

ORAL RETINOID AND UVB RADIATION: A NEW, ALTERNATIVE TREATMENT FOR PSORIASIS ON AN OUT-PATIENT BASIS

Constantin E. Orfanos, Gerd K. Steigleder, Helmut Pullmann
and Peter H. Bloch

Department of Dermatology, University of Cologne, Cologne, Western Germany

Abstract. The combined application of an oral retinoid (Ro 10-9359) and phototherapy with predominantly UVB radiation (Selective Ultraviolet Phototherapy=SUP) is a new, highly effective method of treating psoriasis. It has few side effects and can be performed on an out-patient basis. With the aid of this combined treatment we achieved good or very good improvement in 19 out of 23 patients with generalized psoriasis (=82.6%). The average number of radiation sessions required to achieve this was 22.9, and the mean total therapeutic dose (TTD) was 73 J/cm². In a control group of 40 psoriasis patients, who received only radiation therapy, we achieved good or very good results in only 60% with an average of 26 radiation sessions and 94 J/cm² TTD. The effect of the oral retinoid and UVB radiation therapy is apparently additive, since the retinoid does not increase the sensitivity of the skin to light.

Key words: Psoriasis; Therapy; Retinoid; Vitamin A acid; UVB radiation

The traditional antipsoriatic agents, such as *anthralin*—usually in combination with salicylic acid (9), and *tar*—usually in combination with UV radiation (4), were joined in the sixties by fluorinated corticoids and methotrexate. However, while traditional therapy continues to be used and improved upon, corticoids and cytostatics are being used less and less in the therapy of psoriasis.

Recent years have seen the advent of two new possible ways of treating patients with generalized psoriasis: *photochemotherapy* with psoralens and UVA radiation (PUVA) in its two variants—"PUVA external" (7, 17) and "PUVA internal" (14), and the administration of an aromatic oral retinoid (Ro 10-9359), which was found to be surprisingly effective both alone and in combination with other antipsoriatic agents (8, 10, 13).

The combination of the new retinoid with UV radiation or with external measures in particular appears to be promising for the future. In a recent

study we were able to demonstrate that the oral retinoid administration can be combined with PUVA, leading to (a) an enhancement of its clinical efficacy, (b) a reduction of the total radiation dose, and (c) a reduction of the duration of treatment (*RePUVA*, 11). In the present study we have combined the administration of a retinoid with *UVB radiation* at 292.5–330 nm (Selective Ultraviolet Phototherapy=SUP), which exerts an antipsoriatic effect even by itself.

Our objective was to avoid the oral use of psoralens, which interfere with the DNA of diseased and healthy cells and are still generally considered to be a therapeutic risk for the patients.

PATIENTS AND METHODS

23 patients with extensive psoriasis vulgaris were selected for the combined therapy with oral retinoid administration and UVB radiation at 292.5–330 nm (*ReSUP*). There were 8 women and 15 men, all aged between 20 and 75 years. At least 10% of the body area was affected by the disease. Thorough laboratory testing before the start of therapy revealed no pathological blood, liver or kidney values and no particular concomitant diseases. The administration of the oral retinoid and the phototherapy were commenced simultaneously, in most cases on an out-patient basis.

Retinoid medication. We administered an aromatic retinoid (Ro-10-9359, Hoffmann-La Roche, Grenzach-Wyhlen) at a dosage of approximately 1 mg/kg body weight per day (=50–75 mg/day; initially 50 mg in the morning and 25 mg in the evening); following therapeutic effect—after about 3 weeks—the dose was reduced to 50 or 25 mg/day and continued at this level for several months as maintenance therapy.

UVB radiation (SUP). The irradiation was performed with the "Saalmann Lamp" (Model SUP-PRW with two reflectors; overall output: 76.3 μ W/cm², G. Saalmann, 4900 Herford, Federal Republic of Germany); the maximum emission of this light source is well within the UVB range, between 292.5 and 330 nm. The energy yield in this spectral range of the continuum at a distance of 100 cm from the filament is approximately 0.45 J/cm² per minute.

Table 1. Results of combined oral retinoid–UVB phototherapy (ReSUP; 290–330 nm) in comparison with a control group treated with UVB radiation (SUP) alone

Therapeutic result	No. of pats.	Number of irradiations	Treatment time (weeks)	Total therapeutic dose (TTD)
<i>ReSUP</i> (n=23 pats.)				
Very good	9	22.9 (4.1/week)	5.5	73 J/cm ²
Good	10 82.6%			
Moderate	4			
None	—			
<i>SUP</i> (n=40 pats.)				
Very good	4	26.0 (3.5/week)	7.5	94 J/cm ²
Good	20 } 60%			
Moderate	13			
None	3			

In comparison, the simultaneously emitted UVA fraction is small, appearing to be negligible from a therapeutic point of view.

In a preliminary experiment the minimal erythema dose (MED) was examined with the Saalman lamp in 4 healthy individuals, without the administration of oral retinoid. In spite of individual differences, on the average, 3–4 min was needed to provoke a slight erythema, corresponding to 1.5–2.0 J/cm². This is a reasonable value compared with MED_{297 nm} = 0.03 J/cm² and to MED_{PuVa (366 nm)} = ca. 2.5 J/cm².

As regards the dosage, we applied the following scheme: Prior to irradiation the skin was moistened with cold-saturated saline solution. For the first 3 days we limited the time of irradiation to 1 min each for the front and back of the body and then, as a rule, increased it daily by 1 min up to a maximum of 15 min per side of the body. Irradiation was performed on 4 to 5 days per week. Following therapeutic success the frequency of the sessions was reduced to once or twice per week as maintenance therapy.

Control group. The control group consisted of 40 patients who were likewise suffering from extensive but usually not very infiltrated psoriasis vulgaris. There were no differences between the treatment group and the control group as regards sex distribution, age etc. The SUP therapy was performed in the same manner in both groups. The clinical result in some of the patients of the control group has been evaluated and reported separately (16). Both groups also received daily topical applications of 2% salicylic acid in petrolatum and 1–2 oil baths per week.

Evaluation. All patients underwent regular medical examination, at least once or twice per week, and the course of improvement was recorded until only slight traces were left at the sites of predilection. Peculiarities, side effects etc. were recorded separately on a patient record form. If the results were not satisfactory after a maximum of 30 radiation sessions, the treatment was terminated and the attempt at therapy was regarded as a failure. In analogy to earlier studies, the assessment was based on the following criteria:

Very good improvement (+++) = complete regression
Good improvement (++) = regression apart from slight traces at the sites of predilection
Moderate improvement (+) = more than 50% of lesions responded, but still distinct traces
No improvement (0) = less than 50% of lesions improved.

Very good and good improvements were regarded as therapeutic success, the others as constitution failures. Psoriatic lesions of the hairy scalp and nail changes were not included in this evaluation.

RESULTS

Table 1 shows the results of treatment in the two groups: Very good or good improvement was achieved in 19 (82.6%) of the 23 psoriatic patients treated with ReSUP, moderate improvement being achieved in the other 4. An average of 22.9 radiation sessions in 5.5 weeks were necessary for this, a mean total therapeutic dose (TTD) of 73 J/cm² from the spectral range 292.5–335 nm being applied during the entire therapy course. In none of the patients was the ReSUP treatment ineffective.

We observed 4 cases of diffuse loss of hair and one case each of headache, severe skin irritation and slight elevation of SGPT (41 I.U.) as short-term side effects of the combined ReSUP therapy. The therapy was terminated prematurely in one patient with a good therapeutic response, because of hair loss—an effect which later proved to be reversible. In the long term, i.e. 6 months after continuing therapy with maintenance doses, no changes of any type were seen in 6 controlled patients.

Of the 40 patients in the control group, who were treated with SUP alone, we achieved very good and

Table II. Correlation of MED and TTD with UVA and UVB sources (approximate values of normal variation range)

	Total therapeutic dose (TTD)	
	Without oral retinoid	With oral retinoid
MED _{297 nm} = 0.03 J/cm ²	No data	No data
MED _{295–330 nm} = 1.5–2.0 J/cm ²	94 J/cm ²	73 J/cm ²
MED _{PUVA (366 nm)} = 2.5 J/cm ²	80–100 J/cm ²	55 J/cm ²

good therapeutic results in 24 cases, i.e. 60%. The result was unsatisfactory in 16 patients. To achieve these results we required an average of 26 radiation sessions in 7.5 weeks, the TTD being 94 J/cm².

No particular side effects were recorded in the control group up to 10 months after the beginning of therapy in 6 controlled patients.

DISCUSSION

Recently synthesized oral retinoids apparently have a favourable effect on psoriatic lesions, the side effects at therapeutic dosages remaining within tolerable limits. With a preparation of this nature we were able to achieve positive results in about 61% of the cases involved in a multicentre controlled study from several dermatological clinics in the Federal Republic of Germany (10). Retinoids can be used with good prospects in erythrodermal and pustular forms in particular, thus avoiding in many cases the systemic administration of corticoids or cytostatics (12). The drug is easy to dose and can be administered on an out-patient basis if there are no concomitant diseases and providing that liver values are checked at regular intervals.

Of particular benefit from a clinical point of view is the fact that, in our repeatedly confirmed experience, oral retinoids can be combined with other techniques of anti-psoriasis treatment—and apparently with an additive effect. These include the simultaneous topical application of anthralin (8) and systemic photochemotherapy (RePUVA; 3, 11). In accordance with this, the oral retinoid Ro 10-9359 can play a special role as a basic *oral adjuvant* in various therapeutic schemes and in various dermatoses with disorders of keratinization.

In this study we combined the oral administration of the retinoid with UVB radiation at 292.5–330 nm

which, as *selective ultraviolet phototherapy* (SUP), is employed with success in psoriasis without the ingestion of a sensitizer (18). With the aid of this type of irradiation Pullman et al. (16) achieved a healing rate of 63%, an average of 100 J/cm² TTD being required in 27.1 radiation sessions. In a larger group of patients, who served as the controls in this study, the success rate of SUP therapy alone was 60% in 26 radiation sessions and with a mean TTD of 94 J/cm². In comparison with these data, the combined retinoid–SUP therapy leads to significantly better results, an improvement rate of 82% being achieved, with a mean TTD of 73 J/cm². The success rates with ReSUP therapy are thus equal to those of systemic PUVA treatment.

However, we can recognize certain important advantages of the *ReSUP therapy* over *PUVA*:

1. Oral retinoids are closely related chemically to physiological metabolites of the body; according to the present state of knowledge, their mechanism of action works independent of cellular DNA. As regards mutagenicity and cancerogenicity they therefore represent less risk than psoralens, let alone cytostatics. In fact, numerous findings even suggest that the retinoid Ro 10-9359 has a canceroprotective effect (1, 2, 5, 19).

2. The TTD required in SUP corresponds fairly well in its biological activity to the TTD given in PUVA (Table II). According to the preliminary experiments performed in this study and our previous investigation with PUVA and RePUVA (11) there is a reasonable correlation between MED and TTD with UVA and UVB sources, in spite of the well known individual differences. Table II shows that in both PUVA and SUP (RePUVA and ReSUP correspondingly) the TTD is approximately 20–40× higher than the corresponding MED. In addition, however, UVA rays penetrate more deeply into the skin than UVB and can, therefore, also exert their effects on circulating blood cells.

3. The ReSUP method is more practical than PUVA. The time-linked ingestion of 8-MOP 1–2 hours before irradiation, the wearing of sunglasses because of the accumulation of the psoralen in the corneal epithelium, the general protection from the sun's rays etc. are all unnecessary with retinoid–UVB therapy. The drug is taken continuously on an out-patient basis regardless of the radiation sessions. The appointments for irradiation are made as is practically convenient for both doctor and patient.

4. Finally, there is no particular difference between the two methods as regards side effects. The only side effect of ReSUP therapy which may lead to discontinuation in individual cases is loss of hair, but this effect is easily recognizable by both the patient and the attending doctor; it is of no particular importance, since the loss of hair is reversible after discontinuation of the drug. Long-term controls after 6 months' continuing therapy with SUP and ReSUP on 12 patients revealed no changes of any type.

Overall, our present experience with the retinoid-UVB technique is still too limited for us to make a final assessment of its more extensive use in practice. At the present time we regard the combined retinoid-UVB therapy as an effective method of treating psoriasis and which can also be performed on an out-patient basis without any particular reservations. Needless to say, the crucial question of long-term side effects still remains to be answered. For more extensive use, UVB light sources should be developed which emit a more constant spectrum and which can be easily managed by the patient or by the assisting personnel for optimal treatment. The new retinoid is to be introduced onto the market in the foreseeable future.

REFERENCES

1. Bollag, W.: Therapeutic effects of an aromatic retinoid analog on chemically induced skin papillomas and carcinomas in mice. *Europ J Cancer* 20: 731-737, 1975.
2. Bollag, W.: Prophylaxis of chemically induced epithelial tumors with an aromatic retinoic acid analog (Ro 10-9359). *Europ J Cancer* 11: 721-724, 1975.
3. Fritsch, P. O., Hönigsmann, H., Jaschke, E., Wolff, K.: Augmentation of oral methoxalen-photochemotherapy with an oral retinoic acid derivative. *J Invest Dermatol* 70: 178-182, 1978.
4. Goeckerman, W. H.: The treatment of psoriasis. Continuing observations on the use of crude coal tar and UV-light. *Arch Derm Syph (Chicago)* 24: 446-450, 1931.
5. Mahrle, G. & Berger, H.: Protective effect of aromatic retinoic acid analog on skin tumor. Paper presented at the Annual Meeting of the European Society for Dermatological Research (ESDR). Amsterdam, April 24th-26th, 1978.
6. Mahrle, G., Orfanos, C. E., Ippen, H. & Hofbauer, M.: Haarwachstum, Leberwerte und Lichtempfindlichkeit unter oraler Retinoid-Therapie bei Psoriasis. DMW, in press.
7. Mortazawi, S. A. M. & Oberste-Lehn, H.: Lichtsensibilisatoren und ihre therapeutischen Fähigkeiten. *Z Hautkr* 48: 1-9, 1973.
8. Orfanos, C. E. & Runne, U.: Systemic use of a new retinoid with and without local dithranol treatment in generalized psoriasis. *Br J Dermatol* 95: 101-103, 1976.
9. Orfanos, C. E. & Steigleder, G. K.: Psoriasis-Therapie mit Cignolin®. Das Kölner CSV-Behandlungsschema. *Z Hautkr* 51: 473-480, 1976.
10. Orfanos, C. E. & Goerz, G. et al.: Orale Psoriasis-Therapie mit einem neuen aromatischen Retinoid (Ro 10-9359). *Dtsch Med Wschr* 103: 195-199, 1978.
11. Orfanos, C. E., Pullmann, H., Sterry, M. & Künzig, M.: Retinoid-PUVA (RePUVA): Systemische Kombinations-Behandlung bei Psoriasis. *Z Hautkr* 53: 494-504, 1978.
12. Orfanos, C. E., Pullmann, H., Runne, U., Kurka, M., Strunk, V., Künzig, M. & Dierlich, E.: Die Behandlung der Psoriasis mit Vitamin A, Vitamin-A-Säure und synthetischen Retinoiden. *Hautarzt*, 1978b, in press.
13. Ott, F. & Bollag, W.: Behandlung der Psoriasis mit einem oral wirksamen neuen Vitamin-A-Säure-Derivat. *Schweiz Med Wschr* 105: 439-441, 1975.
14. Parrish, J. A., Fitzpatrick, G. B., Tanenbaum, L. & Pathak, M. A.: Photochemotherapy of psoriasis with oral methoxalen and longwave ultraviolet light. *New Engl J Med* 291: 1207-1211, 1974.
15. Pullmann, H., Zingsheim, M., Steigleder, G. K. & Orfanos, C. E.: PUVA- und Anthralintherapie der Psoriasis. Ein klinischer, histologischer und autoradiographischer Vergleich. *Z Hautkr* 51: 861-871, 1976.
16. Pullmann, H., Wichmann, A. C. & Steigleder, G. K.: Praktische Erfahrungen mit verschiedenen Phototherapieformen der Psoriasis-PUVA-, SUP-, Teer-UV-Therapie. *Z Hautkr* 53: 641-647, 1978.
17. Tronnier, H. & Schüle, D.: Zur dermatologischen Therapie von Dermatosen mit langwelligem UV nach Sensibilisierung der Haut mit Methoxalen. Erste Ergebnisse bei Psoriasis vulgaris. *Z Hautkr* 48: 385-393, 1973.
18. Tronnier, H. & Heidbüchel, H.: Zur Therapie der Psoriasis vulgaris mit ultravioletten Strahlen. *Z Hautkr* 51: 405-424, 1976.
19. Verma, A. K. & Boutwell, R. K.: Vitamin A acid (retinoic acid, a potent inhibitor of 12-O-tetradecanol-phorbol-13-acetate-induced ornithine decarboxylase activity in mouse epidermis. *Cancer Res* 37: 2196-2201, 1977.

Received September 26, 1978

C. E. Orfanos, M.D.
Professor and Chairman
Dept. of Dermatology
Free University of Berlin
Klinikum Steglitz
1, Berlin 45
FRG