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Oral Retinoids in Mycosis Fungoides and Sézary Syndrome: A Comparison of Isotretinoin and Etretinate

A Study from the Scandinavian Mycosis Fungoides Group

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Thirty-nine patients with mycosis fungoides in various stages or Sézary syndrome were treated with isotretinoin and 29 with etretinate as single drug therapy. Complete remission within 2 months was obtained with isotretinoin in 8 cases (21%) and partial remission in another 15 cases (38%). Etretinate induced complete remission in 5 cases (21%) and partial remission in 11 (46%). Only 1 case with Sézary syndrome went into partial remission. The first sign of remission occurred in 2 to 4 weeks. During continued treatment remissions could not always be maintained. Isotretinoin and etretinate were considered to be of equal potency in the treatment of mycosis fungoides. *Key words: Retinoid dermatitis.*
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The retinoids isotretinoin and etretinate have an effect not only on benign skin disorders but also on some malignant skin tumours. Kessler et al. (1) treated 4 cases of mycosis fungoides with isotretinoin and obtained complete remission in 1 and pronounced improvement in 3 cases. Further, Warrell et al. (2) reported improvement in 3 of 7 patients with cutaneous T-cell lymphoma treated with isotretinoin. Claudy et al. (3) treated 5 patients with mycosis fungoides and 1 with Sézary syndrome of whom 5, including the patient with Sézary syndrome, cleared.

The mechanism of action of retinoids in the prevention and treatment of neoplastic diseases still is largely unknown. Although retinoids stimulate immune responses (4, 5) this is certainly not the only anti-tumour mechanism. The ability of retinoids to modify cell proliferation, differentiation and cell surface receptors (6) may well be of more importance.

Recently we reported the short term results of single drug treatment with isotretinoin in various stages of mycosis fungoides (7, 8). In the present paper we present the results of prolonged treatment with isotretinoin. In addition a comparison has been made between isotretinoin and etretinate treatment in different stages of mycosis fungoides and in Sézary syndrome.

MATERIAL AND METHODS

A total of 65 patients treated with oral retinoids are presented. Thirty-four patients with mycosis fungoides and 5 with Sézary syndrome were treated with isotretinoin (13-cis-retinoic acid, Roaccu-

tan®). Twenty-eight patients with mycosis fungoides and 1 with Sézary syndrome were treated with etretinate (Tigason®) (Table I). The patients were not randomized but the two treatment groups were considered comparable as regards age and sex of the patients as well as duration and extent of the disease. Three cases, 2 with mycosis fungoides and 1 with Sézary syndrome were treated with isotretinoin and later with estretinate. During retinoid therapy no other systemic or topical treatment was given apart from emollients.

Out of sixty cases with mycosis fungoides, 18 were in plaque stage with a histologically suggestive but not conclusive diagnosis of mycosis fungoides (MF stage I). In the remaining patients the diagnosis was histologically verified: 28 were in plaque stage (MF stage II), 12 were in tumour stage without signs of extracutaneous dissemination (MF stage III) and 3 were in tumour stage with lymphomatous involvement of lymph nodes (MF stage IV). Five patients had Sézary syndrome.

The first 10 patients in the isotretinoin treatment series received an initial dosage of 2 mg per kg body weight per day. Because of side effects, the starting dose in the subsequent patients was reduced first to 1 mg in 6 patients and then to 0.5 or 0.2 mg per kg in the remaining 23 patients. In 15 cases the isotretinoin dosage was reduced, from 2 or 1 mg per kg body weight initially to 0.5, 0.3 or 0.2 mg.

Etretinate was initially given in the starting dosage of 1 mg (in 4 patients 0.5 mg) per kg body weight per day. In 4 cases the dosage was reduced to 0.5 or 0.2 mg per kg body weight.

Haematological, liver, renal and blood lipid tests were performed before and during the treatment.

RESULTS

Initial response

Within the first 2 months of treatment, isotretinoin induced complete remission in 8 cases (6 plaque stage, 2 tumour stage) (Table I). Partial remission (more than 50% regression) was seen in 15 cases (10 plaque stage, 4 tumour stage, 1 Sézary syndrome). The later 4 tumour patients had extensive tumours and ulcerations and the partial remission with virtual clearing of the skin lesions was seen after 1 to 2 months. Enlarged lymph nodes due to malignant lymphoma involvement present in 1 of these patients also underwent a regression which was verified by lymphangiography. In 16 cases no response (i.e. regression less than 50%, no change or progression) was observed (8 plaque stage, 4 tumour stage, 4 Sézary syndrome).

Alopecia mucinosa, which was present in 2 cases of mycosis fungoides plaque stage, disappeared completely after a few months of treatment with isotretinoin.

Table I. *Results of isotretinoin and etretinate treatment of mycosis fungoides and Sézary syndrome*

MF stage I: clinical not histological diagnostic mycosis fungoides, MF stage II: mycosis fungoides plaque stage, MF stage III: mycosis fungoides tumour stage, MF stage IV: mycosis fungoides with lymphomatous involvement of lymph nodes. SS: Sézary syndrome. Response to treatment: CR: complete remission, verified by histology, PR: partial remission with >50% regression of lesions, NC: no change or remission <50%, PD: progressive disease

Mycosis fungoides stage	Initial response							
	Isotretinoin				Etretinate			
	Total	CR	PR	NC/PD	Total	CR	PR	NC/PD
I	9	2	3	4	4	1	1	2
II	15	4[a]	7	4	12	3	7[a]	2
III	8	1	3	4	5	1	2	2
IV	2	1	1[a]	–	2	–	1	1[a]
SS	5	–	1	4[a]	1	–	–	1[a]
Total	39	8	15	16	24	5	11	8

[a] 3 patients were treated with isotretinoin and later etretinate.

Among the 24 patients treated with etretinate, 5 cases (4 plaque stage, 1 tumour stage) went into complete remission and 11 cases (8 plaque stage, 3 tumour stage) into partial remission while in 8 patients (4 plaque stage, 3 tumour stage, 1 Sézary syndrome) there was no response during the first 2 months of treatment.

In cases responding to either isotretinoin or etretinate, the first sign of remission was observed already after 2 to 4 weeks of treatment and was usually heralded by diminution of itching.

Of 5 patients with Sézary syndrome treated with isotretinoin, 4 did not respond. A pronounced exfoliation and increased redness of the skin occurred after a few weeks of treatment which then had to be discontinued. One of these patients also experienced the same type of aggravation after a few days of etretinate treatment.

Long-term response

The total duration of treatment with isotretinoin was 1–27 months (median 4 months) and with etretinate 1–25 months (median 3 months). Up to date, in the isotretinoin-treated group, 5 cases (plaque stage) are still in complete remission and 12 cases (7 plaque stage, 4 tumour stage, 1 Sézary syndrome) in partial remission while in 12 (11 plaque stage, 1 tumour stage) there was no response, and in the etretinate treated group 3 cases (2 plaque stage, 1 tumour stage) are in complete remission, 10 cases (8 plaque stage, 2 tumour stage) in partial remission while in 8 (5 plaque stage, 3 tumour stage) there was no response (Table I). Relapse of cutaneous lesions despite continued treatment occurred in 15 cases, 10 on isotretinoin (26%) and 5 on etretinate (22%), and one case on etretinate developed malignant lymph node involvement despite complete remission of the skin, indicating that neither with isotretinoin nor etretinate could prolonged treatment always maintain the patients in remission.

Retinoid dermatitis

In 18 cases of mycosis fungoides an apparently aggravation of the skin was observed after an initial period of regression of the lesions with a clinical picture which resembled superficial mycosis fungoides plaques (9). This retinoid dermatitis was eczema craquélé-like. Histology revealed a benign sparse inflammatory dermal infiltrate without atypical lymphoid cells. This dermatitis which appeared both in the isotretinoin (11/39, 28%) and etretinate (7/24, 25%) treated patients was considered to be a toxic effect of the retinoids and disappeared after reduction of the dosage of the retinoid.

Long-term response

Isotretinoin				Etretinate			
Total	CR	PR	NC/PD	Total	CR	PR	NC/PD
9	2	2	5	4	–	2	2
14	3	5	6	11	2	6	3
4	–	3	1	5	1	1	3
1	–	1	–	1	–	1	–
1	–	1	–	–	–	–	–
29	5	12	12	21	3	10	8

Other side effects

Most of the patients tolerated the treatment. Sometimes, however, the dose had to be reduced due to mucosal or skin dryness. No pronounced increase of blood lipids was observed though in half of the cases treated with isotretinoin a slight increase was noted.

In many cases some hair loss was noticed. In 2 cases of more severe hair loss during etretinate treatment the regrowing hair after reduction of the dosage appeared as pili torti (10).

In 1 case an external otitis, which was considered to have been induced by etretinate, prompted the withdrawal of etretinate. Some months later isotretinoin could be instituted without any problem.

DISCUSSION

In this report we have shown that isotretinoin treatment of mycosis fungoides in various stages resulted in a significant improvement (complete and partial remission) in 23 of 39 cases. Treatment with etretinate induced a similar remission in 15 of 23 cases. The initial response rate is the same for the 2 drugs (59 and 66%, respectively).

In the present series, the response to the retinoid therapy appeared rapidly. The first sign of remission was evident after 2 to 4 weeks. When complete remission was obtained this occurred usually within 2 months. It is our impression that, if no effect is observed within 2 to 3 months, further treatment will be useless.

During continued treatment, however, only 5 patients on isotretinoin (13%) and 3 on etretinate (12%) remained in complete remission for 5 to 20 months, while the majority of patients stayed in partial remission.

Sézary syndrome apparently does not respond to retinoid treatment. On the contrary, 5 of 6 patients experienced a striking aggravation of their erythroderma after a few weeks of treatment.

From the data presented here it is evident that isotretinoin and etretinate are of equal potency in the treatment of mycosis fungoides plaque stage as well as advanced tumour stage. We conclude that both these retinoids are of value in the induction of remission in mycosis fungoides of various stages. It is, however, often impossible to maintain the remission with retinoids alone. Our present view is that the initial treatment of mycosis fungoides should be with retinoids. Depending on the degree of remission, other treatment modalities can eventually be added. Our experience points to an integration of retinoids in treatment regimens with PUVA or systemic chemotherapy (11).

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