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Short Communication

Regression of Aggressive Laryngeal Papillomatosis with 13-cis-Retinoic Acid (Accutane)

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Summary: Laryngeal papillomatosis often involves a relentless growth of papillomas on the vocal cords, requiring repeated excisions to maintain an adequate airway. Because of its antiproliferative effects on epithelial tissues, 13-cis-retinoic acid (0.5–2.0 mg/kd/day p.o.) was used in five patients whose disease was poorly controlled by laser beam surgery. Control of disease for 24 +, 5 +, and 12 months has been achieved in three of the patients, with two complete and one partial responses. Side effects of treatment were mild and rapidly reversible, following a 25–50% reduction in drug dose. **Key Words**: Accutane—Laryngeal papillomatosis—Polypoid lesions—Vocal cords.

Laryngeal papillomatosis often involves a relentless growth of polypoid lesions on the vocal cords, requiring repeated surgical excisions in order to maintain an adequate airway. In a minority of patients, even monthly laser beam excisions may not adequately control the disease (1–3). Other forms of treatment have included immunotherapy with specially prepared vaccines (4), bacillus Calmette-Guerin (BCG)(5) and levamisole (6), topically applied 5-fluorouracil (7), and parenteral interferon (8–10). All but the latter therapy have proven to be relatively ineffective. Although interferon has been effective in controlling the disease in over 50% of patients, treatment requires parenteral administration three to four times a week and has been associated with varying degrees of fever, chills, weakness, and anorexia in most recipients (8–10).

Because of its antiproliferative effects on epithelial tissues in animals and humans (11–16), as well as its ease of administration and relative lack of systemic side effects (17), we chose the vitamin A derivative 13-cis-retinoic acid (13-cRA; Accutane) for evaluation in patients with progressive laryngeal papillomatosis. A study of 13-cRA has been carried out in a group of five patients whose disease was poorly controlled

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by laser beam surgery. Two patients remain in complete remission and an additional patient has had a partial response.

MATERIALS AND METHODS

Patients were accepted into this study only if they had undergone surgical excisions of laryngeal papillomas on at least three occasions (median of 6, range 3–10) during the preceding 12 months. All papillomas were reviewed for histologic verification by University of Arizona pathologists.

All patients began treatment with 13-cRA within 60 days of the last laser beam excision of their laryngeal papillomas. Prior to initiation of therapy, informed consent was obtained from all study patients or their legal guardians after the nature of the therapy had been explained fully, according to institutional policies. Prior to initiation of therapy, a full medical history was obtained and physical examination was performed. In addition, a battery of laboratory tests was obtained, including urinalysis, complete blood count (CBC), differential blood cell and platelet counts, blood urea nitrogen (BUN), and serum uric acid, calcium, glutamic-oxaloacetic transaminase (GOT), alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), cholesterol, and triglycerides. During therapy, all laboratory tests were repeated at 2-month intervals, and chest x-rays were repeated following each direct laryngoscopy evaluation. On the basis of recent reports of calcification of the anterior vertebral ligament in patients receiving 13-cRA for longer than 2 years at a dose of 2 mg/kg (18), we have begun to obtain lateral roentgenograms of cervical and thoracic vertebrae in all patients at entry into this study and at 1.5 and 2 years of therapy.

Direct laryngoscopy and laser beam excision of laryngeal papillomas was performed by one surgeon (S.E.C.) in all but one of the patients (No. 4, who remained in the study for only 6 months). All initial medical and follow-up examinations were carried out by one physician (D.S.A.).

Therapy was initiated with 13-cRA at a dose of 1 mg/kg body weight in four patients and at a dose of 2 mg/kg in the fifth patient (No. 5) because of a desire to rapidly achieve a remission from extremely aggressive disease. Therapy was designed to be escalated to 2 mg/kg and then 3 mg/kg at periods of 2 months in the absence of response. The 13-cRA was provided (10-mg tablets and 40-mg capsules) by Hoffmann-La Roche, Nutley, NJ, U.S.A.

Response to 13-cRA was evaluated at monthly intervals by indirect laryngoscopy and, when possible, at 2–3 month intervals by direct laryngoscopy and laser beam excision of any polypoid lesions. A complete response required the disappearance of all papillomas visually and histologically for at least 1 month. A partial response required a greater than 50% regression in the total area of papillomatous growth for longer than 1 month, along with an improvement in performance status to at least 90% (i.e., only mild symptoms that do not interfere with lifestyle or work performance). Improvement required less than a 50% regression of papillomatous growth, no evidence of new growth, and an improvement in performance status to at least 90%. Progressive disease was defined as a greater than 25% increase in the total area of papillomatous growth.

Toxicity to 13-cRA was graded on a scale of 1 + to 4 +, with 1 + representing mild cheilosis and skin dryness that was reversible with emolients and 4 + repre-

TABLE 1. *Patient characteristics and 13-cRA dosing and response*

Patient no.	Age (yr)	Duration of papillomatosis prior to retinoid (mo)	Papilloma resections in prior 12 mo (no.)	Dose of 13-cRA (mg/kg)	Duration 13-cRA therapy (mo)	Type of response[a]	Duration of response (mo)
1	4	16	6	1	20	CR	24+
2	9	11	7	1–1.5	16	PR	5+
3	2.8	12	4	1–2	7	NR	0
4	37	84	3	0.5–1	16	CR	12
5	68	60	10	1–2	5	PD	0

[a]CR, complete response; PR, partial response; IMP, improvement; NR, no response; PD, progressive disease. See Materials and Methods for full definitions.

senting severe cheilosis and dermatitis not reversible with emolients and/or severe hypertryglyceridemia (i.e., >200% increase from a normal baseline of serum triglycerides).

RESULTS

Five patients with biopsy-proven laryngeal papillomatosis were started on 13-cRA, and their clinical characteristics are summarized in Table 1. Patient 1, a 4-year-old white boy, had undergone direct laryngoscopy and laser beam removal of rapidly progressive laryngeal papillomas on six occasions between the ages of 3 and 4 years. He was started on 13-cRA, 1 mg/kg (total dose 20 mg) 50 days after his last surgery, when he developed severe hoarseness and evidence of progressive papillomatous growth on indirect laryngoscopy. Within 3 weeks, there was a marked decrease in the size and number of papillomas, as documented by direct laryngoscopy. During continuous 13-cRA treatment, repeat laryngoscopies revealed further regression at 4 months, followed by a sustained complete disappearance for 24 months. Therapy has been discontinued for an additional 8 months without signs or symptoms of recurrence. Drug-induced toxicity was mild throughout therapy and involved mild cheilosis and skin dryness, which was easily managed with emolients. The serum triglycerides were only mildly elevated (172 mg/dl) on one occasion 14 months after the start of therapy, with normalization 4 months later (56 mg/dl). All other laboratory tests, including liver enzymes and total bilirubin, remained within a normal range throughout therapy.

Patient 2, a 9-year-old Mexican girl, had an 11-month history of decreased voice strength and breathing difficulties, requiring seven laser beam excisions of laryngeal papillomas. After 2 months of 13-cRA therapy, direct laryngoscopy revealed only one papilloma on the anterior half of the true vocal cords. This partial regression, which was associated with improved voice quality and only mild cheilosis, lasted for 5 months, as documented by repeat indirect and direct laryngoscopies. Despite moderate regrowth of papillomas 6 months after initiation of 13-cRA therapy, the patient's disease remained stable on treatment over the subsequent 9 months. The patient's family was then unwilling to return from Mexico for further follow-up examinations.

Patient 3, a 32-month-old white boy had required removal of laryngeal papillomas on four occasions over a period of 12 months. His disease showed no response to 13-cRA at doses of 1–2 mg/kg over a period of 7 months. During therapy, the patient experienced mild to moderate cheilosis and mild, rapidly reversible hypertriglycer-

idemia (i.e., serum triglycerides rose from 112 mg/dl at baseline to 201 mg/dl, transiently).

Patient 4, a 37-year-old white man, had had multiple surgical excisions of his papillomas over a 7-year period. He suffered from extreme hoarseness, which severely hampered his ability to function as a social worker and caused chronic, debilitating depression. Therapy with 13-cRA was initiated following indirect laryngoscopy, which revealed multiple, small laryngeal papillomas. After 4 months of 13-cRA (0.5–1 mg/kg), there was a marked improvement in voice strength and performance status. After 10 months of therapy, direct laryngoscopy documented complete disappearance of all papillomas. While continuing in complete remission, 13-cRA was decreased from 1.0 to 0.5 mg/kg daily because of the onset of mild balanitis, occasional headaches, and slight depression, which responded rapidly to reduction in drug dose. The patient remained in complete remission for 6 months after discontinuation of 13-cRA, at which time regrowth of papillomas was observed by indirect laryngoscopy.

Finally, patient 5, a 60-year-old white man, appears to have had disease progression after 3 months of 13-cRA therapy (1–2 mg/kg/day). Moderate conjunctivitis and epistaxis had required a dose reduction from 2.0 to 1.0 mg/kg/day.

DISCUSSION

The results of this study suggest that 13-cRA may be a useful drug for the treatment of some patients with progressive laryngeal papillomatosis. Two patients who had required almost monthly surgical resections of papillomas have experienced complete remissions, which have lasted 12 and 24+ months. One additional patient experienced a partial response for 5+ months. Side effects of this oral treatment were limited to mild to moderate cheilosis in all patients and mild conjunctivitis, balanitis, and triglyceridemia in one patient each. All of these reactions were rapidly reversible following a 25–50% reduction in dose.

The optimal dose and duration of 13-cRA to be used in the treatment of laryngeal papillomatosis requires further study. A 0.5–1.0 mg/kg daily dose for a period of 4–9 months was required to achieve complete remissions in two of our five patients. The partial remission was also achieved with the 1 mg/kg daily dose, and doubling of this 13-cRA dose did not seem to enhance response but did cause increased cheilosis. Both children who responded experienced maximal regression of their papillomas within 4 months of therapy initiation, whereas it required up to 9 months of therapy to obtain a complete remission in one of two adults. On the basis of these data, we recommend the starting dose of 13-cRA therapy to be 1 mg/kg daily and that total therapy duration in complete responders be limited to the time interval to complete response followed by an additional 4–6 months of maintenance treatment. Thus, 13-cRA treatment in the most responsive group of patients could possibly be limited to 1 year or less. In those patients who experienced only a partial response, the duration of 13-cRA therapy should probably not exceed 2 years, as there is an increasing risk at that point of skeletal toxicity (18).

The antiproliferative effects of 13-cRA on various epithelial tissues and animal tumors (11,12) has led to successful trials of 13-cRA in the treatment of keratoacanthomas and other preneoplastic lesions (13–15), as well as established squamous cell cancers of the skin (14,15) and cutaneous T-cell lymphomas (16). Because of the significant activity of 13-cRA on preneoplastic skin lesions (13–15), we selected it for treatment of our patients with progressive laryngeal papillomatosis. Although

13-cRA proved to be effective in limiting the proliferation of laryngeal papillomas in three of our five patients, consideration should also be given to the use of other retinoids in future clinical trials. The aromatic retinoic acid analog etretinate is one agent deserving such consideration. Etretinate has been shown to inhibit the growth of virus-induced papillomas and related neoplasias in rabbits (19), as well as to eradicate active actinic keratoses of the skin in patients (20).

Although leukocyte interferon has proven to be an effective treatment, with approximately 50% of patients showing long-term responses (9,10), the requirement for parenteral administration and its sometimes severe systemic toxicity (8–10) make it less attractive for the treatment of this benign disease. On the basis of the positive results with 13-cRA, we propose that future studies compare this drug and/or other retinoids with low doses of leukocyte or recombinant interferons.

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