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# A phase I trial of topically applied trans-retinoic acid in cervical dysplasia-clinical efficacy

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## Abstract

Forty-two patients were entered into a phase I trial to evaluate the vitamin A derivative, trans-retinoic acid, in cervical intraepithelial neoplasia. Treatment consisted of four consecutive 24-h applications of retinoids via an inert collagen sponge in a cervical cap. Patients were followed for response at 3-month intervals using cytology, colposcopy, and selected biopsies. Thirty-six patients were evaluable (mild dysplasia, 13; moderate dysplasia, 17; severe dysplasia, 6) with follow-up from 5 to 18 months. Complete regression was seen in 2/14 (14%) patients treated with concentrations of 0.05% → 0.1167% and in 10/22 (45%) patients treated with concentrations of 0.1583% → 0.484% ($p < 0.05$). One patient with negative biopsies at 12 months has subsequently recurred at 18 months.

## Introduction

Vitamin A, and its natural and synthetic derivatives (retinoids), have been shown to be capable of modulating the differentiation of normal and abnormal cells in vitro and in vivo (1, 2). Retinoids may act as antipromoters, preventing the phenotypic expression of malignancy initiated by a variety of carcinogens (2).

These observations suggest a possible role for retinoids in the prevention and treatment of cervical intraepithelial neoplasia (CIN), (commonly known as cervical dysplasia). We have previously reported on the use of topically applied trans-retinoic acid (TRA) delivered via a collagen sponge and diaphragm insert (3). Although problems were encountered with the delivery system, evidence of clinical efficacy was noted, which prompted further trials with an alternate delivery vehicle. We have recently completed a phase I trial of TRA delivered via a cervical cap and have previously published on the toxicity associated with this system (4). We noted mild vaginal toxicity in 75% of patients with no evidence of systemic absorption. This report deals with clinical follow-up on those patients entered into the phase I trial, in an attempt to ascertain whether TRA has activity in cervical dysplasia.

## Materials and methods

### *Patient characteristics*

All patients entered into this trial (in accord with a protocol approved by the University of Arizona Committee on Human Subjects) had colposcopically directed biopsies which showed CIN. The lesion and the entire transformation zone (squamocolumnar junction) were completely visualized. All patients had a negative endocervical curettage and the pre-treatment papanicolaou smear was consistent with the ectocervical biopsy. The extent of disease

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was documented with colpophotographs prior to treatment in all patients. All patients had negative vaginal cultures for *Staphylococcus aureus*.

TRA was delivered in a cream base vehicle which contained polyethelene glycol 400, butylated hydroxytoluene, and 55% alcohol. A starting concentration of 0.05% was chosen, and escalated, using a modified Fibonacci scale, until unacceptable vaginal toxicity was encountered at a concentration of 0.484% (4).

The delivery system consisted of a cervical cap in which a collagen sponge was inserted. The cervical cap is made of the hydrogel Hypan® which, when in contact with wet tissue surfaces, adheres by a process of differential osmotic pressures. The characteristics and properties of the collagen sponge are extensively described elsewhere (5). Briefly, the sponges were made from pure collagen isolated from bovine skin, swollen at ph 3.0, and stabilized into the physical form of a sponge layer. Glutaraldehyde was used as a cross-linking agent to provide high resilience and fluid binding capacity. The average pore size was 400 A (range 80 to 1400 A). The sponges were cut into thin, round wafers approximately 3 to 4 mm thick in diameter and fitted to the cervical caps.

Treatment consisted of four consecutive 24-h applications of 1 cc of retinoids delivered topically via the cervical cap and collagen sponge. All patients had colposcopic lesions present at initiation of therapy. Patients were followed for response at three month intervals using cytology, colposcopy, and selected cervical biopsies of any colposcopic lesion. A complete response was defined as negative cytology and colposcopy, or a negative cervical biopsy if a colposcopic lesion was present concomitant with negative cytology.

## Results

Forty-two patients were entered into this phase I trial. Thirty-six were considered fully evaluable, six patients did not return for post treatment exams and were excluded from the study. Follow-up ranged from 5–18 months. The treatment population consisted of 13 patients with mild dysplasia, 17 with moderate dysplasia, and six with severe dysplasia.

Complete disappearance of disease was seen in 12/36 (33%). Of these 12, four had mild dysplasia, six had moderate dysplasia and two had severe dysplasia. The extent of cervical involvement did not appear to influence response rate. Fifteen patients had lesions involving 3 or 4 quadrants, seven had a CR, eight had no response. Of the 12 patients who had a CR, five had lesions involving 1 or 2 quadrants, seven had lesions involving 3 or 4 quadrants (Table 1). An apparent dose response effect was observed, with a complete remission seen in 2/14 patients treated with concentrations of TRA from 0.05% → 0.1167% and 10/22 (45%) patients treated with concentrations of 0.1583% → 0.484% (Fishers exact test, $p < 0.05$). In patients treated with concentrations of 0.05% → 0.1167%, 5/14 (35.7%) had mild dysplasia, 7/14 (50%) had moderate dysplasia, and 2/14 (14.2%) had severe dysplasia. Of those patients treated with 0.1583% → 0.484%, 8/22 (36.6%) had mild dysplasia, 10/22 (45.5%) had moderate dysplasia, and 4/22 (18%) had severe dysplasia. Ten of 12 patients with a complete response have been followed for a minimum of 12 months. One patient with negative biopsies at 12 months has subsequently recurred at 18 months with dysplasia (Table 2).

*Table 1.* Response vs. lesion size.

| No. quadrants | CR | NR. |
|---|---|---|
| 1 | 4 | 6 |
| 2 | 1 | 10 |
| 3 | 3 | 4 |
| 4 | 4 | 4 |
| Total | 12 | 24 |

## Discussion

The use of chemopreventative agents in an attempt to reverse preneoplastic lesions of the cervix is a relatively new concept. A large body of evidence has accumulated, both experimental and epidemio-

*Table 2.* Patient characteristics.

| Pt. | [TRA] (%) | Pretreatment biopsy | Posttreatment PAD | Posttreatment biopsy | Follow-up (months) |
|---|---|---|---|---|---|
| 1* | 0.05 | moderate | neg | neg | 12 |
| 2 | 0.05 | moderate | neg | severe | |
| 3 | 0.05 | moderate | neg | | |
| 4 | 0.05 | severe | mild | mild | |
| 5 | 0.0667 | mild | mild | moderate | |
| 6 | 0.0667 | moderate | mild | severe | |
| 7* | 0.0667 | moderate | neg | neg | 12 |
| 8 | 0.0833 | severe | neg | mild | |
| 9 | 0.0833 | mild | mild | | |
| 10 | 0.0833 | mild | moderate | moderate | |
| 11 | 0.1167 | moderate | mild | | |
| 12 | 0.1167 | moderate | neg | mild – | 5 |
| 13 | 0.1167 | mild | neg | moderate | |
| 14 | 0.1167 | moderate | neg | mild | |
| 15* | 0.1583 | moderate | neg | neg | |
| 16 | 0.1583 | moderate | neg | mild | |
| 17 | 0.1583 | mild | neg | mild | |
| 18* | 0.1583 | severe | neg | neg | 24 |
| 19 | 0.21 | moderate | neg | mild | |
| 20* | 0.21 | severe | neg | neg | 12 |
| 21 | 0.21 | moderate | neg | mild | |
| 22* | 0.28 | mild | neg | | 13 |
| 23* | 0.28 | mild | neg | | 10 |
| 24 | 0.28 | severe | neg | moderate | |
| 25 | 0.28 | moderate | mild | moderate | |
| 26 | 0.372 | mild | mild | moderate | |
| 27* | 0.372 | mild | neg | | 12 |
| | | | moderate | | 18 |
| 28 | 0.372 | severe | neg | | 18 |
| 29* | 0.372 | mild | very mild | neg | 16 |
| 30* | 0.372 | moderate | neg | neg | 18 |
| 31 | 0.372 | moderate | very mild | mild | |
| 32 | 0.372 | mild | neg | mild | |
| 33* | 0.372 | moderate | neg | neg | 18 |
| 34* | 0.372 | moderate | neg | neg | 18 |
| 35 | 0.484 | moderate | very mild | | |
| 36 | 0.484 | mild | very mild | mild | |

* = Complete response.

tiologic, to support the concept that retinoids have the capability of altering the progression of preneoplastic conditions to malignant disease (1, 2, 6).

As early as 1965. Chu and Malmgren demonstrated the inhibitory effect of Vitamin A on the induction of cervical carcinomas by 1% dimethylbenzanthracene in Syrian hamsters (7). Recent work has demonstrated the efficacy of retinoids in the treatment of a variety of lesions resulting from papilloma virus infections, (8) an agent implicated in the carcinogenesis of CIN (9).

CIN is an ideal model for the study of chemopreventative agents. It represents a well defined pathologic entity that can be easily evaluated in the out-patient setting and is suitable for topical therapy. Uptake of TRA into cervical tissues has been documented using tritiated labeled TRA (unpublished data, Meyskens FL, Alberts DS and Surwit EA).

We have recently shown that TRA can be safely delivered topically using the cervical cap and collagen sponge system (4). Systemic effects were minimal, and local toxicity was clearly dose related and acceptable at concentrations of 0.372%. In the present report, although an apparent dose-response effect was observed, with only 14% of patients responding at low concentrations of TRA vs. 45% at higher concentrations, the phase I nature of this trial does not allow definitive conclusions to be drawn. It may be that a concentration of 0.1584% TRA represents a minimally effective dose, and that dose escalation will not result in increased response rates. Similarly, no definitive conclusions can be drawn regarding the effect of histology on response rate, although it was encouraging to note that responses were seen with all grades of dysplasia. Lesion size also did not appear to influence disease regression. Of the 15 patients with extensive lesions (3 or 4 quadrants), seven had complete disease regression and 8 had no response.

Since long-term follow-up is lacking in the current series, no definitive statement can be made as to the ultimate role of retinoids in CIN. With complete response rates of 45% in this preliminary trial, it is unlikely that trans-retinoic acid will replace ablative surgery as the treatment of choice in cervical dysplasia. However, the more important question to be answered is whether or not biologic modifiers can play a role in the chemoprevention of cervical dysplasia. We feel that this trial does demonstrate that trans-retonic acid is capable of suppressing CIN and the minimal effect seen at lower drug concentrations makes it less likely that spontaneous regression is occurring. The need for maintenance therapy needs to be addressed, as many clinical trials have shown relapse once the drug is discontinued. Currently, a phase III trial is being conducted to compare TRA vs. placebo in a randomized double blind fashion to help further evaluate the role of retinoids in cervical dysplasia.

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