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Severe Psoriasis – Oral Therapy with a New Retinoid

T. FREDRIKSSON and U. PETTERSSON

Department of Dermatology, Central Hospital, Västerås and
Department of Clinical Research, Roche-Produkter AB, Skärholmen

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Abstract. Ro 10–9359 is a retinoic acid derivative, selected for study because of a better tolerance than retinoic acid, shown in animal experiments. Doses of 25 mg b.i.d., 25 mg t.i.d. and 50 mg b.i.d. were administered orally to 27 patients suffering from severe chronic generalized psoriasis. The clinical efficacy was evaluated by means of a new index, psoriasis area and severity index (PASI) based on severity and area of psoriatic lesions. At doses of 25 mg t.i.d. or 50 mg b.i.d. Ro 10–9359 proved to be an extremely potent antipsoriatic drug. A more than 90% reduction of psoriatic lesions could be seen in 10 patients out of 20 after 4–8 weeks of treatment. This good effect lasted about 5 weeks after treatment. Side effects were frequent, but mostly mild and completely reversible after termination of treatment.

Introduction

Orally administered retinoic acid and some of its derivatives (13-cis retinoic acid, retinoic acid ethylamide) have been found effective in the treatment of skin disorders, as well as in premalignant conditions, such as leukoplakia [4, 7, 8, 10, 11]. However, frequent side effects have been reported with daily doses ranging from 20 to 100 mg. A therapy without side effects could only be achieved with 5 mg daily.

A new retinoic acid derivative, Ro 10-9359: ethyl-all-trans-9(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoate, i.e. a 4-methoxysubstitution of the ethylester of retinoic acid (fig. 1) has been developed. It has been found to possess a better therapeutic effect, as well as a better

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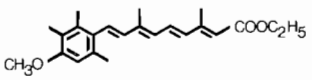

Fig. 1. Chemical structure of Ro 10–9359

tolerance, than retinoic acid in the treatment of chemically induced skin papillomas and carcinomas in animal experiments [1, 2].

This substance acts like retinoic acid on epithelial differentiation, as well as on proliferation of epithelial tissues. The actue toxicity (DL 50) in mice is 3.700 mg/kg p.o., with an observation period of 10 days. However, subacute or chronic toxicity is a more relevant parameter. It was found that dogs tolerated daily doses of 3 and 10 mg/kg for 13 weeks without ill effects, whereas 30 mg/kg per day resulted in reddening of the skin, partial loss of pigment of the fur, and some alopecia of the extremities.

A good overall clinical result has been shown in pilot studies [5, 6, 9] on psoriatic patients treated with a daily dosage of 50–100 mg Ro 10–9359.

The aim of this study was to establish an optimal dosage of Ro 10–9359 in respect to efficacy and side effects. As a more subtle instrument for the evaluation of efficacy, a new index, PASI, is introduced.

Material and Methods

27 patients (3 females and 24 males) with severe, chronic psoriasis were included in this study. Most of the patients could not be controlled with conventional topical therapy like tar, dithranol and steroids, and some patients were also resistant to methotrexate as well as to hydroxyurea. The ages varied between 20 and 59 years with a mean of 38.5 years. The duration of the disease varied between 2 and 50 years with a median of 13 years. Patients with liver insufficiency or renal insufficiency were excluded.

Following a randomized pattern the patients, who were all ambulatory, were divided into three dosage groups: 25 mg b.i.d., 25 mg t.i.d. or 50 mg b.i.d. of Ro 10–9359. The groups comprised 7, 10 and 10 patients, respectively. No concomitant topical or other treatment was allowed except for white petrolatum. The PASI was calculated before entering the study and at weekly intervals. The dosage was not changed for the first 8 weeks, unless intolerance occurred, or a complete remission was established. After this period the patients were followed for some months with a PASI rating approximately every 2nd week.

In order to assess the severity of the disease and any progress during treatment a new index was constructed: psoriasis area and severity index (PASI). For calculation of this, the four main body areas were assessed: the head (h), the trunk (t), the upper extremities (u) and the lower extremities (l), corresponding to 10, 20, 30 and 40% of the total body area, respectively. The *area of psoriatic involvement* of these four main areas (A_h, A_t, A_u

These percentages are different from the formula on the next page. Here, Trunk is 20% and UE is 30%. On the next page, and in other resources on the web, Trunk is 30% and UE is 20%, which is what we used.

In addition, we used results of None, Slight, Moderate, Severe, and Very Severe as these are more commony used than the results below.

and A_I) was given a numerical value: *0* = no involvement; *1* = <10%; *2* = 10<30%; *3* = 30<50%; *4* = 50<70%; *5* = 70<90%, and *6* = 90–100%. In order to evaluate the *severity of the psoriatic lesions* three target symptoms, namely erythema (E), infiltration (I), and desquamation (D) were assessed according to a scale 0–4, where 0 means a complete lack of cutaneous involvement and 4 represents the severest possible involvement. In the case of, e.g. erythema, 0 means no erythema at all (not even 'macular' psoriasis); 1 = slight erythema; 2 = moderate erythema; 3 = striking erythema, and 4 = exceptionally striking erythema.

In order to calculate the PASI the sum of the severity rating for these three main changes was multiplied with the numerical value of the areas involved and with the various percentages of the four body areas. These values were then added in order to obtain the PASI. This formula can be written as follows:

$$PASI = \overbrace{0.1\,(E_h+I_h+D_h)A_h}^{\text{head}} + \overbrace{0.3\,(E_t+I_t+D_t)A_t}^{\text{trunk}} + \overbrace{0.2\,(E_u+I_u+D_u)A_u}^{\text{upper extremities}} + \overbrace{0.4\,(E_l+I_l+D_l)A_l}^{\text{lower extremities}}.$$

The PASI varies in steps of 0.1 units from 0.0 to 72.0. The last mentioned figure thus represents complete erythroderma of the severest possible degree, while 0.0 means no psoriatic lesions at all. Under normal circumstances a patient with a PASI score above 10.0 would be considered for hospitalization with our present treatment policy. The PASI for the patients in the present study varied between 10.5 and 38.2, with a mean of 22.1.

Laboratory controls (hematology, urinalysis, liver and kidney function) were performed at each visit as was questioning for side effects. The study ran between October 1975 and April 1976.

Results

Clinical Evaluation

Before entering the trial the PASI score was assessed for each patient. The mean score was 21.3 in the 25 mg b.i.d. group, 25.6 in the 25 mg t.i.d. group and 19.1 in the 50 mg b.i.d. group. There were no statistical differences between these initial scores ($p<0.05$, rank sum test) [3].

For the 10 patients receiving treatment with 50 mg b.i.d., a reduction in PASI score of more than 90% was obtained in 8 patients, and a 88% reduction in PASI score was obtained in 1 patient. For the 10 patients treated with 25 mg t.i.d., a reduction of more than 90% was registered in 2 patients, and a reduction of 76–90% in 3 patients. Only 1 out of the 7 patients treated with 25 mg b.i.d. had a more than 75% reduction in PASI score. Complete remission (100% reduction) was seen in 1 patient treated with 25 mg t.i.d. and in 4 patients treated with 50 mg b.i.d.

The mean, median and range for the cumulated percentual reduction of PASI score recorded every 2nd week during treatment is shown in table I. All three dosage regimens produced a significant antipsoriatic effect after 8 weeks ($p<0.05$, sign test). However, this effect could be seen already after 4 weeks' therapy in patients treated with either 25 mg b.i.d. or 50 mg b.i.d. ($p<0.05$, sign test).

No differences regarding the efficacy could be seen between the three groups after 2 weeks of treatment. After 4 weeks the 50 mg b.i.d. therapy proved to be superior to 25 mg b.i.d. ($p<0.05$). After a period of 6 weeks

Table I. The mean, median and range for the cumulated percentual reduction of PASI score registered after 2, 4, 6 and 8 weeks, respectively

Dosage group	Parameter	After 2 weeks	After 4 weeks	After 6 weeks	After 8 weeks
		n = 7	n = 7	n = 7	n = 7
25 mg b.i.d.	mean, %	3.9	22.4	35.9	48.0
	median, %	0	20.4	39.2	42.9
	range, %	–9.2–22.2	–5.6–52.6	0–86.5	15.3–85.3
		n =10	n = 9	n = 8	n = 6
25 mg t.i.d.	mean, %	9.3	40.6	72.7	81.3
	median, %	9.9	44.4	70.3	80.8
	range, %	–23.1–34.9	–23.1–71.1	50.0–100.0	67.9–94.7
		n = 10	n = 10	n = 8	n = 4
50 mg b.i.d.	mean, %	23.1	63.1	87.2	95.2
	median, %	22.2	75.2	91.3	96.2
	range, %	0–46.5	0–93.7	43.6–100.0	88.3–100.0

Table II. Clinical observations immediately after end of therapy, and during follow-up period (expressed as percentual reduction in PASI score)

	Results observed immediately after end of therapy (n =13)	Results observed during a follow-up period of					
		1 week (n = 9)	2 weeks (n = 11)	3 weeks (n = 9)	4 weeks (n = 6)	5 weeks (n = 6)	6 weeks (n = 6)
Mean, %	97.5	98.1	94.4	93.1	93.3	91.0	80.5
Median, %	100	100	94.8	100	98.7	90.8	83.7
Range, %	91.7–100	91.7–100	84.5–100	72.2–100	70.4–100	87.3–96.7	55.6–92.0

25 mg t.i.d., as well as 50 mg b.i.d., proved to be superior to 25 mg b.i.d. ($p<0.05$). A significant difference between the three groups could not be established until after 8 weeks' therapy; i.e. 50 mg b.i.d. produced a better amelioration than 25 mg t.i.d. and 25 mg b.i.d. ($p<0.05$ and $p<0.01$, respectively), and 25 mg t.i.d. produced a better amelioration than did 25 mg b.i.d. ($p<0.05$). All these comparisons were tested with a rank sum test [3].

2 patients in the 25 mg t.i.d. group, and 1 patient in the 50 mg b.i.d. group had to have their treatment withdrawn before 8 weeks of therapy due to side effects. For the same reason, 1 patient in the 25 mg t.i.d. group had the treatment changed to 25 mg b.i.d. after 4 weeks. 1 patient in the 25 mg t.i.d. group, and 5 in the 50 mg b.i.d. discontinued therapy before 8 weeks since complete or almost complete remission was obtained.

After the first 8 weeks 13 patients from all three dosage groups received no treatment at all, but were followed for another 2 months with a PASI rating approximately every 2nd week. As seen in table II, the favorable clinical results that were obtained, however gradually deteriorated, but any significant difference between the psoriatic status after therapy, and the status during the follow-up period cannot be seen until 6 weeks after end of therapy ($p<0.05$, rank sum test) [3].

Side Effects

Side effects were frequent, but usually mild and completely reversible after cessation of therapy. A trend towards a possible dose-related severity

Table III. Distribution of side effects within the different dosage groups

	Dosage group		
	25 mg b.i.d.	25 mg t.i.d.	50 mg b.i.d.
Side effects			
Cheilitis	7	10	10
Dryness of nasal and/or oral mucous membranes	3	3	5
Erosions of muc. membranes	1	2	5
Palmoplantar desquamation	2	2	3
Pruritus	2	2	2
Alopecia	–	1	3
Erythema of healthy skin	–	2	1
Conjunctivitis	–	1	1

of side effects was observed, but the differences were not statistically significant. Cheilitis was reported by all 27 patients. 11 patients complained of dryness of nasal and/or oral mucous membranes. Palmoplantar desquamation was seen in 7 patients. Pruritus was reported by 6 patients. Alopecia was recorded in 1 patient. Erythema of the healthy skin was seen in 3 patients. Conjunctivitis was seen in 1 patient, and finally, erosions of the mucous membranes occurred in 8 patients. No laboratory abnormalities were recorded. The distribution of side effects within the different dosage groups can be seen in table III.

Discussion

In spite of the fact that the patients were ambulatory, and thus might have used additional topical therapy, there is no doubt that Ro 10–9359 is an extremely active oral antipsoriatic drug. The clinical response is dose-related, as a more rapid amelioration was observed after administration of 25 mg t.i.d. and 50 mg b.i.d. as compared with 25 mg b.i.d. The overall results also indicate a better antipsoriatic efficacy, when the patients are treated with higher doses of Ro 10–9359. Our results seem to be in good agreement with those reported earlier [5, 6, 9].

The side effects registered in this study are similar to those occurring in vitamin A hypervitaminosis. The patients who developed dry lips were somewhat helped with topical application of petrolatum. Despite the high incidence of side effects the majority of the patients were very positive to treatment with this oral retinoid. However, this treatment is only suitable in severe cases of psoriasis, even though no laboratory abnormalities were noted.

In order to evaluate the effect of systemic treatment it was found necessary to develop a more specific score system, than what is used in most clinical studies of topical antipsoriatic drugs, i.e., 'bad, moderate, good, excellent', as it is essential not to take merely the severity of individual lesions into consideration, but also the areas involved. The PASI was found to be a simple and useful tool to assess the effect of the various dose levels, in our mind much superior to global evaluation. The PASI score is not to be regarded as an 'exact' numerical value, since the severity rating is subjective. However, we found it to be a good basis for judging the effect of a systemic drug in the treatment of psoriasis, particularly when a limited number of patients are involved as was the case in this dose-finding pilot study.

References

1 BOLLAG, W.: Antitumor effect of a new retinoic acid analogue. Experientia *30:* 1198–1200 (1974).

2 BOLLAG, W.: Therapeutic effects of an aromatic retinoic acid analogue on chemically induced skin papillomas and carcinomas of mice. Eur. J. Cancer *10:* 731–737 (1974).

3 DIXON, W. and MASSEY, F.J.: Introduction to statistical analysis (Wiley, Chichester 1957).

4 Editorial Comment: Vitamin A and cancer prophylaxis. Br. med. J. *ii:* 2–3 (1976).

5 ORFANOS, C.E. and RUNNE, U.: Systemic use of a new retinoid with and without local dithranol treatment in generalized psoriasis. Br. J. Derm. *95:* 101–103 (1976).

6 OTT, F. und BOLLAG, W.: Therapie der Psoriasis mit einem oral wirksamen neuen Vitamin-A-Säure-Derivat. Schweiz. med. Wschr. *105:* 439–441 (1975).

7 RUNNE, U.; ORFANOS, C.E. und GARTMANN, H.: Perorale Applikation zweier Derivate der Vitamin-A-Säure zur internen Psoriasis-Therapie. 13-cis-beta-Vitamin-A-Säure und Vitamin-A-Säure rethylamid. Arch. Derm. Forsch. *247:* 171–180 (1973).

8 RYSSEL, H.J.; BRUNNER, K.W. und BOLLAG, W.: Die perorale Anwendung von Vitamin-A-Säure bei Leukoplakien, Hyperkeratosen und Plattenepithelkarzinomen. Ergebnisse und Verrträglichkeit. Schweiz. med. Wschr. *101:* 1027–1030 (1971).

9 SCHIMPF, A.: Zur systemischen Anwendung eines aromatischen Vitamin-A-Säure-Derivates (Ro 10–9359) bei Psoriasis und Keratosen. Z. Hautkr. *51:* 265–274 (1976).

10 SCHUMACHER, A. und STÜTTGEN, G.: Vitamin-A-Säure bei Hyperkeratosen, epithelialen Tumoren und Akne. Dt. med. Wschr. *96:* 1547–1551 (1971).

11 STÜTTGEN, G.: Oral vitamin A acid therapy. Acta derm.-vener., Stockh. *55:* suppl. 74, pp. 174–179 (1975).

T. FREDRIKSSON, MD, Department of Dermatology, Central Hospital, *S–721 89 Västerås* (Sweden)