Long-term Oral Treatment of two Pronounced Ichthyotic Conditions: Lamellar Ichthyosis and Epidermolytic Hyperkeratosis with the Aromatic Retinoid, Tigason® (RO 10-9359)

MAHMOUD EL-RAMLY* and HUGH ZACHARIAE

Department of Dermatology, Marselisborg Hospital, University of Århus, Århus, Denmark

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Five patients suffering from lamellar ichthyosis and 3 from epidermolytic hyperkeratosis (previously called non-bullous and bullous congenital ichthyosiform erythroderma) were treated from 11 to 52 months with the synthetic aromatic retinoid Tigason (RO 10-9359). In all cases of lamellar ichthyosis the results were judged as good to excellent, while none of the patients with epidermolytic hyperkeratosis gave more than a slight response. The reason for the poorer results in the latter condition was that effective therapeutic dosages in relation to ichthyosis invariably produced increased blistering. These and other side effects such as cheilitis, mild dryness of mucous membranes, slight hair loss, and pruritis, in no case necessitated discontinuation of the drug. *Key words: Lamellar ichthyosis; Epidermolytic hyperkeratosis; Congenital ichthyosiform erythroderma; Aromatic retinoid; Tigason; Etretinate.* (Received November 30, 1982.)

M. El-Ramly, Department of Dermatology, Marselisborg Hospital, University of Århus, Århus, Denmark.

Until recently no satisfactory treatments were available for the various ichthyotic conditions. Symptomatic measures such as application of keratolytic creams and urea in water-

* Present address: 464, El-Horida road, Roshdy, Alexandria app. 28, Alexandria, Egypt.

miscible base to reduce dryness have been used, but these compounds are usually not particularly efficacious.

The newly available oral synthetic retinoids (5) which have been found successful in a number of conditions in which hyperkeratosis is a feature, naturally have also been tried in ichthyosiform dermatoses (4, 6) and claimed to be of benefit.

The purpose of this report is to present the results of long-term treatment with the aromatic retinoid Tigason® (etretinate, RO 10-9359) in 8 patients suffering from either lamellar ichthyosis or epidermolytic hyperkeratosis (previously called non-bullous and bullous ichthyosiform erythroderma), both being pronounced ichthyotic conditions.

PATIENTS AND METHODS

Five patients (2 males and 3 females) aged 18 to 34 years, suffering from lamellar ichthyosis and 3 patients (one male aged 16, a boy of 8 and a girl of 11) with epidermolytic hyperkeratosis were studied. All were hospitalized at their first examination and had their clinical diagnosis verified histologically. Laboratory tests performed during the trial included complete blood cell counts, liver enzyme levels, renal function tests, urine analyses, and serum triglycerides.

Tigason was administered in 25-mg capsules at a starting dose of about 0.4 mg/kg body weight/day, which was raised gradually to reach 0.8–1.2 mg/kg according to the patient's condition and the clinical response. Besides Tigason the patients were allowed to continue with a 5 or 10% urea cream, which they all were using prior to the systemic therapy.

Evaluation of the clinical condition was initially done weekly, and the biochemical analyses at approximately 3-week intervals. Later the intervals of controls were increased to about every 6 weeks.

RESULTS

The results of the clinical assessment and the duration of the observation period are shown in Table I.

In all cases of lamellar ichthyosis the results were judged to be good to excellent. Fig. 1 shows patient no. 1 before treatment, Fig. 2 the same patient at her next admission 9 months later. The characteristic large greyish brown, quadrilaterally shaped scales were easily shed after bathing and applying the cream. This had not been the case earlier. Also the moderate hyperkeratosis which was found of the palms and soles diminished, and an amelioration of ectropion, which was pronounced in 3 of the 5 patients, was also noted. A

Table I. *Overall results and side effects of treatment*

LI = Lamellar Ichthyosis, EH = Epidermolytic Hyperkeratosis

Pat. no.	Diagnosis	Sex/Age	Treatment period (months)	Assessment
1	LI	F/18	21	Excellent
2*	LI	M/26	20	Good
3	LI	F/35	18	Excellent
4	LI	F/34	12	Excellent
5*	LI	M/22	11	Excellent
6	EH	M/8	52	Slight
7	EH	F/11	42	Slight
8	EH	M/16	21	Slight

* Pat.no. 2 and no. 5 are brothers.

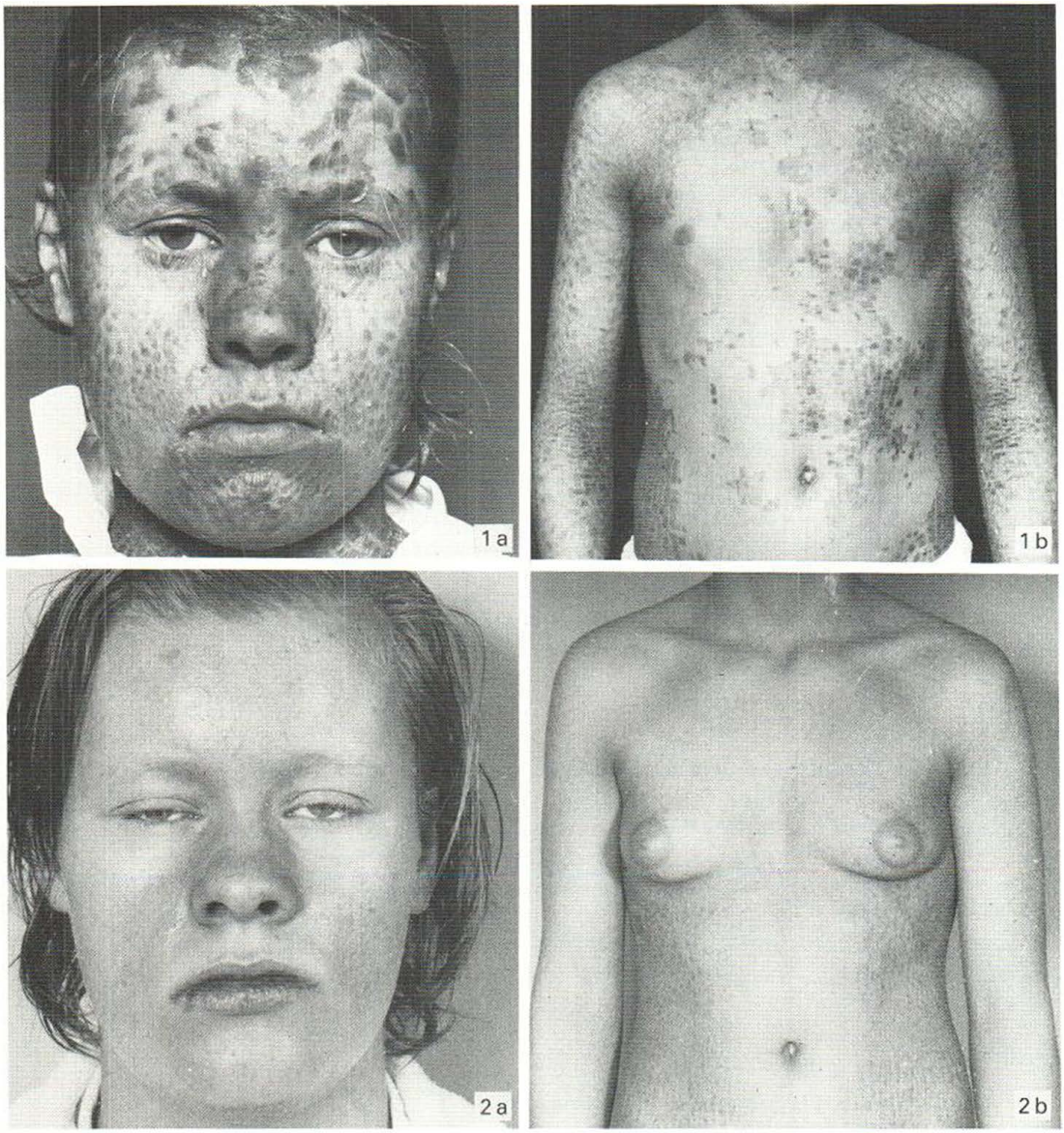

Fig. 1. Face and back of patient no. 1 prior to treatment.

Fig. 2. Face and back of same patient as in Fig. 1, after 9 months' treatment with Tigason® (RO 10-9359).

good clinical effect was obtained after only 2 weeks treatment, and when the patients were on a dosage of from 0.7 to 0.8 mg/kg/day. The clinical side effects, consisting of cheilitis and occasionally fissures of the lips, mild pruritis and minor hair loss, were not considered bothersome by the patients, but resulted in occasional reductions of dosage. All patients were most anxious to continue therapy.

In none of the patients with epidermolytic hyperkeratosis did Tigason give a clinical effect comparable to the results in lamellar ichthyosis. Whenever the dosage was raised above 0.7 mg/kg/day in order to obtain sufficient desquamation, increased bulla formation

followed. Moreover, the two children both experienced loss of hair, all showed cheilitis and one of the children also complained of dryness of the throat and nose. In spite of this, both the young man, the children, and their parents wanted treatment to continue in order to keep hyperkeratosis reduced as far as possible.

Blood counts and blood chemistry as well as urine analyses were normal throughout the observation period, excluding a slight leukocytosis in one of the patients with epidermolytic hyperkeratosis following erysipelas.

All three children showed completely normal growth rates during treatment.

DISCUSSION

In good agreement with earlier results (4, 6) the data from the present study show that the oral retinoid Tigason is a very effective treatment in lamellar ichthyosis, also called non-bullous congenital ichthyosiform erythroderma, while only a limited success was obtained in the bullous form of congenital ichthyosiform erythroderma, now commonly called epidermolytic hyperkeratosis. The reason for the rather poor results in the latter condition is that effective therapeutic dosages in relation to ichthyosis invariably seem to produce increased blistering. The present report gives data from long-term treatment. In this respect it is remarkable that all our patients—like those suffering from Darier's Disease (2)—were unwilling to discontinue retinoid treatment. This is in contrast to patients suffering from psoriasis, persistent palmo-plantar pustulosis or keratotic eczema of hands of feet (2) who, over a similar observation period, have a high drop-out rate in spite of good primary therapeutic responses. We take this high degree of patient acceptance of the drug as proof that in lamellar ichthyosis (and to a lesser degree also in epidermolytic hyperkeratosis) as in Darier's Disease, it is the first time in life that these patients have experienced real drug benefit. This in contrast to psoriatic patients, for example, who know that almost identical results may be obtained with other therapeutic measures with less subjective side effects.

One of the therapeutic effects of Tigason is believed to be a decrease in epithelial cell cohesion (3). This may explain both the beneficial effect of the drug in our patients (1) as well as the limiting effect, i.e. increase of blistering in epidermolytic hyperkeratosis. Besides this, retinoids also seem capable of inhibiting pathologic cornification (7).

Although no laboratory side effects were noted in the present study it is well-known that Tigason can result in hypertriglyceridemia in some patients, and that the drug may be teratogenic (5). Both these parameters have to be taken into consideration. Also, we are not yet in a position to state whether patients with lamellar ichthyosis and others such as those suffering from Darier's Disease should receive retinoids for an indefinite period of time. This decision must await even lengthier studies on the long-term toxic effects of the drug. Until then, careful observation and, in the females, strict birth control are necessary measures.

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