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Effect of oral isotretinoin on dysplastic nevi

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We previously reported a favorable histologic response of dysplastic nevi to topical tretinoin in three patients. To investigate the anticancer and cancer preventive effects of retinoids we have examined the effect of systemic isotretinoin on dysplastic nevi. After confirmatory baseline biopsies, eleven patients with the dysplastic nevus syndrome were treated with oral isotretinoin, 40 mg twice a day for 4 months. At completion of therapy, at least three previously identified and photographed clinically typical dysplastic nevi were rephotographed and removed for histologic evaluation. Eight patients completed the full course of medication. There were no clinical changes in the dysplastic nevi in these patients. Posttherapy biopsy specimens in six volunteers revealed most of the remaining lesions to be dysplastic nevi. The majority of lesions biopsied in two subjects showed normal, benign nevi only. This proportion of clinically typical dysplastic nevi that prove to be normal nevi histologically (28%) is not significantly different from that reported by others. Oral isotretinoin does not appear to have a significant biologic effect on the clinical or histologic appearance of dysplastic nevi in the treatment schedule employed. (*J AM ACAD DERMATOL* 1989;20:257-60.)

Vitamin A has long been known to exert cancer preventive and therapeutic effects,^{2,4} but until recently, toxic side effects limited its usefulness. With the advent of less toxic synthetic derivatives, many investigators have evaluated the effects of retinoids on various malignant and premalignant processes. Actinically induced cutaneous squamous cell carcinomas,⁵ keratoacanthomas,⁶ and basal cell carcinomas^{7,8} often respond dramatically to systemic or topical retinoids. Activity against melanoma also has been demonstrated.⁹

Dysplastic nevi are melanocytic nevi that serve as direct melanoma precursors and as markers for an increased risk for the development of cutaneous melanoma.¹⁰ Patients often have many of these irregular, poorly marginated nevi, which makes management difficult. Surgical removal is impractical for those with large numbers and does not obviate the risk of melanoma because cutaneous melanomas may arise in nonlesional skin. In addition,

patients with dysplastic nevi continue to develop new lesions during adulthood. Because there are no known courses of action that decrease this risk, self-examination, professional observation, photographic examination, and early biopsy of suspicious lesions are the mainstays of management. A therapy that would act as a cancer preventive agent would be a major advance.

Because of favorable histologic responses of cutaneous melanoma metastases¹¹ and dysplastic nevi¹² to topical retinoic acid (all-*trans*-retinoic acid, vitamin A acid; Retin-A) under tape occlusion, we have examined the effect of oral isotretinoin (Accutane) on dysplastic nevi. Systemic administration offers the advantage of treating large numbers of dysplastic nevi in a more practical manner, as well as exposing the melanocyte population of normal-appearing but high-risk skin to the medication.

METHODS AND MATERIALS

Ten men and one woman between the ages of 16 and 70 years with multiple dysplastic nevi were chosen for this phase-two study. Most of the subjects had either a family or personal history of cutaneous melanoma or a family history of dysplastic nevi (Table I). Nursing mothers and women of childbearing potential who were unprotected by contraception were excluded. Patients

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with preexisting hypertriglyceridemia and liver disease also were excluded. The nature and risks of the study were discussed before appropriate consent forms were signed.

Four dysplastic nevi of each of the first two patients enrolled were selected and photographed. Punch biopsy specimens, 3 mm in diameter, were obtained from clinically homogeneous areas of each dysplastic nevus for diagnosis. Because of the likelihood of sampling bias from punch biopsy specimens, total surgical excision was performed on subsequent patients. In these patients six or more similar-appearing dysplastic nevi were identified and photographed. At least three lesions were removed before treatment for histologic confirmation. The following histologic criteria were used as the basis for the diagnosis of dysplastic nevus¹⁰: (1) junctional melanocytic proliferation in large nests with random nuclear atypia; (2) downward proliferation and bridging of adjacent rete ridges by these nests of nevus cells; (3) spread of single large melanocytes along the basal cell layer; (4) a dermal lymphocytic inflammatory response, and (5) a fibrotic mesenchymal response in the papillary dermis.

All subjects were then treated with oral isotretinoin (13-*cis*-retinoic acid; Accutane), 40 mg twice a day for 4 months. This dosage was chosen because it is effective in most diseases for which isotretinoin is used. The duration period of 4 months was selected inasmuch as it was adequate to produce histologic changes in dysplastic nevi previously treated with topical tretinoin.¹¹ Patients were monitored with a baseline complete blood cell count with differential cell and platelet counts, serum multiphasic automated chemistry study (18 factor), and urinalysis. These values were examined monthly during therapy and on discontinuation of treatment. The patients also were followed monthly for the occurrence of side effects. Immediately on discontinuation of isotretinoin, the dysplastic nevi were rebiopsied. The initial two patients underwent punch biopsy of previously biopsied lesions, and subsequent patients were evaluated by deep saucerized shave removal of the remaining dysplastic nevi that were studied.

RESULTS

Eight of eleven patients completed therapy. Two discontinued medication because of adverse reactions, and one discontinued medication because of an intercurrent illness.

Clinically there was no change in the appearance of the dysplastic nevi. Posttherapy photographs were unchanged from baseline photographs. No new dysplastic nevi were identified during the study, and no cutaneous melanomas developed in

Table I. Characteristics of subjects

Patient No.	Age (yr)	Family history	Cutaneous melanoma in patient
1	31	Father and grandmother with cutaneous melanoma	No
2	58	Paternal family unknown	Yes
3	35	Mother with dysplastic nevi	No
4	58	Father and brother with dysplastic nevi	No
5	36	None	No
6	28	Sister with melanoma	No
7	67	Daughter with dysplastic nevi	Yes
8	16	Father with dysplastic nevi	No
9*	61	No	Yes
10*	64	No	No
11*	16	No	No

*Dropped from study.

any subject. The microscopic results are seen in Table II. Dysplastic nevi from six of eight evaluable patients exhibited the histologic criteria of dysplastic nevi before and after treatment with oral isotretinoin, 40 mg twice a day for 4 months. One patient who showed an apparent improvement had been evaluated by punch biopsy rather than total excision.

Adverse reactions to isotretinoin were confined to its well-recognized side effects. Xerosis and cheilitis occurred in all patients. Occasional epistaxis and musculoskeletal pain were experienced by three subjects each. Headaches and mild cutaneous sensitivity to sun and were reported by two subjects each. Serum triglycerides became elevated to the 200 to 400 mg/dl range in four subjects.

DISCUSSION

Dysplastic nevi represent a dilemma for the dermatologist. These often large, irregular, poorly marginated melanocytic nevi sometimes serve as direct melanoma precursors and as markers for an increased risk for the development of cutaneous melanoma in both normal- and abnormal-appearing skin.^{10, 13} Histologically and clinically the nevi appear to be intermediate between benign nevi and cutaneous melanomas. Patients exhibit a variably

Table II. Histologic results

Patient No.	Pretherapy biopsies		Posttherapy biopsies	
	Dysplastic nevi	Benign nevi	Dysplastic nevi	Benign nevi
1*	3	1	4	0
2*	2	2	1	5
3	4	0	3	0
4	3	0	1	2
5	3	0	3	0
6	3	0	3	0
7	3	0	3	0
8	3	0	2	1

*Studied by punch biopsy specimens.

increased risk for the development of cutaneous melanoma. Although this risk can be minimized by the judicious use of sunscreens and avoidance of sunburn, the patient and physician are in the awkward position of waiting for melanomas to appear. Careful observation, comparative photographic examination, and early removal of suspicious or new lesions afford the patient the least risk of morbidity and mortality from melanoma. A therapy that would decrease the risk for the development of melanoma would be an important advance.

Not only are retinoids known to exhibit cancer-preventive effects but isotretinoin also has been observed to exert modest activity against melanoma both in animal models⁹ and in human clinical trials.¹⁴ There are multiple possible mechanisms of action. Changes in gene transcription and protein synthesis occur through steroidlike retinoid receptors.¹⁵ There are cell membrane alterations because of changes in glycoprotein synthesis, which result in changes in cell-to-cell interaction.¹⁶ Both humoral and cell-mediated immune enhancement is another anticancer mechanism.^{17,18} Direct cytotoxicity also occurs as a result of organelle and cell membrane lability.¹⁹

Because of these well-known anticancer properties of retinoids, we recently studied and reported the cases of two patients whose cutaneous melanoma metastases were treated with retinoic acid solution 0.05% applied daily under tape occlusion for 4 months.¹¹ One patient showed complete histologic regression of the treated tumors, and the other showed marked improvement. We then examined the effect of this same treatment in dysplastic nevi in three strikingly affected

patients.¹² Although there was little clinical change in the lesions, punch biopsy specimens of dysplastic nevi in two patients showed a histologic change to benign nevi after topical retinoic acid therapy. The nevi of a third patient showed reversion toward normal, although mild dysplastic features still were present. It is reasonable to assume, but it is certainly not known, that histologic reversion toward normal may be accompanied by a decrease in the risk of malignant transformation. Because severely affected patients may have 100 or more dysplastic nevi, topical therapy would be of little practical value. Systemic administration of a retinoid in the form of oral isotretinoin would offer the advantage of treating not only all dysplastic nevi but also any abnormal melanocytes in normal-appearing skin.

The report shows that oral isotretinoin at a dosage of 40 mg twice a day for 4 months has no clinical or histologic effect on dysplastic nevi. This dosage and schedule was chosen because it has been found to produce responses in other inflammatory and neoplastic changes. Clinically dysplastic nevi from six of eight evaluable patients exhibited the histologic criteria of dysplastic nevi before and after a 4-month course of isotretinoin. One patient who showed an apparent change from dysplastic nevi to a more benign histologic finding was studied by punch biopsy rather than total excision. Our experience and that of others (J. Bangert, MD, personal communication) have shown that sampling errors occur in punch biopsies because of histologic heterogeneity within the nevus.²⁰ Alternatively, the inflammation resulting from the pretherapy punch biopsy may have resulted in a histologic improvement.

The results of this study were unexpected in light of the improvement seen in dysplastic nevi after topical retinoic acid therapy. There are several possible reasons for this discrepancy. First, the concentration of retinoic acid in the nevus may be higher after topical therapy under occlusion than with oral administration. Second, topical retinoic acid sometimes may exert effects different from those of systemic retinoids, as has been shown in animal models.²¹ In addition, in this trial isotretinoin was studied (13-*cis*-retinoic acid) rather than all-*trans*-retinoic acid, which was used previously, and it is possible that different retinoids exert variable degrees of differentiating effects. Also, the patients treated topically were studied by punch biopsy of their nevi, and the sampling error discussed here may have misrepresented the overall histologic findings of the nevus. Finally, the number of patients studied with topical retinoic acid was small. We are presently reexamining the effect of topical retinoic acid therapy on dysplastic nevi with the use of total excisions in a larger number of patients. It is possible that higher doses or a longer course of isotretinoin would effect some change in dysplastic nevi.

At this time, the management of patients with dysplastic nevi remains supportive. Careful and regular follow-up examinations, photographic documentation, and early biopsy to identify curable cutaneous melanomas will afford patients the least risk of morbidity and mortality.

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