Recurrence of condylomata acuminata following cryotherapy is not prevented by systemically administered interferon

L J Eron, M B Alder, J M O'Rourke, K Rittweger, J DePamphilis, D J Pizzuti

Abstract
Objective—To determine whether interferon a-2a, when utilised as adjuvant chemotherapy following ablation of condylomata acuminata (genital warts) by cryotherapy, is effective in the prevention of recurrences.

Design—Randomised, placebo-controlled, double-blind study. Statistical analysis was by 2-tailed Fisher's Exact Test.

Patients—97 patients with recurrent condylomata acuminata.

Intervention—49 patients were treated with cryotherapy plus subcutaneously administered interferon a-2a, and 48 received cryotherapy plus placebo. Of these, 36 and 37 patients, respectively, completed the study and were evaluable.

Main outcome measure—Clinical eradication of condylomata for six months following adjuvant chemotherapy.

Results—By completion of the adjuvant chemotherapy, 10 (28%) interferon recipients and 16 (43%) placebo recipients experienced recurrences. At six months follow-up, 25 (69%) interferon and 27 (73%) placebo recipients experienced recurrences. In the six months following interferon therapy, only 31% of interferon and 27% of placebo recipients remained free of recurrences (p = 0·99).

Conclusions—Interferon a-2a administered subcutaneously offers no benefit as a chemotherapeutic adjuvant to cryotherapy when used alone in the therapy of genital warts in this population of patients with recurrent condylomata.

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Introduction
Condylomata acuminata (genital warts) may recur following treatment, especially if they are large,1 2 have been present for longer than six months,3 are on dry skin surfaces such as the penile shaft and scrotum,1 or if they are associated with an underlying immunodeficiency.2 Interferon, when injected intralesionally into recurrent condylomata, is an effective therapy,2 4 5 but is cumbersome to prescribe owing to the necessity for repeated injections administered in a clinic setting. Moreover, many patients and physicians may prefer ablative or physically cytotoxic therapies for more rapid removal of condylomata. Because recurrences of condylomata are troubling to patients, resulting in costly, repetitive, and often ineffective therapies, it would be especially appealing to use interferon self-injected subcutaneously as a chemotherapeutic adjuvant to an ablative therapy, such as cryotherapy or laser, to prevent recurrences of warts expected to be refractory to treatment. We therefore undertook a double-blind, placebo-controlled trial of subcutaneously administered interferon as a prophylaxis against recurrence following cryotherapy of refractory warts.

Materials and methods
Subjects referred to our clinic (97 men and women) were entered in this study if they were at least 18 years old and had clinically and histopathologically-confirmed external condylomata acuminata. Patients were excluded if they were pregnant or lactating, had concomitant dermatological disease in the area of the condylomata, or if they had significant haematologic, renal, hepatic, cardiac, pulmonary, or neurological disease. They were excluded if they had had any prior treatment of warts within 14 days, any prior treatment with interferon, if they were HIV positive, or if they had other significant immunosuppression.

Patients were initially examined and a complete blood cell count, chemistry profile, urinalysis, and HIV ELISA antibody were performed before therapy. The number, distribution, and appearance of external condylomata were documented. Condylomata were measured in cubic millimeters of wart volume (greatest diameter x height of the perpendicular). One lesion was biopsied for histological confirmation and hybridisation for human papillomavirus (HPV) subtyping.

Assignment of patients to subcutaneous interferon (3 × 106 IU of interferon a-2a 3 times weekly × 8 weeks) (Roferon-A, Hoffman-La Roche, Inc, Nutley, NJ) or placebo was determined by means of a computer-generated, randomised code. Those patients with disease duration less than nine months were assigned from drug code No 1 proceeding sequentially forward. Those with disease greater than nine months' duration were assigned from drug code No 100 working sequentially backwards, to accomplish equal stratification, with regards to disease duration.

All patients then received sufficient cryotherapy (liquid nitrogen—three freeze-thaw cycles once weekly) to clear visible
warts. Interferon treatment began within two weeks of the last cryotherapy treatment. Study personnel taught the proper technique for subcutaneous self-administration of study medication utilising rotating sites (thigh, abdominal fat pad, and deltoid in sequence). They were treated and evaluated in a double-blind fashion at post-interferon therapy months one, three, and six for disappearance or recurrence of their condylomata. Recurrences were considered an endpoint for evaluation of efficacy and those patients were no longer followed in the study. Analysis of results was performed by utilisation of Fisher's Exact Test (2-tailed).

**Results**

Of 97 patients originally entering the study, 49 were assigned to receive interferon and 48 placebo. The demographics of the two groups are illustrated in the table. All patients' HPV types were either six or 11. Of this group, 36 interferon recipients and 37 placebo recipients completed the study with eight and ten patients, respectively, lost to follow-up. A further six patients discontinued therapy because of adverse drug reactions. Thus, 73 of the original 97 were evaluable for efficacy.

Prior to completion of eight weeks of interferon therapy, ten patients (28%) began to develop recurrences, compared with 16 (43%) of the placebo recipients. Recurrences continued to occur during the six month follow-up period such that 25 of 36 (69%) in the interferon group recurred compared with 27 of 37 (73%) in the placebo group. Conversely, 31% and 27% of the respective groups remained free of clinically active disease during the six month follow-up period. The rate of recurrence of condylomata is displayed in the figure. There was no significant difference between these two groups ($p = 0.99$). Nor was there a difference in the total numbers of warts that recurred between the interferon and placebo groups. The interferon group had a median of 6-8 warts per patient pre-treatment and 3.3 at the conclusion of therapy while the placebo group had 7-8 and 4.8 warts.

Adverse drug reactions were noted in 43 of the 49 (88%) interferon recipients and in 20 of 48 (42%) placebo recipients. Adverse experiences resulting in withdrawal from the study included an influenza-like syndrome (fever, chills, headache, myalgia, and nausea) in three interferon and one placebo recipients, bronchospasm in one interferon recipient, and depression in one interferon recipient. Local reaction to the injection was noted in six interferon recipients and one placebo patient.

**Discussion**

We chose to study patients most of whom had received prior therapies a mean of 5.6 times in the interferon group and 4.5 times in the placebo group. Condylomata had been present a mean of 29.6 months in the interferon group and 34.7 months in the placebo group. Both of these factors are strongly correlated with recurrence. We treated a number of males with penile condylomata, a location often refractory to therapy. We chose to treat these patients with cryotherapy, a relatively less cytodestructive procedure than laser, because cryotherapy requires no local anaesthesia. We treated each wart an average of three times but 26 patients (12 interferon and 14 placebo recipients) took more than five treatments to clear which reflects the refractory nature of these warts. Our experience as well as others has demonstrated clearance rates of about 70% are obtained when cryotherapy is used an average of three times on nonrefractory condylomata (such as smaller condylomata present on wet mucosal surfaces for six months).

Following our ablation of condylomata with cryotherapy, many began to recur even prior to completion of the interferon adminis-

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**Table** Demographics of study patients

<table>
<thead>
<tr>
<th></th>
<th>Interferon</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>28/21</td>
<td>35/13</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Mean duration of warts in months</td>
<td>29.6</td>
<td>34.7</td>
</tr>
<tr>
<td>Patients with prior therapy</td>
<td>32</td>
<td>39</td>
</tr>
<tr>
<td>Mean number of prior therapeutic courses</td>
<td>5.6</td>
<td>4-5</td>
</tr>
<tr>
<td>Median number of warts per patient</td>
<td>6-8</td>
<td>7-8</td>
</tr>
<tr>
<td>Median volume of warts (mm²)</td>
<td>135</td>
<td>215</td>
</tr>
</tbody>
</table>

**Figure** Recurrence of condylomata following cryotherapy and treatment with interferon (○) or placebo (●).
Recurrence of condylomata acuminata following cryotherapy is not prevented by systemically administered interferon

...ation (28% of the interferon group compared to 43% of placebo recipients). Further recurrence was noted in the six months following interferon therapy to the point where only 31% and 27% of each respective group remained free of active disease at the end of the study. As in our study, when cryotherapy was used in another study7 as the ablative technique, the addition of systemic interferon was no more effective than cryotherapy alone. Patients in this study were given interferon α-2a 3 x 10^6 IU subcutaneously twice weekly versus placebo in addition to cryotherapy weekly for seven weeks. The interferon group had a clearance rate of 30% and the placebo group 40%.

While no benefit of interferon in the prevention of recurrence following ablation of condylomata with cryotherapy was noted in these studies, efficacy has been noted when laser is utilised. Using extended laser treatment, condylomata were removed and patients then received interferon α-2a or α-2b subcutaneously, 1 to 5 x 10^6 IU 3 times weekly for 4 to 10 weeks. Success rates of 23 to 40% in those treated with laser alone and 52 to 82% in those treated with laser plus interferon were observed.8-10

The discrepancy between failed studies employing cryotherapy as the ablative procedure and successful ones utilising laser with adjuvant interferon may relate to the extension of laser treatment to the adjacent acetowhite areas which may harbour subclinical disease as a reservoir of human papillomavirus. This potential reservoir of virus if not destroyed by cryotherapy may then reinfest denuded areas of epithelium following treatment, resulting in recurrence of the condylomata. Certainly in the setting of suboptimal removal of recurrent condylomata with cryotherapy, subcutaneously administered interferon does not seem to have a systemic effect on prevention of recurrence of condylomata. If the results8-10 utilising laser with interferon as an adjuvant are reproducible in larger studies, it may be that laser in combination with systemic interferon

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