Intra-epidermal Accumulation of Polymorphonuclear Leukocytes in Persistent Palmoplantar Pustulosis during Treatment with Acitretin

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Six patients with persistent palmoplantar pustulosis were treated with acitretin, and the clinical response was compared with the effect on the intra-epidermal accumulation of polymorphonuclear PMN leukocytes. A prompt improvement of pustule formation and subsequently decreased scaling and erythema was seen in all patients. Following discontinuation of therapy, a relapse occurred within 2 weeks. With dosages of 45 or 55 mg/day, the clinical scores were only slightly better than with 25 or 35 mg/day. In patients using 25 mg acitretin a day, the leukotriene B_4-induced intra-epidermal accumulation of polymorphonuclear leukocytes was not affected. However, a dosage of 35 mg/day resulted in a significant inhibition of PMN accumulation, dosages of 45 and 55 mg/day causing an even more pronounced inhibition of this process. Although the effect of different dosages of acitretin is not clearly expressed in the severity scores, the dose-dependent effect on PMN chemotaxis in vivo might be of relevance when combination therapies are considered, in order to achieve a complete clinical clearance. (Received February 19, 1988.)

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Etretinate is a standard treatment for persistent palmoplantar pustulosis (PPP). For this condition, daily dosages of 1 mg/kg body weight have been advised (1–4). An inverse relationship has been shown between the dosage of etretinate and the leukotriene B_4 (LTB_4)-induced accumulation of polymorphonuclear leukocytes (PMN) (5).

The ethyl ester etretinate is hydrolysed in the body to form the acid derivate acitretin (Ro 10-1670). Due to accumulation of the ethyl ester in fatty tissue, the terminal elimination half-life proved to be more than 80 days for etretinate but only 2 days for acitretin (6). Therefore, from a pharmacokinetic point of view, acitretin is much more easily manageable with respect to the teratogenetic properties of these drugs. In psoriasis and PPP, a beneficial effect of acitretin has been described (7–9). However, the optimal dosage has not yet been established.

In the present investigation, we report on the clinical response to acitretin in 6 patients with PPP. In order to further elucidate the dose–response relationship in these variants of psoriasis, the effect of this drug on the LTB_4-induced intra-epidermal accumulation of PMN was measured. This model constitutes a reproducible method of investigating chemotaxis of PMN in vivo, using the dermis and epidermis as a natural diffusion chamber (10, 11).

PATIENTS AND METHODS

Informed consent was obtained from 6 patients (5 females and 1 male). They were suffering from invalidating PPP. The mean age of the patients was 50.5±7.0 years (±SD). No treatment for the

pustulosis had been given 2 weeks before starting acitretin. One patient was treated with etretinate up to 1 month before starting acitretin; the other patients had been without systemic treatment for at least 6 months.

The total duration of the trial was 6 months. Before treatment and at monthly intervals, patients were monitored for clinical efficacy and side effects. The clinical score was recorded on a 0–4 scale for the individual symptoms (pustulation, erythema, scaling), and sequential photographic documentation was carried out. Patients were interviewed regarding side effects, using a standardized record sheet. Before and at various time intervals during treatment, blood parameters were examined, including blood cell count, haemoglobin, bilirubin, urea, creatinin, glucose, alkaline phosphatase, transaminases, cholesterol and triglycerides. Before and after 6 months of treatment, X-ray examination of the vertebral column was carried out. During the first 4 weeks, the dosage was 35 mg/day in all patients. Thereafter, the dosage was adjusted according to maximum acceptability, based upon objective and/or subjective side effects, with an upper limit of 60 mg a day.

LTB_4 challenge, with subsequent quantification of PMN, was carried out immediately before and at regular intervals during treatment with acitretin (after 1 month, 4 months and at the end of the trial). LTB_4 was obtained from Paesel GmbH, Frankfurt, Germany, and challenge was performed as described previously (11). Aliquots of 10 ng LTB_4 in ethanol were applied via glass cylinders (5.5 mm ∅) to the symptomless skin on the upper back. Ethanol was evaporated under a stream of nitrogen. Test sites were covered with impermeable dressings (Silver Patch, van der Bend, Brielle, The Netherlands). After 24 h, the dressings were removed and a biopsy was taken, using a razor blade provided with a metal guard. The biopsies were processed for elastase measurements, as described by Lammers et al. (12). Biopsies were washed thoroughly in phosphate-buffered saline, weighed, homogenized in cetrimide buffer and centrifuged. Using the fluorogenic substrate MeOSuc-AlaAla-Pro-Val-N-methylcoumarin, elastase activity was measured in the supernatant fractions. After correction for endogenous inhibiting activity, the number of PMN per 10 μg skin was calculated from the fluorescence intensity.

RESULTS

Clinical response and evaluation of side effects

After one month of treatment, pustulation had already decreased in 5 out of 6 patients, whereas erythema and scaling responded more slowly. Fig. 1 shows the average scores for the patients who tolerated a gradual increase of the dosage (>35 mg/day) and for those patients who could not tolerate these high dosages. At the end of treatment, the clinical scores for pustulation and scaling tended to be slightly better for the high-dosage group. Within 2 weeks following discontinuation of acitretin, a relapse was seen in all patients.

All patients except one tolerated an initial dosage of 35 mg/day during the first month. In 2 patients, the dosage could be increased up to 45–55 mg. However, in 2 patients the dosage had to be reduced to 25 mg/day. Mucocutaneous discomfort was experienced by 6 patients: dry lips (4 patients), dry skin and pruritus (1 patient) and hair loss (1 patient, discontinuing acitretin for this reason after 3 months of treatment). In 2 patients, a transient increase in triglycerides was seen, and 2 patients showed increased transaminases. In one of these cases, liver functions reverted to normal values during acitretin treatment. However, in the other patient liver function tests did not normalize and acitretin was discontinued after 5 months of treatment. In this patient histological examination of a liver biopsy revealed a seronegative active hepatitis.

Effect on intra-epidermal accumulation of PMN

Although the clinical scores of low-dose treatment did not differ dramatically from the scores with high-dose treatment, the LTB_4-induced PMN accumulation appeared to be dose dependent. After 1 month of treatment with acitretin, the values of LTB_4-induced PMN accumulation averaged 47% of the values observed immediately before treatment.

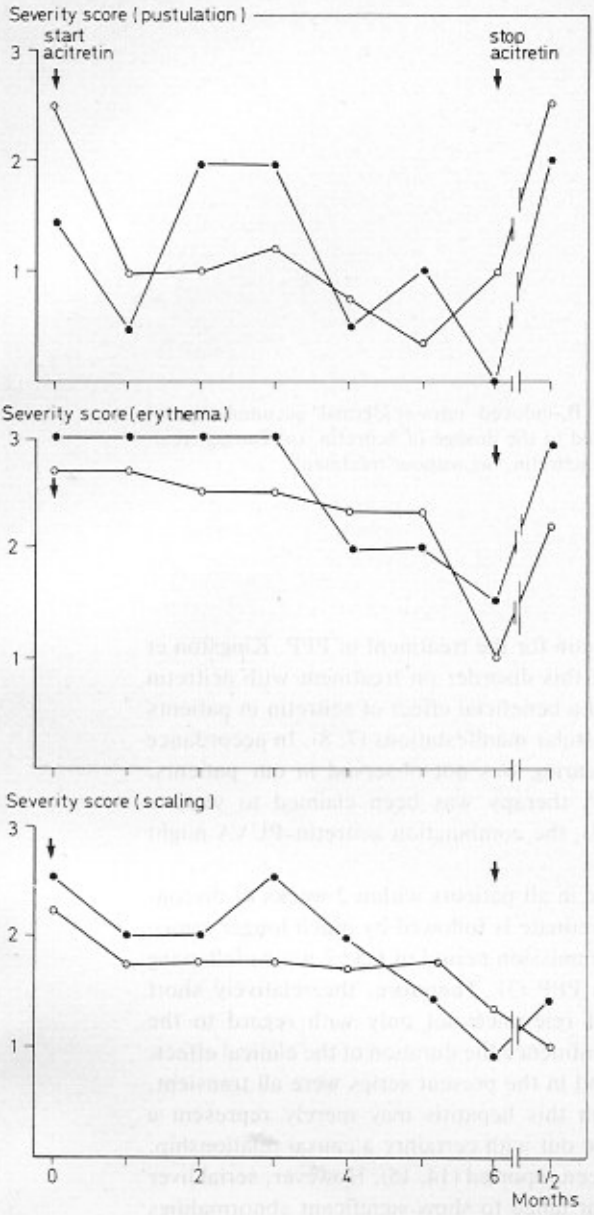

Fig. 1. Average severity scores in patients treated with acitretin. ●, Patients who tolerated a gradual increase in the dosage (n=2); ○, patients who did not tolerate an increased dosage (n=4 up to 3 months; n=3 between 3 and 6 months).

In those patients who did not tolerate a further increase in the dosage, these values remained constant after 4 months and 6 months of treatment with acitretin. If the PMN accumulations at different time intervals of treatment are pooled, a marked dose dependency is seen (Fig. 2). Patients using 25 mg acitretin had baseline values for PMN accumulation. After being treated with 35 mg of acitretin, LTB_4 applications resulted in reduced PMN accumulation compared with the levels before treatment ($p<0.01$, Wilcoxon ranking test). After being treated with 45 mg or 55 mg of acitretin, LTB_4 applications resulted in a further reduction compared with the reduction already achieved by a dose of 35 mg.

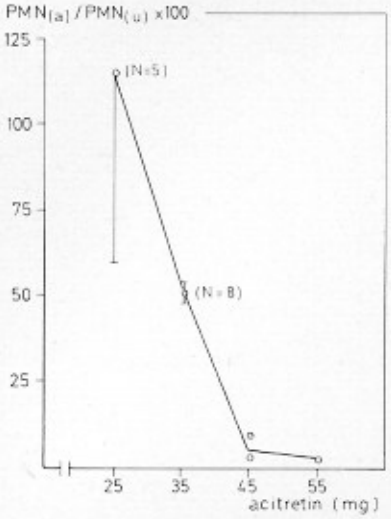

Fig. 2. LTB_4-induced intra-epidermal accumulation of PMN related to the dosage of acitretin. (*a*) During treatment with acitretin, (*u*) without treatment.

DISCUSSION

The present study confirms the efficacy of acitretin for the treatment of PPP. Kingston et al. have documented a marked improvement of this disorder on treatment with acitretin (9). Geiger et al. and Lassus et al. also reported a beneficial effect of acitretin in patients with severe psoriasis and some patients with pustular manifestations (7, 8). In accordance with these previous observations, complete clearing was not observed in our patients. Since a combination of etretinate with PUVA therapy was been claimed to yield a complete remission in 100% of the patients (13), the combination acitretin–PUVA might also result in total remission.

A remarkable observation is the rapid relapse in all patients within 2 weeks of discontinuing acitretin. In contrast, treatment with etretinate is followed by much longer remission periods. Lassus et al. reported an average remission period of 6.3 ± 2 weeks following discontinuation of treatment with etretinate in PPP (3). Therefore, the relatively short terminal half-life of acitretin is presumably of relevance not only with regard to the teratogenicity of the drug, but it also appears to influence the duration of the clinical effect.

The undesired clinical manifestations observed in the present series were all transient, except for the one case of hepatitis. Although this hepatitis may merely represent a coincidence, at this point in time we cannot rule out with certainty a causal relationship. Hepatitis during treatment with etretinate has been reported (14, 15). However, serial liver biopsies in patients treated with etretinate so far failed to show significant abnormalities (16–18).

After 6 months of treatment, the clinical scores of the patients treated with increasing dosages (up to 45 and 55 mg/day) were slightly better than those of the patients treated with dosages between 25 and 35 mg/day. The study by Lassus et al. suggests that dosages of 25 mg/day and 50 mg/day have an equal effect on psoriasis, whereas a dosage of 10 mg/day had an effect intermediate between the high dosages and the placebo (3). The optimal dosage of acitretin in the treatment of pustulosis of palms and soles and psoriasis has not yet been established.

The clinical assessment is qualitative and can easily be confused by subjective interpretations. Therefore, in the present study the effect of acitretin was assessed using the in vivo model for pustule formation: i.e. the intra-epidermal accumulation of PMN following

epicutaneous application of a standard dose of LTB_4. The model permits objective quantification of PMN accumulation in skin which is the fundamental process for PPP. In this in vivo model, acitretin in a dose of 25 mg/day did not have a significant effect, whilst 35 mg/day caused a significant inhibition of PMN accumulation and 45 mg or 55 mg/day caused a larger inhibition of this process compared with a dose of 35 mg. This difference was not clearly expressed in the clinical scores; however, the enhanced efficacy of higher dosages of acitretin on PMN accumulation in skin may be of relevance if complete clearing is aimed for, by prolonged treatment or combination therapy.

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