ma proteins (6). Our impression was that the fluorescence seen in the psoriatic epidermis (especially in the parakeratotic horny layer) quite closely resembled that seen in control sections stained with anti-rabbit IgG conjugate only. We therefore think that this fluorescence is not caused by fibronectin alone but is largely a result of unspecific binding. In part it may represent the staining of autoantibodies against stratum corneum antibodies, as speculated by Fyrand (2).

Fibronectin is produced mainly by fibroblasts (8). Cell culture studies have suggested a stimulating effect of retinoid on fibronectin synthesis in fibroblasts. Retinoic acid induced the formation of cell surface-associated fibronectin in fibroblasts, which was accompanied by increased cell-to-substratum adhesiveness (4). Even in chick embryo chondrocyte culture a fibronectin-like surface glycoprotein was reported to be induced by retinoic acid (3). Under etretinate treatment, dermal fibroblasts show enhanced cytoplasmic activity (9). In the beginning of the treatment of psoriasis, fibronectin seemed to accumulate in the DEJ, suggesting that retinoid has a stimulatory effect on fibronectin formation in vivo, too.

Retinoids are also known to be able to modulate glycoprotein synthesis in biological membranes by inducing the incorporation of various sugar residues into glycoproteins (1), which might be one mechanism accounting for the effect of retinoid on fibronectin. This ability of retinoids has also been suggested to be a conceivable mechanism for the increase in fine granular, possibly mucoid material in the intercellular space of the psoriatic epidermis during the initial phase of treatment with etretinate (5). In our patients no fibronectin appeared in the epidermis during etretinate treatment, which suggests that the above-mentioned material does not consist of fibronectin-like cell surface-associated glycoprotein. Keratinocyte culture studies might give additional information about this subject.

So far, it is impossible to say whether the increase in fibronectin plays any part in the healing process. It may be only a secondary sign of the stimulatory effect of etretinate on dermal cells, especially fibroblasts, or it may be related in part to the previously observed oedematous changes in DEJ with rarefication of anchoring fibrils during initial etretinate treatment. On the other hand, it might have some influence on the dermo-epidermal interaction.

REFERENCES

1. DeLuca, L.: The direct involvement of vitamin A in glycosyl transfer reactions of mammalian membranes. Vitam Horm *35:* 1, 1977.
2. Fyrand, O.: Studies on fibronectin in the skin. II. Indirect immunofluorescence studies in psoriasis vulgaris. Arch Dermatol Res *266:* 33–41, 1979.
3. Hassel, J., Pennypacker, J., Yamada, K. & Pratt, R.: Changes in cell surface proteins during normal and vitamin A-inhibited chondrogenesis in vitro. Ann NY Acad Sci *312:* 406, 1978.
4. Jetten, A. M., Jetten, M. E. R., Shapiro, S. S. & Poon, J. P.: Characterization of the action of retinoids on mouse fibroblast cell lines. Exp Cell Res *119:* 289–299, 1979.
5. Kanerva, L., Lauharanta, J., Niemi, K.-M. & Lassus, A.: Fine structure of the intercellular space of psoriatic epidermis during retinoid (Ro 10–9359) and retinoid–PUVA treatment. Acta Dermatovener (Stockholm) *61:* 319, 1981.
6. Kimura, S. & Nishikawa, T.: A further study on the mechanism of deposition of plasma protein in psoriatic scale. Arch Dermatol Res *268:* 79–84, 1980.
7. Lauharanta, J.: Retinoids in the treatment and prevention of dermatoses and epithelial neoplasias. Ann Clin Res *12:* 123–130, 1980.
8. Ruoslahti, E. & Vaheri, A.: Interaction of soluble fibroblast surface antigen with fibrinogen and fibrin. Identity with cold insoluble globulin of human plasma. J Exp Med *141:* 497, 1975.
9. Tsambaos, D. & Orfanos, C.: Effects of oral retinoid on dermal components in human and animal skin. *In* Retinoids. Advances in Basic Research and Therapy (ed. C. Orfanos et al.). Springer-Verlag, Berlin, 1981.
10. Vaheri, A. & Mosher, F.: High molecular weight, cell surface-associated glycoprotein (fibronectin) lost in malignant transformation. Biochim Biophys Acta 516: 11, 1978.

A Three-year Follow-up Study of Psoriasis Patients Treated with Low Dosages of Etretinate Orally and Corticosteroids Topically

Machiel K. Polano,[1] Hendrik J. van der Rhee[2] and Jan Gerrit van der Schroeff[1]

[1]Department of Dermatology, University Medical Center, 2333 AA Leiden, and [2]Department of Dermatology, Leyenburg Hospital, The Hague, The Netherlands

Received November 10, 1981

Abstract. Etretinate 0.5 mg/kg body weight combined with 0.1% triamcinolone acetonide and 5% salicylic acid in an O/W cream gave more than 70% improvement in

Table I. *Results of combined treatment with low dosages of etretinate orally and corticosteroids topically*

Very good: at least 80% improvement; good: 70–80% improvement; moderate: 50–70% improvement; poor: <50% improvement

			Condition at the time of evaluation					
	No. of pat.	No. of drop-outs	Very good	Good	Mode-rate	Poor	Daily dosage etretinate (mg/kg)	Weekly dosage cream (g)
Start of trial	87							
After 18 weeks	75	12	39	15	10	11	0.5	≤100
After 1 year	59	16	20	17	18	4	0.1–0.3	5–50
After 2 years	43	16	20	11	10	2	0.1–0.3	5–50
After 3 years	29	14	12	10	3	4	0.1–0.3	5–50

62% of 75 patients. Of this satisfactorily improved group, at least 41% were still in the same condition after 3 years on a maintenance dose of, on average, 0.3 mg/kg body weight etretinate daily and 20 g weekly of a relatively strong corticosteroid cream. The side effects were acceptable and the convenience for the patients is great as compared with other treatments.

The evaluation of a new form of therapy generally occurs in a number of consecutive steps. After the necessary pharmacological and toxicological studies, a pilot study is undertaken to gain an impression as to whether the short-term results of the drug are satisfactory and whether the benefits outweigh the side effects. The next step is a double-blind trial to establish the therapy's value relative to the best treatment available until then. This is the type of trial that is most frequently reported in the medical literature. However, follow-up studies on the long-term results and chronic toxicity are equally necessary. This is true especially for chronic diseases such as psoriasis, in which the treatment is symptomatic, and we must be content with the induction and maintenance of remissions.

In this paper we report a follow-up study performed on psoriasis patients to evaluate treatment with a combination of etretinate (Tigason®, aromatic retinoid, Ro 10-9359) given orally and corticosteroid creams, topically. In 1978, we reported (1) on the results of a pilot study in which 1 mg/kg etretinate as monotherapy at the dosage recommended by Ott & Bollag (1975), gave good therapeutic results, but also side effects which in our opinion were unacceptable. At the time, a lower oral dosage combined with 0.1% triamcinolone acetonide and 5% salicylic acid in a cream, topically, seemed to give good therapeutic results, the side effects being acceptable.

In 1980, we reported (2) on a double-blind 6-week trial and a consecutive 12-week open trial in which this combined treatment was used in 87 patients with at least 15% involvement of the skin. These patients had previously been treated with various currently accepted therapies, including potent topical corticosteroids under plastic and in 13 cases even with PUVA. In this series, 62% of the patients showed more than 70% improvement, including 10% with complete clearance and 35% showing an improvement of 90%.

Table II. *Reasons for dropping out, for each period*

Period	Side effects	Inadequate improvement	Other reasons	Specification of the side effects	
18 weeks	4	0	8	Cheilitis and dry nose	4
1 year	5	5	6	Alopecia	3
				vocal nodules	1
				Palmo-plantar desquamation and dry lips	1
2 years	5	6	5	Gastric complaints	4
				Alopecia	1
3 years	0	9	5		

Table III. *Most frequently observed side effects*

	Dry lips	Dry nose	Alopecia	Epistaxis	Pruritus	Paronychia	Atrophy
18 weeks	53	15	3	2	17	1	2
18 weeks – 1 year	13	2	13	1	9	1	1
2 years	9	0	2	0	0		1
3 years	15	1	0	2	0	1	11

In November 1980 we discussed the results obtained in the same cohort over one and 2 years (3), and we now present data on this (inevitably depleted) cohort for the third year. As Table I shows, after 3 years 22 (41%) of the 54 patients who responded satisfactorily to the initial treatment are still in a very satisfactory condition (more than 70% improvement) on a maintenance regime comprising on average 0.3 mg/kg etretinate daily and a weekly dose of on average 20 g corticosteroid cream. It is of course impossible for anyone to adhere to an absolutely rigid schedule for 3 years. When the condition clears up the patient naturally uses less cream and we try to lower the dosage of etretinate. Sometimes the oral treatment is stopped. Relapses respond well to an increase in or resumption of the oral therapy. Generally, we are able to establish, in cooperation with the patient, the dosage at which the therapeutic results balance the side effects. When only a few dime-sized patches persist, we prefer to give a stronger steroid cream, generally betamethasone-17-valerate cream (Betnovate) or clobetasol-17-propionate (Dermovate), rather than increase the dose of etretinate. To economize on topical steroids we give the patients a bland cream as well to use as an emollient.

Table II gives the reasons for dropping out. The distinction between side effects, inadequate results (cases where the decision to stop the treatment was taken after discussion with the patient), and 'other reasons' is difficult to make. Furthermore, several patients left the region and others did not keep their appointments. In the later group, side effects and inadequate results may have played a role too, but also a number of them might have been in a satisfactory condition.

Table III gives the most frequently observed side effects. Alopecia occurred chiefly between the third and ninth month. After that, it was rare, of course, those who were most sensitive having already dropped out, and the maintenance dose was generally lower than the initial one. It is remarkable that during the second year, 4 patients dropped out because of gastric complaints which could not be more precisely defined and which disappeared after discontinuation of the treatment.

The relatively high incidence of dry lips after 3 years might be explained by the fact that we specifically asked at that time about this symptom; otherwise, we noted only spontaneous complaints.

Because at an earlier presentation of our results objections were made to the prolonged use of topical corticosteroids, we paid special attention to possible topical side effects arising from this part of the therapy. The weekly dose of cream was unquestionably far below the amount that causes systemic effects.

One of the difficulties in the evaluation of skin atrophy was that at the start of the treatment many of the patients already had marked atrophy due to previous intensive topical corticosteroid treatment. Several of them remarked spontaneously that during the combined treatment the pre-existing atrophy had diminished. At the last evaluation we paid special attention to this symptom. In 9 patients we found patches of moderate atrophy, chiefly on the lower legs and the backs of the hands and 8 of them occasionally showed bruises as well; 2 other patients showed marked atrophy.

In all patients comprehensive laboratory tests were carried out. Since elevation of the triglyceride levels has been reported (4), triglyceride and cholesterol determinations were made during the last year. Four patients showed a slight increase in triglyceride level, the highest value being 2.30 mmol/l. It is open to doubt whether this finding is of any pathological importance. Laboratory data and other findings during the first and second years have been published elsewhere (1, 2, 3).

From our findings over a period of 3 years, we conclude that in 62% of our patients with extensive, persistent psoriasis, a combination of 0.5 mg/kg etretinate and relatively small amounts of topical 0.1% triamcinolone acetonide and 5% salicylic acid

in O/W cream without occlusion gave very satisfactory initial results (4 months). After 3 years on a dosage ranging from 0.1 to 0.3 mg/kg etretinate, combined with topically applied steroids of the two most potent classes at, on average, 20 g a week, 41% of those who did well after the initial treatment were still in a good condition.

The question remains as to whether the absence of relapses in a proportion of our patients was due to the maintenance treatment or to spontaneous remissions. Data on untreated psoriasis patients followed up for 3 years are lacking, for obvious reasons. Vella Briffa et al. (5) reported that the proportion of patients who can be expected to be in a good condition 16 months after clearing by dithranol treatment without further therapy is about 20%.

We found (Table I) after 2 years that at least 20 (51%) of the 39 patients whose condition was evaluated as 'very good' after the initial treatment were just as well 2 years later. Although it is not possible to compare these two sets of data by statistical methods, they point to a favourable effect of the maintenance treatment. A similar indication is given by the finding that incipient relapses reacted favourably to an increase in both the oral dosage and the topical theraphy.

The proposed treatment offers a valuable addition ot the available treatment modalities for psoriasis, affords results comparing favourably with dose obtained with PUVA, UVB, Dithranol, or other combinations with etretinate (Re-PUVA, Re-UVB, and Re-anthralin), is also more convenient for the patient and is safer, provided that women of child-bearing age use a safe form of contraception.

ACKNOWLEDGEMENTS

The authors wish to thank Hoffmann-La Roche (Mijdrecht, The Netherlands) for providing the etretinate (Tigason®) capsules throughout the trials; M. A. C; van den Dries, M. D., for his cooperation in the organization of the trial; and Prof. H. de Jonge, Department of Medical Statistics of the Leiden University Medical Centre for his valuable advice.

REFERENCES

1. Polano, M. K. & Van der Rhee, H. J.: Ro 10-9359 and corticosteroids. Int Psor Bull *5:* 1, 1978.
2. Ott, F. & Bollag, W.: Therapie der Psoriasis mit einem oral wirksamen neuen Vitamin-A-Säure-Derivat. Schweiz Med Wochenschr *105:* 439, 1975.
3. Van der Rhee, H. J., Tijssen, J. G. P., Herrman, W. A., Waterman, A. H. & Polano M. K.: Combined treatment of psoriasis with a new aromatic retinoid (Tigason®) in low dosage orally and triamcinolone cream topically: a double-blind trial. Br J Dermatol *102:* 203, 1980.
4. Van der Rhee, H. J. & Polano, M. K.: Treatment of psoriasis vulgaris with a low dosage Ro 10-9359 (Tigason®) orally combined with corticosteroids topically. *In* Retinoids. Advances in Basic Research and Therapy (ed. C. E. Orfanos), pp. 193–201. Springer, Berlin, 1981.
5. Gollnick, H.: Elevated levels of triglycerides in patients with skin disease treated with oral aromatic retinoid. The significance of risk factors. *In* Retinoids. Advances in Basic Research and Therapy (ed. C. E. Orfanos), pp. 503–506. Springer, Berlin, 1981.
6. Vella Briffa, D., Greaves, M. W., Warin, A. P., Rogers, S., Marks, J. & Shuster, S.: Relapse rate and long-term management of plaque psoriasis after treatment with photochemotheraphy and dithranol. Br Med J *282:* 937, 1981.

More comprehensive bibliography in refs. 1, 3 and 4.

Onychotillomania Treated with Pimozide (Orap®)

Knud Hamann

Department of Dermatology, Gentofte Hospital, DK-2900 Hellerup, Denmark

Received December 9, 1981

Abstract. A case of onychotillomania in a 70-year-old woman is presented. The disease had persisted for 5½ years. All her fingernails were plucked away. The patient had a fixed hypochondrial delusion of nail disease. After treatment with pimozide (Orap®) for 7 months the nails were normal.

Key words: Onychotillomania; Paranoia hypochondriaca; Pimozide (Orap®)

Very few cases of onychotillomania have been published (1, 2). The condition is usually regarded as a manifestation of a compulsive neurosis (1, 2) though Combes & Scott (1951) presented a case of delusions of infestation where the symptoms were focused on the nails.

CASE REPORT

A 70-year-old woman with no previous psychiatric disease was referred because of a nail disease of 5½ years' dura-