–45)
PASI score	12.6 (2.2–38.6)	13.1 (5.2–35.2)

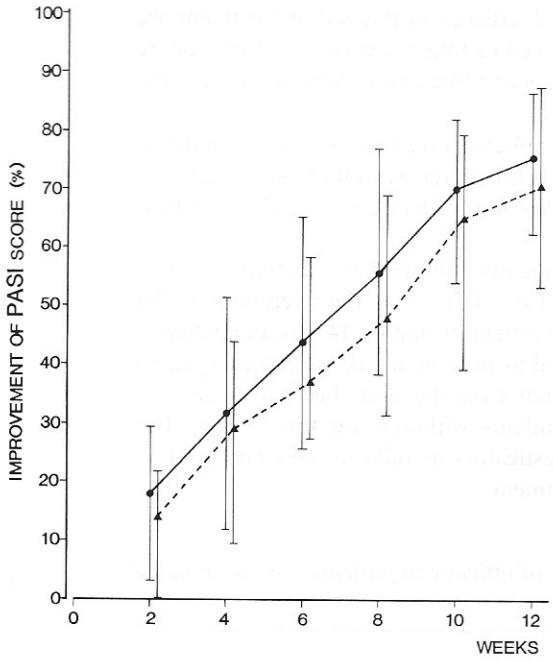

Fig. 1. Percent improvement of PASI scores in psoriatic patients who completed the study: acitretin, $n = 99$ (●) and etretinate, $n = 24$ (▲). Values are medians and interquartile range (50% of patient values). Acitretin vs. etretinate: NS.

Values were considered to be abnormal if they were outside the normal range given by the testing laboratories.

Statistical analysis

Demographic data: The two treatment groups were compared with regard to sex, age, weight, height and baseline PASI score. The x^2-square test was used to compare the sex distribution. The Wilcoxon two-sample test was used to compare age, weight, height and baseline PASI score.

Efficacy: The Wilcoxon two-sample test was used to compare the percent improvements of PASI score, and the investigators' and patients' assessments at week 12. The absolute changes of PASI score from baseline (difference between PASI score at baseline and PASI score at week 12) were compared in both groups by using the Wilcoxon one-sample test.

Tolerability: The incidence of the main adverse events were compared by using the Fisher's exact probability test (two-tailed). The investigators' and patients' assessments on tolerability were compared by using the Wilcoxon's two-sample test. The level of significance was 5% for all tests.

RESULTS

At baseline (week 0), the 2 treatment groups were similar regarding the distribution of a variety of parameters (Table I). During the treatment phase with varying doses (weeks 4–12), the median acitretin dose (40 mg/day; 0.54 mg/kg/day) was slightly lower than the median etretinate dose (49.7 mg/day; 0.65 mg/kg/day). However, this difference was not statistically significant.

The number of patients who completed the study were 88% for acitretin and 95% for etretinate. PASI score evaluations were done correctly by the investigators in 99 patients on acitretin and in 24 on etretinate. Figure 1 shows the improvements of PASI scores in patients who completed the study. The improvement was time-dependent and occurred in parallel for the two treatment groups. At week 12 the PASI score improvement was 75.8% for acitretin and 70.8% for etretinate. However, the PASI score had not reached a plateau at the completion of the study (week 12).

Investigators' and patients' assessments of overall efficacy at the end of treatment are listed in Table II. A satisfactory improvement (marked or totally cleared), as assessed by investigators, was obtained in 84% of the patients on acitretin and in 80% of the patients on etretinate.

All patients experienced adverse events, which affected primarily the mucocutaneous system (Table III). Such events occurred more frequently in the acitretin group than in the etretinate group. Only for scaling of palms and soles and for hairloss was this difference statistically significant (Table III).

Assessments of overall tolerability by both investigators and patients showed a statistically significant difference in favour of etretinate (Table IV). Thus, the tolerability in the acitretin group was rated as poor by 10% of the investigators and by 14% of the patients. In the etretinate group the tolerability was not rated as poor in any of the patients (Table IV). Five % of the acitretin-treated patients withdrew from the study because of adverse events, whereas none of the etretinate-treated patients withdrew for this reason. The majority of adverse events were rated by the investigators as mild to moderate, and all changes reversed to normal after cessation of treatment.

Table II. *Investigators' and patients' assessments of efficacy in patients who terminated the study*

	Acitretin (N=112)	Etretinate (N=39)
Investigator		
Remission	12 (11%)	7 (18%)
Marked improvement	82 (73%)	24 (62%)
Slight improvement	16 (14%)	8 (21%)
No change	1 (1%)	0 (0%)
Worsening	1 (1%)	0 (0%)
Patient		
Very good	37 (33%)	15 (38%)
Good	48 (43%)	12 (31%)
Moderate	22 (20%)	10 (26%)
Poor	5 (4%)	2 (5%)

Acitretin vs. etretinate: NS.

Table III. *Frequency of the main clinical adverse reactions in both treatment groups*

	Acitretin (N=127) (%)	Etretinate (N=41) (%)	Fisher's exact test
Dry lips/cheilitis	99	98	NS
Dry mouth	66	61	NS
Dry nose	84	78	NS
Dry eyes/conjunctivitis	49	41	NS
Dry skin	70	59	NS
Scaling (palms/soles)	83	49	$p< 0.05$
Scaling (elsewhere)	43	27	NS
Hairloss	48	20	$p< 0.05$
Nail fragility	28	15	NS

With regard to laboratory findings no differences were detected between the two treatment groups. Regarding ASAT, 12% and 11% of the patients had values which were normal before and became abnormally elevated under acitretin and etretinate treatment, respectively. With regard to blood lipids, 10% (cholesterol) and 12% (triglycerides) of patients developed abnormal elevations in the acitretin group, whereas 8% (cholesterol) and 11% (triglycerides) of patients developed abnormalities in the etretinate group. One patient developed toxic hepatitis after treatment with acitretin for 12 weeks. The diagnosis was confirmed by liver biopsy, and other known causes of hepatitis were excluded. After stopping therapy, the serum transaminases gradually normalized.

DISCUSSION

In the present study, acitretin and etretinate were equally effective in psoriasis. These results are in accordance with those of previous studies in which acitretin and etretinate were compared in smaller numbers of patients (9, 11, 13). The improvements of PASI scores at week 12 were 75.8% for acitretin and 70.8% for etretinate. However, a therapeutic plateau was not reached at this time point, indicating that the therapeutic effectiveness might be greater if the treatment had been continued.

Both acitretin and etretinate produced side-effects similar to those of hypervitaminosis A. The incidence and the severity of some of the side-effects was greater in the acitretin-treated patients than in the etretinate-treated patients. This difference in tolerability between acitretin and etretinate was not observed in previous studies (13). One explanation of the high frequency of side effects in our patients treated with acitretin may be the use of an initial higher daily dose of acitretin than in the previous studies, in which 30 mg/day was generally used. Our present findings may indicate that at a higher dose (e.i. 40 mg/day or more) the ratio of efficacy to tolerability (the therapeutic index) is lower for acitretin than for etretinate. This difference may possibly be explained by the different pharmacokinetic profiles of acitretin and etretinate. Because etretinate is only partially converted to acitretin in the body, treatment with acitretin may result in higher serum peak values of acitretin than with equivalent doses of etretinate. It is, however, unsolved whether the occurrence of mucocutaneous side effects during retinoid therapy is related to the peak values in serum.

In the present study, it has been demonstrated that acitretin and etretinate have similar

Table IV. *Investigators' and patients' assessments of tolerability in all patients treated*

	Acitretin (N=127, assessable 126)	Etretinate (N=41)
Investigator		
Very good	26 (21%)	17 (41%)
Good	63 (50%)	17 (41%)
Moderate	24 (19%)	7 (17%)
Poor	13 (10%)	0 (0%)
Patient		
Very good	25 (20%)	15 (37%)
Good	56 (44%)	18 (44%)
Moderate	27 (21%)	8 (20%)
Poor	18 (14%)	0 (0%)

therapeutic effectiveness in psoriasis. Although the tolerance to acitretin was slightly lower than to etretinate, acitretin offers the important advantage of a much shorter period of potential teratogenicity and is, therefore, to be preferred in women of childbearing potential.

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