Oral treatment of ichthyosis with an aromatic retinoid

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SUMMARY

An aromatic retinoid (Ro-10/9359) was used for oral treatment of five cases of ichthyosis (three lamellar, two X-linked).

Complete clearing of the skin lesions was achieved in all five patients within 24.2 ± 3.2 days (X-linked 21.75 ± 6.5, lamellar 23 days). Histopathology showed reduction of the hyperkeratosis, and thickening of the granular layer.

Clinical side effects were of mild intensity and included cheilitis, conjunctivitis and pruritus. All side effects were reversible upon reduction of the daily dosage.

In three patients treatment was discontinued after clearing of lesions. Fresh lesions re-appeared 6 weeks later.

One patient with X-linked ichthyosis developed two recurrences during maintenance treatment; one patient with lamellar ichthyosis was kept in complete remission for 9 weeks on a reduced daily dosage.

Ichthyosis is the generic term applied to a group of different disorders of keratinization all characterized by varying degrees of hyperkeratosis and scaling (Frost & Van Scott, 1966).

Vitamin A acid has a favourable effect on hyperkeratosis, and has been used in different hyperkeratotic conditions (Eriksen & Cormane, 1975; Orfanos et al., 1973; Orfanos & Runne, 1975; Prutkin et al., 1973). Symptoms of hypervitaminosis A limit dosage and duration of therapy. This fact has lead to a search for derivatives with lower toxicity but comparable therapeutic efficacy. One such aromatic retinoid derivative, code number Ro 10/9359, (kindly provided for therapeutic trial by Hoffmann-La Roche, Vienna), exhibited a particularly good therapeutic ratio in animal experiments (Bollag, 1974). This paper presents the results of a therapeutic trial with Ro 10/9359 in five patients with ichthyosis.

PATIENTS (see Table 1)

Five patients, two girls and three boys, with ichthyosis were classified according to Frost & Van Scott.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Type of ichthyosis</th>
<th>Time of onset</th>
<th>Clearing phase</th>
<th>Maintenance phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Duration (days)</td>
<td>Daily dose (mg)</td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>M</td>
<td>88</td>
<td>XLI</td>
<td>8 years</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>M</td>
<td>53</td>
<td>XLI</td>
<td>Birth</td>
<td>22</td>
<td>50</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<td>21</td>
<td>50</td>
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<td>14</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>M</td>
<td>16</td>
<td>LI</td>
<td>Birth</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>F</td>
<td>25</td>
<td>LI</td>
<td>Birth</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>F</td>
<td>45</td>
<td>LI</td>
<td>Birth</td>
<td>23</td>
<td>50</td>
</tr>
</tbody>
</table>

XLI = X-linked Ichthyosis, LI = Lamellar Ichthyosis.
Scott (1966) and selected for therapy. Three of them (Cases 3–5) were siblings with lamellar ichthyosis (LI); two unrelated boys suffered from X-linked ichthyosis (XLI).

Onset of the disease was at birth in all cases except one boy with XLI (Case 1) who developed the disorder during childhood. Due to the severity of their disease, all patients had been treated unsuccessfully by several topical and systemic therapeutic regimens. Patients were kept without specific therapy for 2 weeks prior to the onset of the study. Histologically, hyperkeratosis and a prominent granular layer were observed in all specimens. The number of mitoses (high in LI, few in XLI) served to distinguish these two forms from one another.

**TREATMENT**

The aromatic retinoid Ro 10/9359 (ethyl all-trans-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-1-2,4,6,8-nonatetraenoate) was provided in capsules containing 25 and 10 mg of the substance. The drug was administered orally according to body weight: initially, the patients received ≥1 mg/kg body weight, daily (details see Table 1). After complete remission, therapy was discontinued in the three younger patients. The two older cases were kept on a reduced dosage as maintenance therapy. During the initial phase of treatment all patients were hospitalized. They did not receive any local therapy at all.

**Laboratory tests**

The following laboratory tests were performed at weekly intervals (every 3 weeks during maintenance treatment): blood pressure, erythrocyte sedimentation rate, urinalysis, complete blood cell counts, clotting time, fasting blood sugar, SGOT, SGPT, alkaline phosphatase, LDH, serum bilirubin, serum electrolytes, serum iron, cholesterol, triglycerides, uric acid, blood urea nitrogen and serum creatinine determinations.

Six mm punch biopsies were obtained from involved buttock skin and repeated after clearing close to the previous biopsy sites.

**RESULTS**

Complete clearing of the skin lesions was achieved in all five cases. The mean duration to clearing was 24.2±3.2 days (for LX 21.75±6.5 days and for LI 23 days) (+ = standard deviation). After 2 weeks of treatment a mild erythema appeared and shedding of scales occurred beginning on the extensor surfaces of the extremities. Eventually, after clearing of lesions, slight hyperpigmentation and striae appeared at the predilection sites of the disease.

**Maintenance treatment**

To avoid possible side effects of hypervitaminosis A, such as growth disturbances, and to observe the duration of remission, therapy was discontinued after clearing of lesions in the 3 younger patients (Cases 1, 3, 4). They remained in complete remission for at least 6 weeks without any therapy at all. Subsequently slight scaling and hyperkeratosis started again at the previously involved sites.

The two other patients, one girl with LI (Case 5) and one boy with XLI (Case 2), were treated with a reduced dose (see Table 1), and showed a different course: the girl (Case 5) was kept completely free receiving 10 mg of Ro 10/9359 daily for 9 weeks. The pruritus she had suffered initially decreased, and finally disappeared without any additional treatment. In contrast, the boy with XLI (Case 2) experienced two recurrences within a period of 4 months on maintenance treatment. Both
FIGURE 1. Patient no. 5 (female, age 16 years); (a) legs, (b) shoulder, before treatment; (c) legs, (d) shoulder, after treatment. Twenty-three days of oral aromatic retinoid (Ro 10/9359) were required for clearing.
Ichthyosis treated with aromatic retinoid

recurrences were severe, but of lesser intensity than before treatment, and responded well to re-institution of higher dosage as used in the clearing phase. Complete remission was achieved again within 2 weeks.

**Histopathological changes during therapy**

All control biopsies obtained after the clearing phase showed histopathological differences when compared to the pretreatment specimens: The pronounced hyperkeratosis found in the untreated skin had disappeared and a normal stratum corneum was found in all patients. However, the granular layer appeared thickened in all slides as compared to the untreated skin.

**Laboratory tests**

The laboratory tests performed before and during treatment did not show any significant abnormalities. Only the alkaline phosphatase was slightly increased to 214 /ul in one patient (Case 3) during the initial treatment phase, but was found to be normal when the drug was discontinued.

**Side effects**

All patients developed cheilitis, which was treated without success with steroid free ointments, and remained a therapeutic problem. Reduction of dosage during maintenance phase improved the cheilitis. Pruritus was observed in three patients (only during the initial phase of therapy) and was treated with antihistamines. No erythema of the palms and soles, or other side effects as reported elsewhere (Ott, 1977), could be observed.

**DISCUSSION**

This clinical study demonstrates the therapeutic effect of the new aromatic retinoid Ro 10/9359 in two types of ichthyosis, the lamellar type and the X-linked type. All five patients responded equally well by complete remission. No significant differences in dosage were needed to clear the skin lesions nor was there a difference in duration of the initial clearing phase between XLI and LI. The time interval for reappearance of the skin lesions, when therapy was discontinued, seems to be the same in LI and XLI. The only difference noticed between the two forms was the appearance of recurrences during maintenance treatment. Case 5 suffering from LI could be kept completely free during maintenance therapy whereas Case 2 (XLI) showed two recurrences. Our preliminary results are at variance with those of other therapeutic trials (Ott, 1977), since side effects proved to be mild and did not force us to terminate treatment. Cheilitis is a problem, however, occurring in all cases and being unresponsive to local measures.

In summary, oral treatment with aromatic retinoids, such as Ro 10/9359, appears to be a promising therapy for ichthyosis, both of the LI and XLI types. Therapeutic efficacy can be achieved with a regimen of 1 mg/kg body weight. Side effects of systemic aromatic retinoids will have to be studied in future trials involving greater number of cases.

**ACKNOWLEDGMENT**

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**REFERENCES**

H. Pehamberger, H. Neumann and K. Holubar


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