

## Efficacy and Skeletal Side Effects of Two Years' Acitretin Treatment

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**In this prospective study, 51 patients suffering from psoriasis and ichthyosis were treated with acitretin for 2 years. The average dose was 0.5 mg/kg/day. We have evaluated the efficacy and side effects, focusing on skeletal side effects. X-ray examinations were done before treatment and after 1 and 2 years. Forty-five patients completed the study. Acitretin had a good clinical effect, with 75% improvement in 35 of the patients. Apart from the well-known side effects affecting the mucous membranes, one patient developed biopsy-proven toxic hepatitis. In 2 patients we observed unusual skeletal calcifications located in the forearms and in the hip. These were considered to be caused by the drug. In this study, which included patients up to 71 years, only radiographs of the pelvis and the forearms were of value as routine follow-up films. Key words: Psoriasis; Ichthyosis; Skeletal calcification; Radiographs.**

(Accepted June 29, 1992.)

Acta Derm Venereol (Stockh) 1992; 72: 445-448.

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The different disorders of keratinization respond dramatically to retinoid therapy. Much experience with isotretinoin and etretinate has been gathered during the last decade, and the side effects of these drugs are now well known.

An increasing number of bone changes during systemic retinoid therapy have been reported (1-7). Skeletal toxicity is a risk factor during long-term retinoid therapy.

In 1947 Wolbach (8) demonstrated changes induced by vitamin A excess in the bones of rats and guinea pigs. He demonstrated acceleration in all processes of bone growth and premature closure of the epiphyses. In 1962, Pease (9) described 7 children hospitalized for severe symptoms of accidental hypervitaminosis A. In 3 of the children the growth of the legs was seriously impaired. Pittsley & Yoder (10) reported in 1983 the development of diffuse idiopathic skeletal hyperostosis - the so called DISH syndrome, in 4 of 9 patients receiving high dose long-term treatment of isotretinoin for ichthyosis.

One of the first reports of skeletal damage attributed to etretinate was made by Smitt & de Mari (11) in 1984. A 19-year-old patient with lamellar ichthyosis developed ossifications of both forearms after 5 years of etretinate treatment. In 1986 Digiovanna et al. (12) found that 32 of 38 patients who had received etretinate had radiographic evidence of extraspinous tendon and ligament calcification. The data on bone toxicity from long-term treatment with retinoids are uncertain.

In this study we have prospectively evaluated the efficacy and skeletal side effects in patients treated with acitretin, the main metabolite of etretinate, for 2 years.

The study was approved by the local ethical committee. The study drugs were kindly supplied by F. Hoffmann-La Roche.

### MATERIALS AND METHODS

Fifty-one patients, 14 women (mean age 56.6 years, range 38.1-71.0 years) and 37 men (mean age 44.5 years, range 18.1-65.4 years) were included in the study.

Our patients suffered from different disorders of keratinization: psoriasis vulgaris in 35, ichthyosis in 10, pustulosis palmoplantaris in 3 and pustular psoriasis in 3 patients.

The starting dose of acitretin was 30 mg daily for the first 4 weeks. Thereafter the dose was individually adjusted according to effect and side effects. The average daily dose of acitretin for all the patients during the study was 0.5 mg/kg/day. Most of the patients used the drug continuously.

Clinical and biochemical examinations were done monthly during the first 3 months and thereafter every third month.

Twenty-eight of our patients had previously used etretinate. Nine patients received winter UV-B treatment and 15 patients used topical steroids periodically during the study.

The clinical efficacy was evaluated every third month during the 2 years' treatment. Marked improvement indicated disappearance of more than 75% of the skin changes and mild improvement a 50%-75% reduction.

Baseline radiographs were taken in all patients. Forty-five patients had follow-up radiographs after 1 and 2 years. The radiographs were exposed in standardized projections. The x-ray films were first examined routinely by different radiologists who were aware of the intentions of the study. All radiographs were later reviewed by one experienced radiologist, and consensus was sought if opinions differed. In patients with equivocal findings, either further projections were included or more frequent follow-up films were taken.

The following radiographs were performed routinely in all patients before treatment, and after 1 and 2 years: Cervical spine side projection, thoracic spine side and front projections, lumbar spine side and front projections, pelvis front projection, forearms front projections, knees side projections and feet side projections. The patients who developed pronounced calcifications were also examined by bone scintigraphy using Technetium 99m-labelled phosphonate, with 750 MBq given by intravenous injection.

There were 6 drop-outs during the treatment period of 2 years.

### RESULTS

#### Clinical efficacy

Forty-five of 51 patients completed the study. After 2 years' treatment 3 patients showed remission, 32 patients showed marked improvement while 10 patients experienced mild improvement. The patients who combined acitretin with either UV-B or topical steroids all experienced marked improvement. Three of 6 drop-out patients stopped the treatment because of side effects, a slight increase in liver transaminases, severe cheilitis, and marked hair loss, respectively. One patient died of acute myocardial infarction while 2 patients dropped out for other reasons not related to the drug. The patients experienced the well known side effects of acitretin as dry lips (35 patients), conjunctivitis (22 patients), dry mouth (19 patients), dry nose (11 patients) and hair loss (6 patients).

In addition, a 49-year-old man with psoriasis developed a biopsy-verified toxic hepatitis probably due to acitretin. He

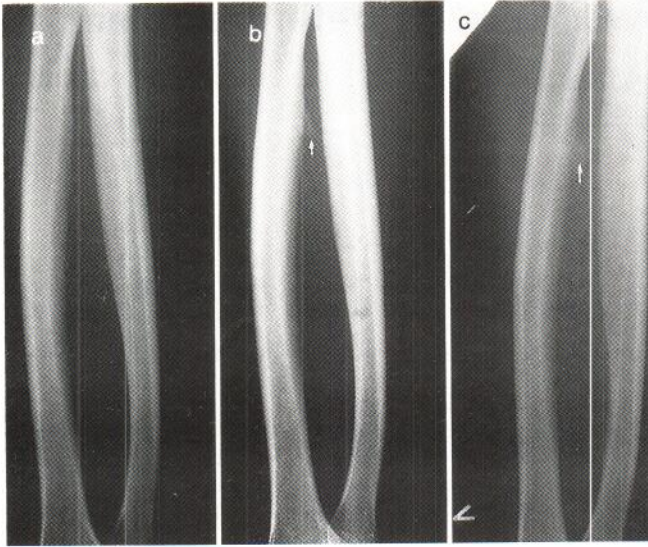


Fig. 1. Radiographs of left forearm of a 36-year-old male with ichthyosis. (a) February 1987. Normal findings after etretinate treatment since 1983. (b) February 1989 when changing to acitretin treatment. Ossification of interosseous membrane (arrow). (c) May 1989. Progression of ossification (arrow).

had used the drug for 5 months with a total dose of 7210 mg acitretin. We examined the patient thoroughly without finding any other reason for his liver damage. The liver changes normalized 10 weeks after stopping the treatment. His psoriasis worsened and acitretin was reintroduced in a lower dose. During 15 months of follow up there has been no evidence of liver damage using the reduced dose.

#### Skeletal findings

During these 2 years, the appearance or growth of ligamentous – or soft tissue – calcifications occurred in 11 of 45 patients. In 6 of the 11 patients the calcifications occurred in usual loca-

tions such as the left trochanter region (1), upper patellar rim (1) and as spinal osteophytes (4). These had normal appearances and were considered as probably co-incident. Three patients developed calcifications of somewhat unusual density and size within the observation period. Two of these were cervical spurs and one acetabular. These spurs were judged as possibly drug-induced. The patients had no previous injuries to these regions. Bone scintigraphic examinations were normal in all 3 patients.

In the remaining 2 of the 11 patients the calcifications were clearly abnormal and judged as most likely due to the drug. We want to present these 2 patients in more detail.

The first patient was a 36-year-old man with x-linked recessive ichthyosis. He had used etretinate 75 mg daily since 1983. The total dose of etretinate was 164 g. From February 1989 we changed to acitretin 50 mg daily. In May 1989 he noticed pain in the left forearm with reduced pronation and supination without any history of previous injury. Acitretin treatment was then stopped after a total dose of 4750 mg.

Figs. 1a-c show the x-ray findings of his left forearm. The patient had a tiny hyperostotic process in February 1989 when acitretin was introduced. During the following 3 months of acitretin treatment the calcifications increased. The patient's ichthyosis rapidly deteriorated after stopping acitretin treatment, and in February 1990 acitretin therapy was again started.

Between February 1989 and February 1990 a hyperostotic process developed in his left hip (Figs 2a, b).

Figs. 3a-b show the x-ray findings of left and right forearms in February 1990 when acitretin was reintroduced. A small calcification had also developed in the right forearm.

Since February 1990 he has taken 30–40 mg acitretin daily. Neither clinical nor x-ray examinations have shown further side effects and he has no pain in his arms.

The other radiographs of this patient were normal.

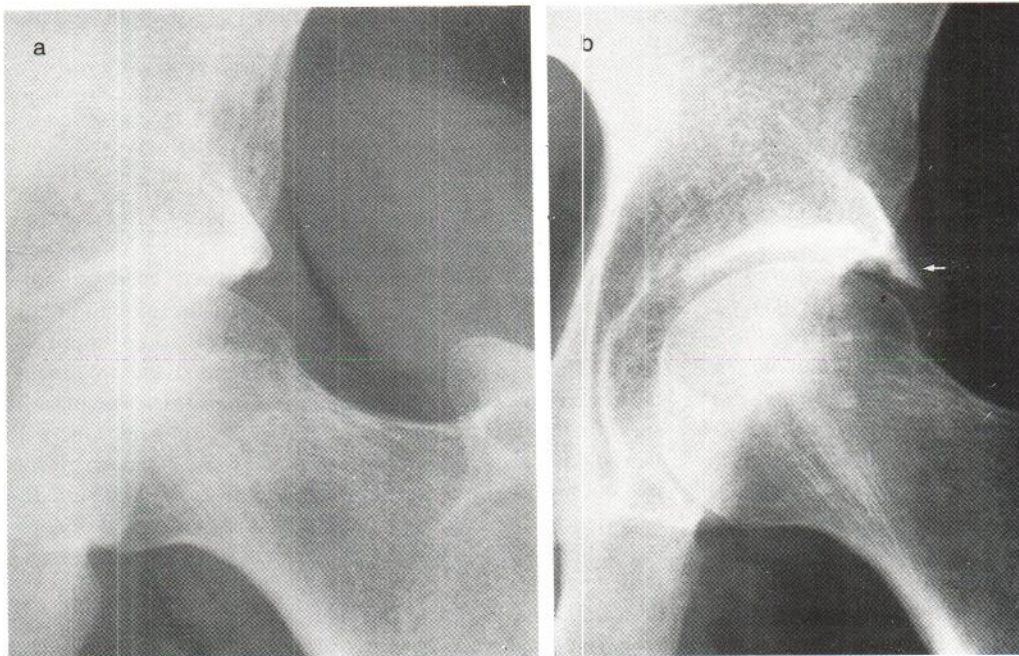


Fig. 2. Left hip of same patient as in Fig. 1. (a) February 1989 at start of acitretin treatment. (b) February 1990. A bony spur has appeared (arrow).

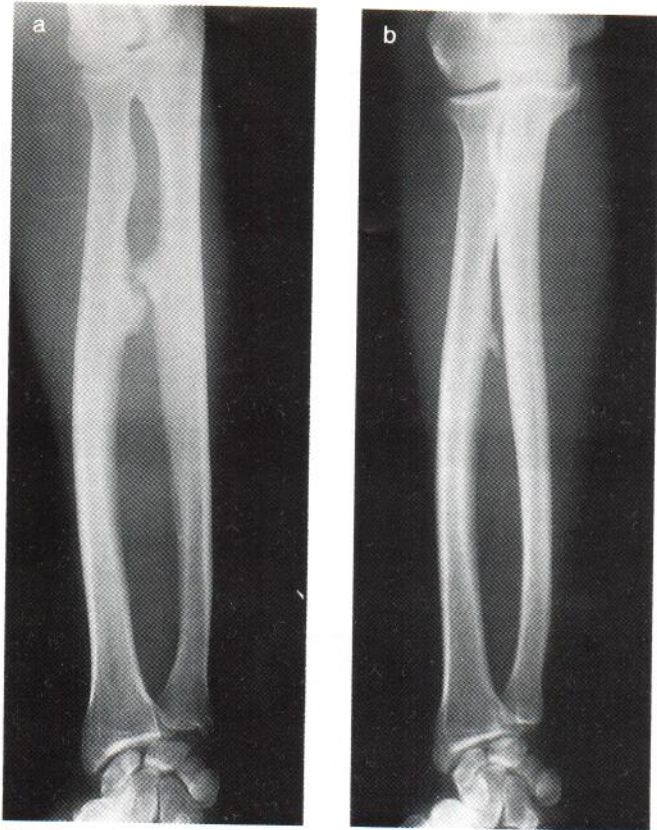


Fig. 3 a. Same patient as in Fig. 1. (a) Radiograph of left forearm February 1990 after 8 months without treatment. Further progression. (b) Right forearm in February 1990. Exostosis from the radial diaphysis.

Bone scintigraphic examination showed increased uptake of radiolabel in the left forearm but no increased activity in the right forearm or the left hip.

The second patient who developed an abnormal drug-related calcification was a 66-year-old woman with pustulosis palmoplantaris, who had never previously used etretinate. In December 1988 she started acitretin therapy 30 mg daily until the treatment was stopped in April 1989 due to hair loss. The total dose of acitretin was 4530 mg. In June 1989 a small, laminar hyperostotic process had developed in the right forearm (Fig. 4). She had not experienced any previous injury to this arm. In February 1990, 10 months after the acitretin therapy was stopped, this hyperostotic process had disappeared.

All other x-ray films were normal in this patient. Bone scintigraphic examination showed increased uptake of radiolabel in left clavicle, but no increased activity in her right forearm. X-ray film of her left clavicle was normal.

None of these patients with calcifications showed any abnormal haematological parameters, including serum electrolytes, calcium and phosphate.

## DISCUSSION

This study confirms the beneficial effect of acitretin in psoriasis and ichthyosis. A daily dose of 30–40 mg resulted in more than 75% improvement in 35 of 45 patients.

Twenty-four of the psoriatic patients completing the study used topical steroids or UV-B for shorter periods in addition to acitretin. This allowed a lowering of the acitretin dose and gave a better therapeutic control in periods of active disease.

Our patients experienced the same side effects from the skin and mucous membranes as reported in other studies (13, 14). The side effects were generally well tolerated and only 2 patients stopped the treatment because of cheilitis and hair loss.

In the patient who developed toxic hepatitis, acitretin was reintroduced in a lower dose without any further liver problems. Liver necrosis due to etretinate has been reported earlier (15, 16). A biopsy-proven hepatic injury has also been reported using acitretin (13).

Török et al. (17) found that scintigraphic examinations were a suitable method for early screening of bone changes occurring after etretinate and isotretinoin treatment. Our patient with calcification in his left forearm also showed consistent scintigraphic findings. In the other 4 patients, however, there was *no correlation* between radiographic and scintigraphic findings. Wilson et al. (18) also reported that bone scintigraphy was an insensitive method to register changes of hyperostosis seen in patients receiving long-term etretinate.

In our study radiographs of the spine were of little practical value. Spinal calcifications appeared in 6 patients, as hyperostotic spurs extending from the anterior or lateral rim of the vertebrae. Skeletal abnormalities are frequently found in people past the age of 50, and patients suffering from psoriasis in addition have increased incidence of bone changes (19). Such

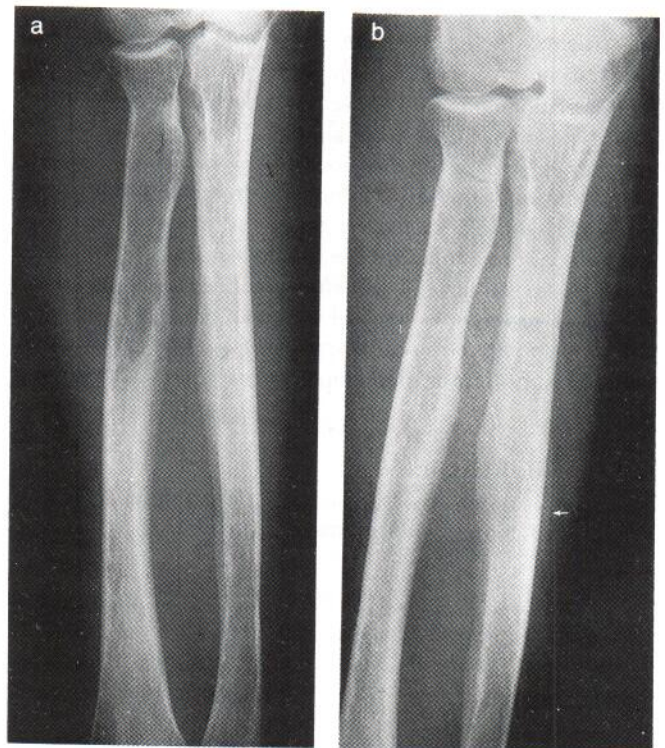


Fig. 4. Radiographs of right forearm of a 66-year-old woman with pustulosis palmoplantaris. (a) December 1988. Normal findings. (b) June 1989 after a total dose of 4530 mg acitretin. Periosteal bone growth of the ulna (arrow).

findings might therefore be purely co-incidental. Kilcoyne, in 236 patients treated with acitretin, found spine x-ray abnormalities in 86% at the start of therapy and concluded that increasing hyperostosis during treatment is not a proof of acitretin side effects (20).

We have now started a prospective study of patients below 45 years of age using long-term acitretin therapy. They all have normal pre-treatment x-rays, including the spine. This study will hopefully better evaluate the efficacy of spine radiographs in monitoring the skeletal side effects of acitretin.

The 36-year-old man had a tiny hyperostotic process in his left forearm when etretinate was stopped and acitretin was started. During the months that followed this calcification rapidly increased. He also developed calcifications in the right forearm and in his left hip. The osseous findings in this patient may be due to etretinate, acitretin or to the combination of these drugs.

The 66-year-old woman had never used etretinate, and in this patient the calcification developed during the use of acitretin, and completely disappeared 10 months after the acitretin therapy was stopped. This is an important observation and indicates that drug-induced calcifications may resolve. For the whole group there was no progression in skeletal side effects during the second year of treatment.

In this study, which included patients up to 71 years of age, only radiographs of pelvis and forearms were of practical value. Here, clearly abnormal calcifications were observed, whereas changes in other regions could have been co-incidental. In young patients one may include the spine, since skeletal abnormalities in general are less frequent.

We did not perform x-ray examinations of the lower legs in our patients. In hypervitaminosis A hyperostosis has been observed in long bones (21). It is debatable, therefore, whether radiographs of the lower legs should also be included.

We have shown that skeletal side effects may be severe. However, in our experience to date this is not an absolute contraindication for further long-term treatment with acitretin. X-ray controls should be taken. A proposed protocol based on our present knowledge should include baseline skeletal survey, as we have done before treatment. Follow-up examinations of forearms and pelvis should be performed after 12 and 24 months. Clinical suspicion of skeletal involvement should prompt further radiographs of the region in question.

#### ACKNOWLEDGEMENT

Our thanks to Dr. Noel McFadden, Dept. of Dermatology, Ullevål sykehus, Oslo, for reviewing the manuscript.

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