

# Topic and systemic administration of natural alfa interferon in the treatment of female and male HPV genital infections

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*Summary:* The aim of the study was to evaluate the effectiveness and tolerance of topic and systemic administration of natural alfa-interferon from normal human leukocytes in the treatment of HPV lesions of the lower genital tract. From May 1991 through May 1992, 70 women (mean age = 29; range 16-42) and 51 men (mean age = 28; range 18-48) with histologically proven HPV genital lesions were studied. 43 patients and 32 male partners with subclinical infection underwent cream therapy (4 applications/day for 30 days) composed of natural alfa interferon and containing 1,000,000 IU/gr. 27 women and 19 men affected by florid infection underwent systemic i.m. therapy with natural alfa interferon in doses of 3,000,000 IU on alternate days for 30 days. The percentage of therapeutical success amounted to 55.8% for women and 78.1% for men subjected to topic therapy; for the 27 patients and 19 male partners treated with systemic therapy the final percentages of success were 70.3% respectively. Natural alfa interferon from normal human leucocytes seems to be a drug of good efficacy and tolerance in the treatment of HPV genital pathology.

*Key words:* Human papillomavirus; Condylomata; Alfa interferon.

## INTRODUCTION

HPV genital pathology is probably the most widespread sexually transmitted disease. The incidence of this infection is greater in the age range from 20 to 30 years (<sup>1-3</sup>) and since it is a "disease of the

couple" the necessity of studying and treating adequately both the patient and her partner (<sup>4-9</sup>) has by now been largely recognized.

Up to now, thanks to the newer methods of molecular biology, it has been possible to demonstrate the existence of more than 60 different types of HPV; among these, types 6, 11, and 42 are regarded as being at low-risk of oncogenic transformation, whereas types 16, 18, 31, 33, and 39 are considered to be at high risk (<sup>10-14</sup>).

Due to the possibility of oncogenic risk, treatment of HPV infections must not only aim at the elimination of lesions, but also at the control of recurrences.

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Physical destructive therapies, laser surgery in particular, are without doubt effective in the treatment of this pathology; furthermore, up to now, several drugs such as podophyllin, FU-5, trichloroacetic acid, etc. have been used against genital condylomatosis. However, in view of the well-known role and involvement of the immune system, particularly of its cell-mediated function, in the defence against viral infections, it seems more natural today to use as drugs those substances able to modify the biological response to viral infections.

Among these, those more widely used are interferons since these cytokines can carry out immunomodulatory, antiviral, and anti-proliferative functions at the cell level <sup>(15)</sup>.

Based on these presuppositions, we studied 70 patients and 51 male partners affected by HPV viral lesions of the lower genital tract in order to evaluate the effectiveness and tolerance of natural alfa interferon from normal human leukocytes administered both topically and systematically via i.m.

## MATERIALS AND METHODS

From May 1991 through May 1992, at the Colposcopic and Laser Therapy Unit of the II Clinic of Obstetrics of the University of Rome "La Sapienza", 121 patients — 70 women and 51 partners — with histologically assessed HPV genital infections were studied.

Mean age of female patients was 29 years (range = 16-42); mean age of partners was 28 years (range = 18-48). All women underwent colposcopic examination of the entire lower genital tract (vulva, vagina, cervix, and perineum) and in all cases we performed both eso- and endocervical cytology as well as a directed biopsy of the suspected lesions.

Partners underwent peniscopy and biopsy of the suspected lesions.

The area of lesion extension was measured in cm<sup>2</sup>.

On the basis of the results of the clinical-colposcopic evaluations, our two study groups were further divided into 4 subgroups.

The 70 women were divided into two groups: the first was composed of 43 patients with sub-

clinical infections and the second of 27 patients with florid lesions; of the 51 male partners, 32 were affected by subclinical condylomatosis and 19 presented florid lesions.

In the group of 43 female patients, subclinical lesions were distributed as follows: 13 (30.2%) cases of micropapillary lesions, 8 (18.6%) of macular lesions, 6 (14%) of papular lesions, and 16 (37.2%) cases of mixed type; the site of the lesions was the vulva with involvement of the labia minora in 18 (41.9%) patients, the fourchette in 7 (16.3%) patients, urethral meatus in 4 (9.3%), and multiple-sited infections in 14 (32.5%) patients.

As for the group composed of 27 pts. with florid condylomatosis, 20 (74.1%) of them had infections in the vulvo-perineal region, in 2 (7.4%) cases the site involved was the vagina, and in 5 (18.5%) cases vulvo-perineal and cervical infections coexisted.

As for the group of 32 partners, in 13 (40.6%) cases the lesions were of the papular type, in 10 (31.3%) of the macular type, in 7 (21.9%) the lesions were acuminata and 2 (6.2%) partners had a mixed form; the sites of infection were the frenulum in 14 (43.8%) cases, the glans in 7 (21.9%), the balanopreputial sulcus in 5 (15.6%) partners, the shaft in 2 (6.2%), while 4 (12.5%) patients had multiple-sited infections.

Out of the remaining 19 partners affected by florid and extended condylomatosis, 11 (57.9%) patients had lesions on the shaft, 3 (15.8%) cases involved the scrotum, 2 (10.5%) cases the glans, and in 3 (15.8%) partners we recorded multiple-sited lesions.

Tables 1, 2, and 3 show the clinical findings of all the patients included in the study.

We ruled out of our study patients previously subjected to medical of physical destructive therapies, pregnant women, patients affected by pre-invasive forms, those with autoimmune pathologies, hepatitis, bronchial asthma, patients subjected to chemo-, anti-blastic, immunosuppressive and corticosteroid treatments and HIV seropositive patients.

All the patients gave their verbal consent to take part in the study.

Both the 43 female patients affected by subclinical vulvar infections and the 32 partners with subclinical HPV penile infections underwent topical therapy with a cream (in carboxymethylcellulose and glycerine) containing natural alfa interferon from normal human leukocytes and 1,000,000 IU per gram of substance (\*), administered 4 times a day for 30 days.

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(\*) Alfaferone cream, Alfa Wassermann.

Table 1. — *Type and site of lesion in the 43 patients affected by subclinic vulvar condylomatosis.*

Type of lesion				Site of lesion			
		N.	%			N.	%
Micropapillary	. .	13	30.2	Labia minora	. . .	18	41.9
Macular	. . . . .	8	18.6	Fourchet	. . . . .	7	16.3
Papular	. . . . .	6	14	Meatus	. . . . .	4	9.3
Mixed forms	. . .	16	37.2	Multiple sites	. . .	14	32.5

Table 2. — *Type and site of lesion in the 32 men affected by flat condylomatosis of the penis.*

Type of lesion			Site of lesion		
	N.	%		N.	%
Papular . . . . .	13	40.6	Frenulum . . . . .	14	43.8
Macular . . . . .	10	31.3	Corona glandis . .	7	21.9
Acuminata . . . . .	7	21.9	Sulcus . . . . .	5	15.6
Mixed forms . . . .	2	6.2	Shaft . . . . .	2	6.2
			Multiple sites . . .	4	12.5

The 27 women and 19 partners with florid genital condylomatosis underwent a systemic i.m. therapy with natural alfa interferon in a dose of 3,000,000 IU(\*\*) on alternate days for 1 month.

Follow-up required clinical-colposcopic controls 1, 3, and 6 months after the end of therapy.

Immediately before systemic therapy and 15 days after it began, we checked patients' hemochrome, platelets, and liver markers, in order to evaluate possible hematochemical variations.

Furthermore, we assessed both the nature and the extent of any side effects of the systemic therapy.

We considered negative findings at the end of follow-up as total response to therapy, a 50% reduction of lesions as partial response, and a lesion improvement of less than 50% as no-response to therapy.

## RESULTS

Of the 43 patients subjected to topical therapy with natural alfa IFN, 14 (32.6%) showed a total response to treatment at 3 and 6 months from the end of therapy; 10 (23.2%) patients reacted partially to treatment; 18 (41.9%) patients did not respond to therapy, and 1 (2.3%) patient was lost at follow-up.

(\*\*) Alfaferone phial, Alfa Wassermann.

Table 3. — *Lesions distribution in 27 patients and 19 male partners affected by florid condylomatosis.*

W O M E N			M E N		
	N.	%		N.	%
Vulva + Perineum .	20	74.1	Shaft . . . . .	11	57.9
Vagina . . . . .	2	7.4	Scrotum . . . . .	3	15.8
			Glans . . . . .	2	10.5
Vulva + Perineum + Cervix . . .	5	18.5	Multiple sites . . .	3	15.8

Table 4. — *Subclinical vulvar condylomatosis: topical treatment with natural alfa interferon.*

	I		II		III	
	N.	%	N.	%	N.	%
Total response . . .	7	16.3	14	32.6	14	32.6
Partial response . .	14	32.6	10	23.2	10	23.2
No response . . . .	21	48.8	18	41.9	18	41.9
No follow-up . . .	1	2.3	1	2.3	1	2.3
Total . . . . .	43	100	43	100	43	100

Total percentage of response to therapy, given by total recoveries plus partial remission was 55.8% (Table 4).

As for the partners subjected to topical therapy, 23 (71.9%) of them responded completely to treatment with confirmed recovery at the end of follow-up: 13 (40.6%) partners were already healed by the first control after therapy, 8 (25%) showed total recovery at the second control and 2 (6.25%) by the end of the study. In 2 (6.2%) patients we observed a reduction of lesions more than 50%, 6 (18.8) partners did not respond to therapy at all, and 1 (3.1) was lost at follow-up (Table 5).

From the group of 27 patients with florid condylomatosis of the lower genital tract treated with systemic therapy, we obtained the following results at the end of follow up; in 14 (51.8%) patients we observed a total response (6 at the first control and 13 at the second); 5 (18.5%) patients responded partially to therapy; 7 (26%) (1 vaginal infection,

4 vulvo-perineal infections, and 2 vulvo-perineal and cervical infections) did not respond to treatment; 1 (3.7) woman was lost at follow-up.

Total percentage of response, i.e. total recoveries plus partial remissions, was 70.3% (Table 6).

As for the 19 partners affected by HPV florid infection we recorded total response to therapy in 11 (57.9%) patients (5 at the first control and 10 at the second), partial response to therapy in 3 (15.8%) patients, and no response to treatment in 5 (26.3%), although we did observe a slight regression of the lesions.

No partner was lost at follow-up.

In this group, total percentage of response to treatment was equal to 73.7% (Table 7).

In both groups of patients subjected to topical therapy we observed no significant side effects.

On the other hand, 11 (40.7%) patients among those subjected to systemic therapy showed side effects that can be

Table 5. — *Flat and acuminata condylomatosis of the penis: topical treatment with natural alfa interferon.*

	I		II		III	
	N.	%	N.	%	N.	%
Total response . . .	13	40.6	21	65.6	23	71.9
Partial response . .	8	25	4	12.5	2	6.2
No response . . . .	11	34.4	6	18.8	6	18.8
No follow-up . . .	—	—	1	3.1	1	3.1
Total . . . . .	32	100	32	100	32	100

Table 6. — Results of systemic treatment with natural  $\alpha$  interferon in 27 women affected by florid condylomatosis.

	I		II		III	
	N.	%	N.	%	N.	%
Total response . . .	6	22.2	13	48.1	14	51.8
Partial response . . .	13	48.2	6	22.2	5	18.5
No response . . . .	8	29.6	7	26	7	26
No follow-up . . . .	—	—	1	3.7	1	3.7
Total . . . . .	27	100	27	100	27	100

defined as "flu-like syndrome", with the main symptom being an increase in body temperature up to 39°C.

Such symptoms appeared after the first 3-4 administrations of the drug, and disappeared during continuation of therapy.

In no case was it necessary to suspend treatment; hematochemical parameters of the patients treated did not show significant variations.

Out of the 19 partners subjected to systemic i.m. administration of natural  $\alpha$  interferon, 9 (47.3%) showed symptoms classified among the drug's side effects. However, no patient required suspension of treatment.

Total incidence of side effects ascribable to the systemic use of the drug was equal to 43.5% in the two groups as a whole.

## DISCUSSION

Today the treatment of genital condylomatosis is still a major problem and the difficulties in eradicating HPV infections

are witnessed by the numerous therapies used up to now.

In the case of florid genital infection, physical destructive therapies provide effective treatment of visible lesions; CO<sub>2</sub> laser surgery is the method of choice as it enables one to operate with precision using a colposcopic guide, thus avoiding complications both in the short and long term.

Also in the case of subclinical genital infections, i.e. those lesions detectable only by colposcopy, physical destructive therapies can remove lesions effectively; on the other hand, different diagnostic and therapeutical implications arise when the virus is detectable only with the techniques of molecular biology.

However, it is commonly accepted that destruction of florid or subclinical lesions alone is not sufficient for total recovery from the disease, since the virus is able to detect its genoma in the cells adacent to the lesions and bring about a process of maintenance and re-induction

Table 7. — Florid condylomatosis of the penis. Results of systemic treatment with natural  $\alpha$  interferon.

	I		II		III	
	N.	%	N.	%	N.	%
Total response . . .	5	26.3	10	52.7	11	57.9
Partial response . . .	7	36.8	4	21	3	15.8
No response . . . .	7	36.8	5	26.3	5	26.3
Total . . . . .	19	100	19	100	19	100

of infection (<sup>16</sup>), thus confirming that recurrences and persistence of the disease are among the most crucial problems caused by this type of viral infection. Patients also experience, among other things, stressful psychological difficulties.

The clinical course of HPV infections is therefore unpredictable, although a major role seems to be played by the immune mechanisms, particularly the cell-mediated function (<sup>17</sup>), in the development, as well as, regression of the disease. For this reason, "pro-host" immuno-therapies have recently gained wide approval, and among the available drugs, interferon offers a range of extremely promising possibilities.

Alfa interferon used in our study is a glycoprotein composed of 166 aminoacids and produced by human leukocytes at their physiological status; we have knowledge of at least 18 subtypes of alfa interferon and probably in nature there is a sort of cooperation and reciprocal interaction among them.

Alfa interferon does not act directly on viruses, however, in the not yet-infected cells it produces a series of modification able to repel viral aggression.

After binding itself to a specific membrane receptor, alfa interferon forms a complex that is assimilated and that triggers a series of processes in the nucleus leading to the synthesis of various enzymes (<sup>18, 19</sup>):

- one 2'-5' oligoadenylate synthetase which activates an endoribonuclease that destroys viral RNA thus blocking its replication;

- one protein-kinase that through the phosphorylation by ATP stops the IF-2 peptide which is responsible for initiating viral proteic synthesis;

- one phosphodiesterase that inhibits ribosomic insertion of aminoacids, thus blocking viral proteic synthesis.

Furthermore, alfa interferon seems able to modify some properties of the cell membrane making it more resistant to

viral penetration; another typical function of interferon is the enhancement of the activity of the NK cells.

In HPV genital infections, interferon can be administered both topically, by the intra- and perilesional way, systemically via i.m. and subcutaneously.

In the literature there are many reports of studies giving satisfactory results of the use of interferon in the treatment of genital condylomatosis and pre-invasive lesions (<sup>20-24</sup>); in contrast, other studies report unreliable, if not discouraging, findings about the use of interferon (<sup>25-27</sup>).

In our study, we chose topical administration of alfa interferon for the 43 cases of subclinical vulvar condylomatosis and for the 32 patients suffering from subclinical and acuminata penile infection.

We observed a remarkable difference in response at the end of follow-up: 71.9% of the total response for male partners compared to a final 32.6% of the total response for the women, although by adding the partial responses the final percentage increased to 55.8%.

We assume that this gap is due to the size of the vulvar lesion, to the possible presence of keratosis or also to the difficulty in spreading the cream adequately over the infected area.

However, one of the advantages of topical administration is undoubtedly that it has no side effects.

As for the 27 patients with florid genital condylomatosis (vulvo-perineal, vaginal, and cervical) and the 19 partners affected by florid infection of the penis and scrotum we decided to administer alfa interferon systemically via i.m., which in theory offers the advantage of being able to reach all the infected cells, including those with latent infection. At the end of follow-up, we recorded similar percentages of total response among patients and male partners, although the latter showed a slightly higher score (57.9% vs 51.8%).

Furthermore, taking partial response to treatment into account, total results at the end of follow-up overlapped: 73.7% for male partners and 70.3% for patients.

Analysis of the results of each group of patients showed that there was a remarkable difference in response between the first and second control, whereas a slight difference was observed between the second and third control at the end of follow-up.

In view of these encouraging findings, we believe that the role of interferon as a monotherapy in the treatment of florid genital condylomatosis should be carefully evaluated further, whereas it is definitely an excellent complement to traditional destructive therapies, particularly in the prevention of recurrence and re-infection.

We devoted particular attention to the evaluation of side effects produced by use of the drug: in our study the incidence of side effects was equal to 43.5% out of a total of 46 patients treated.

The main symptom was an increase in body temperature, easily controlled with common antipyretics; in no case did we record variations of hemochromocytometric indexes or hepatic markers such as to require suspension of therapy; therefore, the drug produced a satisfactory tolerance in relation to the doses applied.

Another advantage of natural alfa interferon is that it has poor immunogenic power, since there is no induction of anti-interferon antibodies.

In conclusion, the use of interferon today in the treatment of HPV pathologies requires further study, and to this aim research is being directed on the one hand to a deeper knowledge of HPV viral biology, and on the other hand to a deeper knowledge of the actual physiological role of interferons.

In fact, understanding the new mechanisms of action and regulation is essential for widening the field of clinical application of these cytokines, optimizing therapeutic doses, choosing the best means

of administration of the drug, possibly modifying the "vector" of the preparation and, last but not least, minimizing side effects.

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