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Comparative study of systemic Interferon alfa-2a with oral isotretinoin and oral isotretinoin alone in the treatment of recurrent condylomata accuminata

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Abstract. *Objectives:* We attempted to test the hypothesis that the combination of systemic interferon alfa-2a and oral isotretinoin is more effective than isotretinoin alone in the treatment of recurrent condylomata accuminata. *Study design:* Fifty seven women with recurrent condylomata accuminata were randomly assigned in two groups. Group A (n=24) received isotretinoin alone (Roaccutan, Roche) 1 mg/kgr orally daily for 3 months or until a remission was achieved; Group B (n=33) received Interferon alfa-2a (Roferon-A, Roche) 3 million units subcutaneously three times for 8 weeks plus isotretinoin 1 mg/Kg orally for 3 months or until a remission was achieved. *Results:* There was no statistically significance in remission rates between the two groups (18/24 vs 28/33, $p>0.1$). However the duration of treatment was statistically significantly shorter in Group B (1.9 vs 2.5 months, $p<0.01$). Side effects were minimal.

Key words: Interferon alfa-2a – Isotretinoin – Recurrent condylomata accuminata

Introduction

Condylomata accuminata are very common, affecting up to 10% of the population, and are very difficult to treat (Deligeoroglou et al. 1992). Traditional forms of therapy involve topical podophyllin, trichloroacetic acid or 5-fluorouracil or electrocautery, cryosurgery, CO_2 laser or scalpel excission (Cardamakis et al. 1991b). Local treatment is often difficult because of the associated pain and has a high recurrence rate (Olsen et al. 1989). The recurrence of genital warts may be due the difficulty of treating mucosal surfaces or the existence of a latent virus in an otherwise normal skin (Ferenczy et al. 1985). Systemic treatment for condylomata accuminata may lead to more lasting remissions.

Interferon is an inducible protein with inherent antiviral, antiproliferative and immunomodulatory activities (Ringenberg and Anderson 1986). In previous stud-

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ies using parenteral interferon alfa-2a in combination with other therapeutic modalities, up to 77% of patients with condylomata accuminata, refractory to standard therapies, had complete and longlasting (more than 1 year) remissions (Cardamakis et al. 1991b, Deligeoroglou et al. 1992).

Retinoids are vitamin A derivatives that also have antiproliferative activities on various epithelial tissues. These agents have some effect on human papillomavirus-infected tissue as shown in studies with common warts (Gross et al. 1983, Boyle et al. 1983, Cardamakis et al. 1991a, Deligeoroglou et al. 1992), epidermodysplasia verruciformis (Jablonska et al. 1981, Litzner 1981) or laryngeal papillomatosis (Alberts et al. 1986).

The purpose of the present study was to evaluate the effectiveness of isotretinoin versus isotretinoin plus systemic interferon alfa-2a in the treatment of histologically confirmed HPV infection.

Material and methods

Patients were randomly assigned in Group A (n=24) who received isotretinoin alone (Roaccutan, Roche) 1 mg/kgr per os daily until remission was achieved but not more than 3 months or in Group B (n=33) who received interferon alfa-2a (Roferon-A, Roche) 3 million units subcutaneously three times weekly until remission was achieved but not more than 8 weeks plus isotretinoin in the same dosage. All the women had condylomata accuminata (histologically confirmed) lasting from 1 to 5 years before the beginning of treatment (mean 2.5 years) and the average age was 23.4 years (age 18–29). All patients had previously been treated with several topical conservative therapies and/or surgery.

Treatment with isotretinoin was suspended before the third months if lesions dissappeared. Colposcopic examination was performed monthly during treatment and every third month thereafter. In all patients effective contraception was prescribed during and for two months after treatment.

The following laboratory tests were performed on all patients before, after 1 month and after termination of treatment: total blood cell count, differential count, white blood cell count, platelets, prothrombin time, erythrocyte sedimentation rate, blood urea, blood glucose, creatinine, serum protein, electrolytes, bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvate transaminase, alkaline phosphate, cholesterol, triglycerides, β-chorionic gonadotropine and urine analysis.

Follow-up ranged from 3 to 20 months (mean 11.8 months). Recurrences observed within the first year post-treatment were considered as treatment failure. Statistical analysis was performed by the Chi-Square test.

Results

Of 24 women treated with isotretinoin, 18 were completely free of lesions and without recurrence for the follow-up period (mean 12.04 months, range 3–20) (Table 1). In 4 patients the condylomata had disappeared one to three months after the drug was discontinued with no further treatment. Twenty eight out of 33 patients treated with interferon alfa-2a and isotretinoin were completely free of lesions and without recurrence for the follow-up period (mean 11.45 months, range 5–18) (Table 2). Three patients had an increase of condylomata during the first month visit with resolution one to three months later.

A statistically significant shorter treatment period to achieve remission was observed in Group B (1.9 vs 2.5 months, $p<0.01$) (Table 3). However the number of

Table 1. Analytic overview of women treated with Isotretinoin

No	Age	Kind of lesion[a]	Length of treatment (months)	Treatment results	Follow-up (months)
1	22	C.A.	3	Recurrence in 6 months	18
2	22	C.A.	1	Remission	17
3	20	C.A.	2	Recurrence in 2 months	13
4	21	C.A.	2	Remission	6
5	18	C.A.	1	Remission	6
6	23	C.A.	3	Remission	5
7	29	C.A.	1	Recurrence in 1 month	3
8	18	C.A.	3	Remission	3
9	26	C.A.	3	Remission	11
10	28	C.A.	3	Remission	8
11	22	C.A.	2	Recurrence in 3 months	11
12	28	C.A.	3	Remission	20
13	27	C.A.	3	Remission	20
14	28	C.A.	3	Remission	14
15	26	C.A.	3	Remission	17
16	26	C.A.	3	Remission	14
17	24	C.A.	3	Recurrence in 3 months	14
18	21	C.A.	3	Remission	14
19	26	C.A.	3	Recurrence in 6 months	17
20	24	C.A.	3	Remission	14
21	28	C.A.	3	Remission	17
22	29	C.A.	3	Remission	8
23	28	C.A.	2	Remission	8
24	25	C.A.	1	Remission	8

[a] C.A. = condylomata accuminata

patients experiencing remission of condylomata accuminata, was not statistically significantly different ($x^2 = 0.85$, $p > 0.5$) in the two groups (Table 4).

All patients had dry skin, dry eyes and cheilitis (inflammation of the lips), which never led to the suspension of treatment. Four patients of the isotretinoin group complained of local irritation of condylomata, two patients complained of fatique and one patient noted alopecia that resolved after discontinuation of treatment. Four patients had elevation of triglycerides greater than two times the baseline and in four patients liver function tests (transaminases) became slightly abnormal. All the abnormalities observed were transient and the values returned to normal limits when isotretinoin was discontinued.

Flu-like symptoms (fever, chills and/or malaise) were the most common side effects reported by patients (56%) at initiation of therapy. Fever usually occurred only with the first 3 injections. The most persistent symptom was fatigue which continued until interferon therapy was discontinued. No episodes of leukopenia (≤3,000 WBC/ml) or thrombocytopenia (platelets <100,000/ml) occurred in any of the patients treated with interferon. There were no increases in triglyceride nor cholesterol levels during the combination therapy from that seen with isotretinoin alone. Liver function test results of two patients receiving the combination were abnormal. One patient's results returned to normal when interferon alfa-2a was discontinued and the other patient's results returned to normal when isotretinoin was discontinued.

Table 2. Analytic overview of women treated with Isotretinoin and Interferon alfa-2a

No	Age	Kind of lesion[a]	Length of treatment (months)	Treatment results	Follow-up (months)
1	22	C.A.	2	Remission	18
2	25	C.A.	1	Remission	18
3	23	C.A.	1	Remission	17
4	20	C.A.	2	Remission	17
5	22	C.A.	1	Remission	17
6	20	C.A.	2	Remission	17
7	22	C.A.	2	Remission	15
8	22	C.A.	1	Remission	15
9	20	C.A.	2	Remission	15
10	29	C.A.	1	Remission	15
11	29	C.A.	1	Remission	15
12	20	C.A.	1	Remission	15
13	26	C.A.	2	Remission	15
14	22	C.A.	3	Remission	13
15	21	C.A.	2	Recurrence in 3 months	8
16	18	C.A.	1	Remission	5
17	19	C.A.	2	Remission	8
18	29	C.A.	2	Remission	8
19	20	C.A.	3	Recurrence in 6 months	8
20	26	C.A.	2	Recurrence in 6 months	11
21	24	C.A.	2	Remission	14
22	26	C.A.	2	Remission	8
23	28	C.A.	1	Remission	11
24	27	C.A.	3	Remission	8
25	29	C.A.	3	Recurrence in 6 months	8
26	28	C.A.	2	Remission	11
27	25	C.A.	1	Remission	8
28	29	C.A.	2	Recurrence in 6 months	8
29	26	C.A.	2	Remission	11
30	28	C.A.	3	Remission	17
31	22	C.A.	1	Remission	8
32	28	C.A.	3	Remission	8
33	27	C.A.	3	Remission	5

[a] C.A. = condylomata accuminata

Table 3. Duration of treatment to achieve remission

Groups of patients	Duration of treatment			Total
	1 month	2 months	3 months	
Isotretinoin	4	4	16	24
Isotretinoin + Interferon	10	16	7	33
Total	14	20	23	57

$x^2 = 2.16$ $p < 0.01$

Table 4. Treatment failures

Groups of patients	Treatment failures		Total
	No	Yes	
Isotretinoin	18	6	24
Isotretinoin* + Interferon	28	5	33
Total	46	11	57

$x^2 = 0.85, p > 0.5$

In general, combination therapy of interferon alfa-2a and isotretinoin was well tolerated.

Discussion

This study, which was an extension of previous studies (Cardamakis et al. 1991a, Deligeoroglou et al. 1992), confirms the efficacy of interferon alfa-2a and isotretinoin in treating recurrent condylomata accuminata in women.

Retinoids may be of benefit in warts because they are able to "normalize" the keratinizing epithelia (MacGuire et al. 1982, Connor and Lowe 1984) and because they modulate the immune system (Claudy et al. 1982, Dicken and Connolly 1982, Pigatto et al. 1984, Rusciani et al. 1984, Shapiro and Edelsonn 1984). Moreover, experimental observations concerning retinoids as inhibitors of carcinogenesis (Moon and MacCormick 1982, Munkvad et al. 1983, Bertram and Martner 1984, Boutwell et al. 1984, Lotan 1984, Ympa and Lichti 1984) are extremely interesting. These agents also seem to demonstrate activity in preventing and treating some tumors (Peck et al. 1982, Meyskens 1982, Moon and MacCormick 1982, Pochi 1982, Ympa and Lichti 1984, Claudy et al. 1984, Molin et al. 1984, Peck 1984, Verret et al. 1984, Lippman et al. 1992).

Our previous studies showed that subcutaneous injections of interferon alfa-2a in combination with other treatment modalities were successful in curing genital condylomata (Cardamakis et al. 1991b, Deligeoroglou 1992).

Douglas et al. (Douglas et al. 1986) reported that the presence of antibody to human immunodeficiency virus correlated significantly with a negative response to intralesional interferon alfa-2b treatment in patients with condylomata. All of our patients were human immunodeficiency virus antibody negative.

The hallmark of human papillomavirus infection is epithelial hyperplasia (Lutzner 1983) and retinoids have an endogenous antiproliferative effect through control of epithelial cell differentiation (Sporn 1981). Retinoids also have an immunomodulatory effect that we believe may have been of particular benefit in patients with recurrent human papillomavirus-related tumors and could complement the same effect seen with interferons (Borden and Ball 1981).

We found a statistically significant shorter treatment period was required to achieve remission in the group of patients who received interferon alfa-2a plus isotretinoin (1.9 vs 2.5 months). In our previous study (Deligeoroglou et al. 1992) in adolescents where etetrinate alone (Tigason, Roche) and etetrinate plus interferon

alfa-2a were used, we did not observe significantly different cure rates between the two groups, but we observed a shorter treatment period to achieve remission in the group of patients who received interferon alfa-2a plus etetrinate (2 vs 2.75 months). These results confirm the possible synergistic effect of retinoids with interferon.

Our results (28 of 33 patients with a complete remission of the lesions with a mean follow-up of 11.45 months) seem satisfactory because of the high percentage of remissions (84.8%) and the relative short treatment time (1.9 months). Moreover, the isotretinoin dosage was limited to 1 mg per kg per day, as is usually suggested for treatment of other common diseases that are isotretinoin responsive. Parenteral therapy with interferon alfa-2a for recurrent condylomata accuminata is associated with side effects but, generally, these are well tolerated by patients and disappear with repeated injections. Patients are also able to administer subcutaneous injections at home, and thus can avoid frequent visits.

It is important to remember that long-term therapy with isotretinoin may cause serious side-effects such as bone toxicity (Pittsley and Yoder 1983, Sillevis-Smitt and De Mari 1984) and for this reason isotretinoin therapy for recurrent condylomata accuminata should be used only for a few months in carefully selected patients. The women should not become pregnant during and 2 months after treatment because of the teratogenic effects of this drug.

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