Treatment of Localized Scleroderma and Lichen Sclerosus with Etretinate

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Eight patients with lichen sclerosus and 8 patients with localized scleroderma were treated with etretinate (Tigason®) at doses of 0.5 mg/kg body weight for between 3 and 12 months: 2 of 3 patients with juvenile type lichen sclerosus cleared, whereas the lesions of 5 patients with balanitis xerotica obliterans, kraurosis vulvae and extragenital lichen sclerosus were unchanged or even progredient. 2 of the patients with localized scleroderma cleared with

slight atrophy. The lesions of 5 others failed to resolve but progression was halted under continued therapy; after drug withdrawal, the lesions resumed progression in 2 patients. We conclude that only moderate therapeutic effects can be achieved with etretinate in both lichen sclerosus and localized scleroderma. *Key words: Etretinate; Localized scleroderma; Lichen sclerosus.* (Received September 6, 1983.)

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Oral synthetic retinoids are now extensively used in the treatment of a wide spectrum of skin disorders of epithelial differentiation (1, 2, 3), whereas no attempts have been made to survey the potential uses of retinoids in diseases of the connective tissue. As exceptions, Janssen de Limpens (4) reported flattening of hypertrophic scars by topical retinoic acid, and Diller (5) refers to the unsuccessful treatment with etretinate of a sporadic case of localized scleroderma.

In vitro retinoic acid affects mesenchymal cells similarly profoundly as epithelial cells.. Growth of human and animal fibroblasts is inhibited, cell-to-substratum adhesiveness is increased and the synthetic profile of cell surface glycoproteins, glycolipids and glycosaminoglycans is altered (6, 7). Recently, a decrease of collagen production of dermal fibroblasts by retinoic acid has been independently demonstrated by two groups (8, 9). It therefore appears justified to investigate the effects of retinoids on skin diseases characterized by excess collagen formation.

In this paper, we report the results of a pilot study designed to test for relevant therapeutic effects of etretinate (Tigason®) on localized scleroderma (LS) and lichen sclerosus et atrophicus (LSA). These sclerosing disorders were chosen for the following reasons: 1) increased collagen synthesis is a well documented pathogenetic factor in both systemic and localized scleroderma (10). 2) LSA, although unlikely to be related to scleroderma, shares certain clinical and histological features with LS; increased collagen synthesis, however, has not been demonstrated in LSA. 3) For both LS and LSA only unsatisfactory therapeutic measures are available; as an exception, penicillin is dramatically effective in some cases of early stage plaque type scleroderma (much less so in the other variants of localized scleroderma).

It is our experience from the present study that only limited beneficial effects, if any, can be achieved with etretinate in LS and LSA under the conditions employed by us.

PATIENTS AND METHODS

Selection of patients. Eight patients each with active LC and LSA were entered into the study (Table I). All patients treated were otherwise healthy adults except for three prepuberal girls.

The group of LSA patients included the entire spectrum of clinical subtypes of LSA: juvenile genital LSA (3 patients), balanitis xerotica obliterans (3 patients) and one patient each with extragenital LSA and kraurosis vulvae. The group of LS patients included one patient with plaque type LS, one patient with both plaque-type and linear lesions and 5 patients with linear scleroderma either of the lower extremities or the head (coup de sabre type). One patient had an unusually extensive and rapidly progressive form of generalized linear scleroderma. None of the patients had features of extracutaneous involvement. Many patients had previously undergone various types of topical or systemic treatment. LS patients were only included into this study if they had undergone at least three unsuccessful courses of penicillin treatment; for this reason, the majority of our patients were of the linear type of localized scleroderma.

Design of study. The study was conducted as an open, uncontrolled clinical trial. Diagnoses were made on clinical grounds, biopsies were performed in 10/16 patients. The patients (or their parents, respectively) were fully informed about their disease as well as the effects and side effects of etretinate, and informed consent was obtained.

Etretinate was administered in doses of 0.5 mg/kg/day for at least 3 months up to 12 months; in one case, treatment was extended to 19 months at the instigation of the patient. Minor dose adjustments

were occasionally performed, allowing for doses up to 1 mg/kg/day for several weeks in 5 patients. One patient received etretinate for only 2 months and was then continued with isotretinoin (Accutane®) for 2 more months. Similarly, another patient received a 3 months' course of isotretinoin following 4 months treatment with etretinate. Of the 13 females 7 were of child bearing age and consented to take oral contraceptives for the period of etretinate administration and for one year following drug withdrawal.

No other systemic or topical medication was given during etretinate treatment except local application of emollients. Controls were performed initially at biweekly, later at monthly intervals and included clinical examination, photography (at approximately 3 months' intervals) and laboratory investigations (blood count, sedimentation rate, transaminases, alkaline phosphatase, blood urea nitrogen, serum creatinine, serum electrolytes, triglycerides and cholesterin).

RESULTS

All 16 patients had taken etretinate regularly and subjected themselves to the clinical and laboratory controls and were thus rated evaluable.

Lichen sclerosus. Only 2 of the patients, both of them of the juvenile genital type, had cleared after the treatment period except for barely perceptible thinning and hypopigmentation of the lesional skin. All the others showed equivocal or no favourable responses at all except some scaling and thinning of the hyperkeratotic lesional skin. In 4 patients the lesions remained stable during etretinate treatment and continued to do so after drug withdrawal. In one patient with balanitis xerotica obliterans frank progression occurred; another patient with balanitis xerotica obliterans showed moderate improvement in one region whereas the disease progressed in another. A control biopsy of a persisting lesion in one patient still demonstrated the diagnostic criteria of LSA.

Localized scleroderma. Clearing of lesions of linear scleroderma resulting in slight atrophy and hyperpigmentation was observed in 1 patient. In another patient one plaque type lesion cleared whereas lesions of the linear type persisted. Halt of progression was observed in 5 patients with linear scleroderma; in 2 of these, the lesions resumed progression soon after drug with-drawal. In one patient with generalized linear scleroderma, the lesions were unrelentingly progressive under retinoid therapy.

Side effects. Mild cheilitis occurred in all patients; mild telogen effluvium was observed in one, palmoplantar desquamation in 3 patients. No laboratory abnormalities were detected.

DISCUSSION

In the sclerosing disorders tested, etretinate obviously fails to produce therapeutic effects in any way near to those in disorders of keratinization. A more moderate and partial action, though, is still open for consideration.

Regarding our findings in LSA, it is important to note that both patients who underwent clearing were of the juvenile type which often runs a capricious course and may unexpectedly resolve spontaneously. Conversely, no significant improvement was seen in any, but progression was seen in some of the patients with the balanitis xerotica obliterans and kraurosis vulvae types of LSA, both of which are characteristically chronically progressive and little amenable to any kind of drug therapy. It must be left to speculation whether the mere absence of progression in 4 patients can be attributed to the action of the drug rather than to the natural course of the disease.

The responses of our patients with LS appear to be somewhat more encouraging. Two of the 8 patients improved and finally cleared with slight atrophy as characteristic for the end stage of localized scleroderma. Five of the 6 others showed no sign of resolution, but remained stable while on etretinate therapy. Two of these resumed progression soon after

drug withdrawal, suggesting a suppressive effect of etretinate in the active stage of scleroderma. Only one patient progressed during retinoid therapy and must thus be considered an obvious treatment failure.

Cautious interpretation of the above data certainly does not permit to rule out spontaneous resolution or fluctuations of disease activity as the cause underlying the reactions to etretinate observed in both LS and LSA; on the other hand, the overall response of our patients with LS may indicate a moderate in vivo suppressive effect of etretinate on collagen synthesis interfering with progression of the lesions and promoting their advance into the atrophic end stage. Clearly, more extensive studies would be necessary to definitively prove any such action.

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