Systemic interferon therapy for female florid genital condylomata

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Summary: A prospective randomized study comparing systemic interferon therapy with placebo in women with florid genital condylomata was carried out. A first group of 22 patients received alpha-interferon (Alfaferone: Alfa-Wassermann Bologna, Italy). 3×10^6 IU by i.m. injectoin every other day for four weeks (total of 12 injections). A second group of 20 patients was treated with a placebo. All patients, before therapy, were submitted to a colposcopic and vulvoscopic examination, a Pap smear and biopsy, in order to confirm the clinical diagnosis. Controls were carried out on all patients as a distance of three, six and twelve months from the end of treatment using colpocytologic, colposcopic and vulvoscopic examinations.

One year after the termination of the therapy with interferon 45.4% of patients had a complete recovery compared with 10% of spontaneous recovery in the control group ($p=0.028$).

The systemic side effects of alfa-interferon, though very frequent, did not limit the use of the product.

Our results suggest that systemic alfa-interferon treatment is effective in female genital condylomata, above all in those patients with multifocal florid lesions, both in terms of complete remission and number of relapses.

Key words: Genital condylomata; Alpha-interferon.

INTRODUCTION

Epidemiological data have shown that genital condylomata is the most common viral type of sexually transmitted disease found in Western countries ([1]). Signs of infection from human papillomavirus (HPV) have been found in percentages varying from 2% to 10% during colposcopic screening programs ([2, 3]). The types of virus most frequently found in association with condylomata acuminata are types 6 and 11, and less frequently 18 ([4]). The genital infection from HPV has been seen as being closely correlated to genital neoplasia. In reality, the viral DNA was found in about 90% of Cervical Intraepithelial Neoplasia (CIN) and cervical carcinoma and with lesser frequency also in vulvar, anal, and penile neoplastic lesions ([5, 6]). Due to this oncogenic potential and to reduce the possibility of contamination and spreading of the infection numerous kinds of treatment were proposed, such as surgical excisions, trichloroacetic acid, DTC, cryotherapy, and laser therapy.

Inasmuch as surgical techniques are efficient in the destruction of the viral lesions, they are complicated by a high frequency of relapses (30-40% of the cases)

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likely caused by the persistence of a subclinical infection ([7, 8, 9, 10]). The certain role that the immune systems has in the development and the control of HPV infection, as documented by studies conducted on immunosuppressed patients ([11]), induced some authors to use immunomodulatory drugs in the therapy of this infection. Among these substances, defined also as biological response modifiers, the most used nowadays are the interferons that both live and, in vitro, are shown to have specific anti-viral properties, an anti-growth effect and immunostimulative activity. The interferon that we used, is an alpha interferon obtained from normal human leucocytes (Alfaferone-Alfa-Wassermann Bologna, Italy). The aim of this study was to evaluate the efficiency of alpha interferon by systemic means in the treatment of florid condylomata of the female genital tract.

MATERIALS AND METHODS

From January 1990 to June 1992, 42 patients with multiple genital florid condylomatous lesions, controlled at the Colposcopy and Colpocytology Clinic of the 1st Obstetric and Gynecological Department of the University of Bologna, were recruited for this study. Not all of the patients, who were between the ages of 17 and 48 years (average age 29), had had previous treatment for this pathology.

All patients were submitted to a colposcopic and vulvoscopic examination, a Pap smear and a biopsy, in order to confirm the clinical diagnosis. Those patients having multiple viral florid lesions without signs of CIN and Vulvar Intraepithelial Neoplasia (VIN), and who were available for follow-up were included in the study. We excluded pregnant women, patients affected by systemic illnesses or autoimmune pathologies, and those with immunosuppression. A first group of 22 patients, chosen at random, were treated with alpha interferon according to the following therapeutic model: 3×10^6 IU by intramuscular injection every other day for four weeks, for a total of 12 injections. The remaining 20 patients were treated with a placebo. The patients given interferon, having been informed of the drug's possible side effects, were advised not to take any drugs, such as acetylsalicylic acid, indomethacin, and cortisones that could interfere with the interferon.

Controls were carried out on all patients at a distance of three, six and twelve months from the termination of treatment using colpocytologic, colposcopic, and vulvoscopic examinations. The effects of the therapy were evaluated as complete response (complete disappearance of overt warts) partial response (reduction of the dimensions and number of warts), no response, and progression of the infection. The data collected was statistically analyzed using the χ^2 test.

RESULTS

In Table 1 the distribution of the HPV lesions in the two groups treated with interferon and placebo is illustrated. It can be observed that the areas most commonly hit are the vulva, the vagina, and the perineum, while in about a third of the cases the condylomata are multifocal.

At a distance of three months from the termination of the therapy with interferon seven patients (31.8%) showed complete disappearance of lesions during a colposcopic examination, eight patients had partial disappearance (36.4%) and seven (31.8%) no response to treatment. At the next examination, at a distance of six months, two patients with partial response and one patient who initially had no response were found to have complete disappearance of the lesions with a total percentage of recovery of 45.4%. One year after treatment no further disappearance of the viral lesions has been found. In no case did we observe a progression of the disease, while in one patient who

Table 1. — *Localization of genital florid condylomata in patients treated with interferon (group A) and placebo (group B).*

Area	Group A	Group B
Vulva perineum	11	13
Anus	4	3
Vagina	5	4
Cervix	2	0
Multi-focal	8	6
Total	22	20

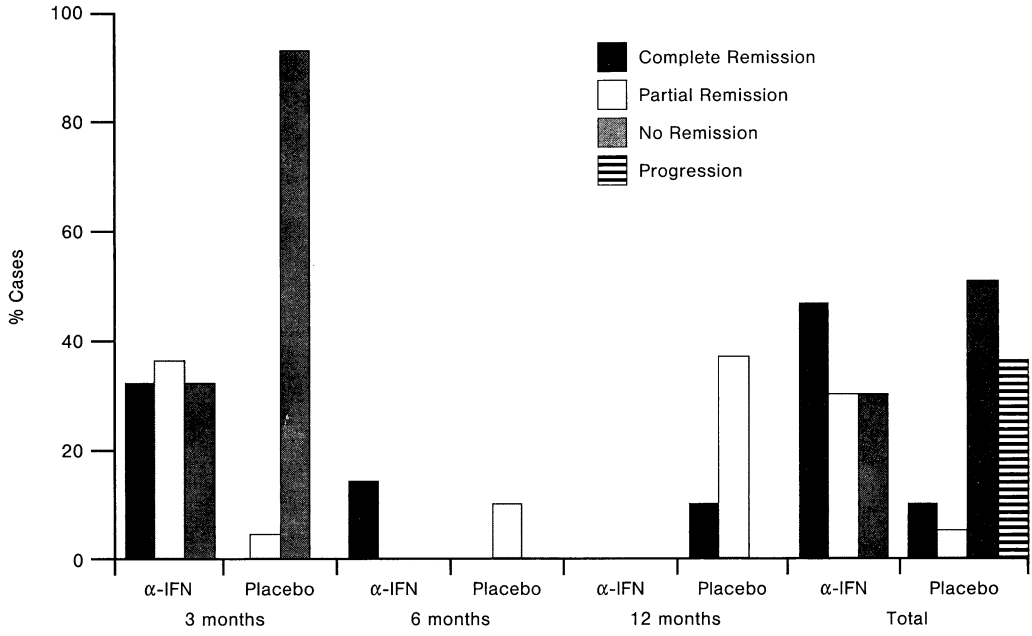

Fig. 1. — Results of treatment of genital condylomata with α - interferon or placebo.

had a complete response, a relapse occurred after six months (Fig. 1). In the control group treated by placebo the partial disappearance of lesions was observed in one case after three months and in two cases after six months. At a distance of twelve months, these two patients were observed to have a complete disappearance of lesions, therefore having a 10% total rate of spontaneous recovery.

In ten patients the clinical aspect remained almost unchanged after one year, while in seven cases the viral lesions had advanced both in number and in extent (Fig. 1). The statistical analysis of the rate of recovery observed in the two groups showed a significant difference ($p=0.028$). Side effects of the interferon were observed in 17 patients (77.2%), even if they were most often mild and did not require the suspension of the treatment. The most frequent side effects were found to be: fever, headaches, myalgias and asthenia as illustrated in Table 2. The fevers, which were never above 38.5 C°, appeared on the average 4-5 hours after the injection and were more frequent at the beginning of the treatment. Other side effects such as weight loss, anorexia and hair loss were observed in only a few cases and usually appeared during the second week of treatment, and could persist even after the end of the therapy.

Table 2. — *IFN therapy side effects.*

Side effects	Mild	Moderate	Severe	Total
Fever	13	2	–	15 (68.1%)
Myalgias	6	1	–	7 (31.8%)
Headache	1	1	–	2 (9%)
Asthenia	2	–	–	2 (9%)
Anorexia	2	–	–	2 (9%)
Weight loss	1	–	–	1 (4.5%)
Alopecia	–	–	–	–

CONCLUSIONS

Regardless of the progress observed in the last few years, we still do not have a specific treatment for complete eradication of the HPV infection. The local destructive treatments, carried out by colposcopic means, though having a high rate of recovery (90%), are burdened with a high percentage of relapses that vary from 7% to 33% ([9, 10]).

Systemic interferon therapy has the advantage of action on the entire infected epithelium independently of the clinical and colposcopic aspect of the lesion. This offers noteworthy advantages, not only in cases of spread lesions, but also in all other clinical features where the physical therapy, unable to resolve the problem of the latent infections, causes a clinical but not biological recovery.

The results we obtained using a systemic treatment of natural alpha interferon from human leucocytes are satisfactory for the high rate of complete recovery (45.4%), significantly superior in respect to the group of women treated by placebo (10%). In addition, in only one case did we observe a relapse six months after the end of the treatment. Other authors, having used different forms of interferon and different doses, obtained even better results than our own with percentages of complete remission varying between 50% and 80%. Using interferon alpha-2a Gall *et al.*, obtained complete recovery in 50% of the cases of persistent HPV infection ([12]); Schönfeld *et al.* obtained a success rate of 82% of the treated patients with beta interferon, compared to 20% in the control group ([13]).

Welander and Friedman reported complete remission in 43.8% and 62% of the cases respectively using interferon alpha by intra-lesional injection ([14, 15]). It needs to be underlined that, in our study, we selected patients having widespread viral florid lesions, which are considered by some authors to be less responsive to interferon therapy ([16]). Eron *et al.* have also demonstrated that repeated cycles of interferon can be effective in cases where the lesions tend to recur ([17]). The possibility of repeating interferon cycles in cases with high risk of relapse and further studies for optimizing the dosage and the concentration of the drug at the level of the genital epithelium may improve the results. The systemic side effects, though very frequent, did not limit the use of alpha interferon. Probably the use of a natural product, obtained from normal human leucocytes, improved the tolerability of this drug which, being a very active biological substance, can cause numerous systemic effects.

In conclusion it seems to us that excellent results, above all in those patients with multifocal florid lesions, both in terms of complete remission and number of relapses could be obtained through a combination of treatments including interferon with destructive physical therapies.

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