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Arotinoid Ethyl Ester (RO 13-6298): A Long Term Pilot Study in Various Dermatoses

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The arotinoid ethyl ester Ro 13-6298 is a third generation retinoid shown to be thousand-fold more potent than etretinate (Tigason®, Tegison®) in animal testing and in human therapy. In an open uncontrolled trial, we treated 57 patients suffering from psoriasis (32) and various severe skin disorders (25) with daily doses ranging from 20 to 150 μg, during 1 to 130 weeks (mean = 12 weeks). Four patients were treated for 1 year or more. Given in μg per kg range, Ro 13-6298 showed a spectrum of clinical activity and mucocutaneous side effects similar to that of etretinate given in mg per kg range. One patient developed diffuse idiopathic skeletal hyperostosis after 2 years of continuous therapy. No increase in either serum triglycerides or cholesterol levels was observed, even in patients treated for 33 to 130 weeks. This might prove to be an advantage of this new retinoid. Furthermore, this series suggests that potent mucocutaneous (therapeutical and side) effects are not necessarily linked to all other signs of retinoid toxicity. *Key words: Retinoids; Serum lipids; Side effects.* (Received July 19, 1986.)

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The arotinoid ethyl ester Ro 13-6298 is a polyaromatic synthetic retinoid which belongs to the third generation of retinoic acid derivatives. Up to date, it is the most potent synthetic vitamin A derivative, with a thousand-fold greater activity than etretinate (Tigason®, Tegison®) in producing regression of skin papillomas in mice (1). However, the toxicity score between the antipapilloma activity and the toxic hypervitaminosis A syndrome is the same for both retinoids (1). In humans, the therapeutic properties of Ro 13-6298 are not well established so far, but oral daily doses of about 100 μg have been shown to be effective in psoriasis (2, 3), psoriatic arthropathy (4), and in precancerous and cancerous conditions of the skin (5, 6), including cutaneous T cell lymphomas (7).

In preliminary studies on 25 patients (8), we observed good efficacy of Ro 13-6298 in psoriasis but an absence of significant sebosuppressive and antiacneic effects (9), as well as a lack of influence on serum lipid levels. Because increases in cholesterol and triglycerides and reduction in high-density lipoproteins are well-established side effects of synthetic retinoids (10–19), and might be associated with an increased risk of atherosclerosis and thus of coronary heart disease (20, 21), the lack of serum lipid alterations under Ro 13-6298 therapy could be an important therapeutic advantage of this drug over other retinoids when long term treatment is needed. We, thus, extended this study to 57 patients, some of whom have been now treated for one year or more.

PATIENTS AND METHODS

Fifty-seven patients (37 males and 20 females) (Table I) have been treated with the arotinoid ethyl ester Ro 13-6298 between October 1982 and April 1985. Nine out of the 20 female patients still

belonged to the fertile age group. The age of the patients varied from 21 to 87 years (mean and standard deviation: 49.2 ± 13.8 years). Thirty-two patients suffered from psoriasis, including 6 with psoriatic arthropathy, and others from various skin disorders listed in Table I. Most of the patients were resistant to other conventional therapies including etretinate (Tigason®, Tegison®) or etretin. Ro 13-6298 was started immediately following etretinate or etretin in 5 patients, two weeks after stopping etretinate in 2 patients and in 9 additional patients, 3 to 15 months (mean 8.2 months) after etretinate. Informed consent was obtained from all patients and the protocol was approved by the hospital ethical committee.

Arotinoid ethyl ester was administered orally initially at doses of approximately 1 μg/kg body weight/day for 2 to 4 weeks. The dosage was then adapted for each patient to produce the best therapeutic response while minimizing the mucocutaneous side effects. The mean daily dosage of each patient was 68 μg (±56 μg). The treatment duration ranged from 1 to 130 weeks (median 12 weeks). Four patients (2 psoriasis, 1 prurigo nodularis, 1 multiple actinic keratoses) were treated for 1 year or more. Five patients were treated for 4 weeks or less. In most of the patients other therapies had to be added, usually 2 weeks after monotherapy with Ro 13-6298.

For psoriasis, 9 patients received concomitantly PUVA, 2 UVB, 7 topical anthralin and 7 topical corticosteroids. In the other skin disorders, 6 patients were additionally treated with topical corticosteroids, 2 with systemic corticosteroids, 3 with topical nitrogen mustard and 1 with topical 5-fluorouracil and intramuscular interferon. In 19 out of 57 patients no other treatment was given except for emolients.

The treatment was started with most of the patients hospitalized and was then continued in the outpatients department. Clinical assessments and laboratory checks were performed before treatment of Ro 13-6298 and at regular time intervals according to clinical efficacy, tolerance and patient convenience. Patients fasted before blood sampling. Most of the patients had clinical assessments and laboratory checks on at least day 14 and day 31 of the study. The efficacy was judged as follows: excellent, almost all lesions cleared; good, more than 75% improvement; moderate or poor, less than 75% improvement; and none, if no beneficial effect was observed. The side effects were recorded at each check (Table II). The following laboratory parameters were measured: serum triglycerides, cholesterol and liver enzymes (LDH, SGOT, SGPT).

RESULTS

Efficacy

The results are summarized in Table I. The best results were obtained in psoriasis and in palmoplantar pustulosis. Altogether, 66% of the patients with psoriasis showed an excellent or good response. A beneficial effect on swelling and pain of joints was noted in all 3 patients with active psoriatic arthropathy. In lichen planus and prurigo nodularis, a beneficial response was noted in about half of the patients. Concerning skin cancers or related diseases, good effects were noted only in a patient with multiple actinic keratoses. The effect was judged as excellent in one patient with pityriasis lichenoides and another with acrokeratosis verruciformis (Hopf). A flare was observed after 1 week of treatment (20 μg/day) in a patient with epidermolysis bullosa dystrophica. In no patient with cystic acne or acne conglobata, improvement was observed; new acne lesions appeared under Ro 13-6298 treatment (9).

Clinical side effects

The clinical side effects recorded in 54 patients treated for more than 2 weeks are listed in Table II. The most common mucocutaneous side effects were dryness of mucous membranes (lips, mouth, nose) especially dryness of the lips which occurred in 89% of the treated patients. The treatment had to be interrupted in 7 patients (13%) because of severe side effects: pruritus in 4 cases; scaling, hair loss and retinoid dermatitis in one case each respectively.

A serious effect possibly related to the drug was noted in a 62-year-old male psoriatic

Table I. *Therapeutic effect of arotinoid ethyl ester Ro 13-6298 (57 patients treated)*[a]

Diagnosis	No. pat.	Excell.	Good	Mod./ Poor	None	Not evaluable
Psoriasis						
Vulgaris en plaque	23	8	9	5	1	0
Vulgaris guttata	3	1	0	1	1	0
Vulgaris inversus	1	1	0	0	0	0
Palmoplantar	3	1	0	2	0	0
Erythrodermic	2	0	1	1	0	0
Arthropathy	6[b]	1	2	0	0	3
Palmoplantar pustulosis	3	1	1	1	0	0
Acne						
Congl./cystic	4	0	0	0	4	0
Lichen planus						
Cutaneous	4	2	0	2	0	0
Oral erosive	1	0	0	1	0	0
Prurigo nodularis	3	1	0	2	0	0
Skin cancer and related diseases						
Mult. act. keratoses	1	0	1	0	0	0
Mult. carc. (BCC+SCC)	2	0	0	1	1	0
Leucoker. of the lip	1	0	0	0	0	1
Bowenoid papulosis	1	0	0	0	1	0
Mycosis fungoides	1	0	0	0	1	0
Cut. T-cell lymphoma	1	0	0	1	0	0
Others						
Pityriasis lichenoid.	1	1	0	0	0	0
Epidermol. bull. dyst.	1	0	0	0	1	0
Acroker. verrucif. (Hopf)	1	1	0	0	0	0

[a] Most patients (32/57) were psoriatics.
[b] Six patients out of the total of 32 psoriatic patients had also psoriatic arthropathy.

Table II. *Clinical side effects of arotinoid ethyl ester Ro 13-6298 and their incidence in 54 patients treated for more than 2 weeks*

Type of side effect	Number of patients	Percentage incidence
Dryness of lips	45	83
Cheilitis/chapped lips	36	67
Dryness of mouth	26	48
Pruritus	25	46
Dryness of nasal mucosa	23	43
Scaling (palms/soles)	18	33
Scaling (healthy skin, elsewhere)	18	33
Facial erythema	17	31
Hair loss	11	20
Sweating	11	20
Conjunctivitis	9	17
Retinoid dermatitis	6	11
Chilling	2	4
Thirst	1	2
Other[a]	3	6

[a] Nausea, dizziness, fatigue, headache, sensation of swelling in the eye area.

Table III. *Effects of arotinoid ethyl ester (Ro 13-6298) on serum lipids and liver enzymes*

Parameters	Upper normal limit	Total no. of patients	Number of patients with abnormal values		Means values ± standard deviation	
			At baseline	End of treatment	Baseline	End of treatment
LDH	240 IU	37	1	0	144.3±41.6	143.5±29.3
SGOT	F 32 IU M 50 IU	53	6	3	30.3±11.7	30.4±12.4
SGPT	F 36 IU M 60 IU	53	7	4	39.5±36.0	33.9±15.8
Cholesterol	7.3 mmol/l	52	3	4	5.52±1.30	5.69±1.06[a]
Triglycerides	2.1 mmol/l	52	13	9	1.71±0.94	1.62±0.81

[a] Not statistically significant: d=p>0.05.

patient after treatment for more than 2 years at a daily dose of 50 to 100 µg. Such a treatment was justified by the fact that this patient had severe erythrodermic psoriasis, unresponsive to etretinatePUVA and had previously received large amounts of methotrexate. He was free of lesions while on Ro 13-6298 treatment. Clinically, severe rigidity of the cervical, dorsal and lumbar spine, without involvement of limb joints, occurred between October 84 and June 85, after several months of pain in the back. X rays showed clear signs of ankylosing vertebral hyperostosis (maladie de Forestier or diffuse idiopathic skeletal hyperostosis). Between October 1984 and June 1985, aggravation was marked in the cervical spine with numerous bony bridges between vertebrae C4, 5, 6 and 7. In the dorsolumbar spine, parasyndesmophytes were noted. Tomographies of the sacroiliac joints showed partial fusion of the joint surface.

Laboratory findings

The values of serum lipids and liver enzymes are listed in Table III. These parameters were not significantly affected by the treatment. No patient had to interrupt therapy because of laboratory abnormalities. In Table IV, details on serum cholesterol and triglyceride levels are summarized, with grouping of patients according to the duration of treatment. There was no significant increase of either serum cholesterol or triglycerides even in the 10 patients treated over 33 weeks and for up to 130 weeks.

Table IV. *Detailed cholesterol and triglyceride levels, and duration of treatment*

Duration time of treatment (weeks)	Number of patients	Mean arotinoid 13-6298 dosage/day µg±SD	Cholesterol level (mmol/l)±SD		Triglyceride level (mmol/l)±SD	
			Baseline	End of treatment	Baseline	End of treatment
1 to 8	10	64.75±22.47	5.36±0.78	5.12±0.78	1.32±0.67	1.04±0.41
9 to 16	23	64.80±18.76	5.69±1.29	5.77±1.01[b]	1.98±1.07	1.72±0.70
17 to 32	9	56.83±15.71	5.77±1.96	6.41±1.28[b]	1.93±0.94	1.93±1.40
≥33[a]	10	59.6 ±19.13	5.07±1.12	5.47±0.96[b]	1.28±0.69	1.67±0.49[b]

[a] Mean 55 weeks, up to 130 weeks.
[b] Unpaired t-test: difference statistically not significant.

DISCUSSION

Since this was an open and uncontrolled pilot study, it does not allow complete analysis of the value of Ro 13-6298 in dermatological therapy. It serves however to outline the potential spectrum of activity and side effects of this new synthetic retinoid.

Our observations, in terms of therapeutical values are in agreement with previous studies based on limited open series (2–4; 7, 19, 22, 23). By and large, it can be said that, given in μg range per kg, Ro 13-6298 has a spectrum of clinical activity similar to that of either etretinate (Tigason®, Tegison®) or etretin (Ro 10-1670) which are given in mg range per kg. Even if some patients who were poor responders to etretinate or etretin were found to do better with Ro 13-6298, this greater therapeutic benefit should be further analysed by controlled studies. Side effects were very similar to those induced by etretinate, etretin and isotretinoin (except for blood lipids, see further). Mucocutaneous side effects were of the same nature and occurred, with variations from patient to patient, when the dose of about 1 μg/kg was reached. This agrees very well with the observations made in animals and further confirms the value of the "therapeutic ratio" described by Bollag (1). Diffuse idiopathic hyperostosis occurred in one patient with severe psoriasis after a maintenance treatment of two years. Therefore, it appears that Ro 13-6298 exerts potent retinoid type (therapeutical and side) effects in humans at a dosage a thousand times lower than that of isotretinoin and etretinate/etretin; contrary to other synthetic retinoids no alterations in blood lipid were seen.

Synthetic retinoids induce disturbance of lipid metabolism including an increase of VLDL-triglycerides and LDL-cholesterol levels and a decrease of HDL-cholesterol levels (10–19). This occurs in up to 25% of the patients treated and is reversible after arrest of treatment. This is not only true for etretinate and isotretinoin, but also for etretin (Ro 10-1670) which is the main and active metabolite of etretinate (24). According to Gollnick et al. (19), there is no relationship between the serum lipid alterations and synthetic retinoid dosage. In this study we did not observe any alterations of either serum cholesterol or triglyceride levels under arotinoid Ro 13-6298 even in 10 patients who have been treated for more than 6 months (33 to 130 weeks; mean: 55 weeks). This confirms the data previously reported with shorter treatment periods (2–4, 7, 19, 22, 23). Furthermore, in some patients, abnormal values which developed under etretinate or etretin therapy returned to normal values under arotinoid Ro 13-6298.

Therefore, while exerting a potent therapeutic action and inducing almost all the other side effects observed with the other synthetic retinoids, Ro 13-6298 was not found to cause detectable alterations of triglyceride levels. It appears, therefore, that a dissociation might exist between the effects of these compounds on mucocutaneous tissues and on lipid metabolism. This is an important observation which, if it is confirmed by a detailed analysis of the various lipoproteins fractions, could prove to be very significant when its mechanism is analysed in depth. Indeed, the future of synthetic retinoid therapy has been said to be in the tailoring of new drugs with lower side effects than those presently available (1). The understanding of why Ro 13-6298 does not induce an increase of triglycerides may be one important step in this direction.

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