

VULVO-VAGINAL CONDYLOMATOSIS AND RELAPSE: COMBINED TREATMENT WITH ELECTROCAUTERIZATION AND BETA-INTERFERON

R. PICCOLI (*) - M. G. SANTORO (*) - C. NAPPI (*)
M. CAPODANNO (*) - V. DE SANTIS (*) - P. C. LA TORRE (**)
S. COSTA (***) - U. MONTEMAGNO (*)

(*) Department of Gynaecology Obstetrics and Physiopathology of Human Reproduction
II Faculty of Medicine and Surgery - University of Naples (Italy)

(**) Clinical Pharmacology Dept. "Serono" - Roma (Italy)

(***) "S. Orsola Hospital" - II Department of Obstetrics and Gynaecology
Faculty of Medicine and Surgery - University of Bologna (Italy)

Summary: The therapeutical effectiveness of beta-interferon and the possibility of reducing the incidence of relapses were evaluated by selecting three groups of patients affected with three forms of condylomatosis and submitting them to various treatments.

In the first group of sixty patients treated with beta-interferon, we obtained the best results in micro-condylomatosis (a 100% response), while florid condylomatosis responded less well to the treatment (72% with no response).

In the second group of ten patients, electrocoagulation of florid condylomata determined a complete response (CR) in seven cases (70%). Moreover, immunoperoxidase identified three cases of sub-clinical infection, two of which relapsed.

In the third group of ten patients, we combined electrocoagulation with beta-interferon. This combination showed the effectiveness of beta-interferon in decreasing relapses. This result is evident if we consider that only one out of four patients with immunoperoxidase-positive biopsy relapsed.

HPV = Human Papillomavirus; IFN = Interferon; CR = Complete response; PR = Partial response; AR = Absence of response; DTC = Diathermocoagulation.

INTRODUCTION

Vulvo-vaginal condylomatosis is nowadays one of the most common sexually transmitted diseases. Its incidence has been greatly increasing during the last years, assuming an almost epidemic aspect in some areas. The therapy and relapses of condylomata acuminata have not been standardized either for the absence of an "in vitro" growth model (HPV has never been found proliferating in cell cultures) or for the unpredictable evolution of HPV lesions. In fact a possible evolution of microcondylomatosis and/or condylomata acuminata to more complicated, dyskeratotic and dysplastic forms, such as Cervical Intraepithelial Neoplasia and Vulval Intraepithelial Neoplasia, has been observed (^{1, 2, 3}).

Different therapeutical approaches have been attempted, including caustics and keratolytics: podophyllin, trichloroacetic acid, 5fluorouracil, colchicine, deoxyuridine, together with physical therapies, such as electrocoagulation, cryotherapy and laser-vaporization (⁴).

All of these treatments provided short-term improvements but the results were particularly unsatisfactory when relapsing forms occurred.

Some years ago, a new therapeutical chance presented itself with the use of interferon (IFN), an antiviral glycoprotein which can be synthesized by human leucocytes (alpha-IFN), fibroblasts (beta-IFN) and lymphocytes (gamma-IFN) (⁵).

Interferon does not act directly on the virus. Its anti-infectious effectiveness re-

sults from preventing the infection of the undamaged cells, determining conditions interfering with or stopping different metabolic pathways on which reproduction and survival of the viral agents depend⁽⁶⁾.

Interferon seems to affect protein synthesis by inhibiting transcription and/or translation. Interferon also inhibits viral assembly. Another property of IFN is stimulation of immunocompetent cells as

MATERIAL AND METHODS

In order to assess the therapeutical effectiveness of beta-IFN, we selected 60 patients presenting three different forms of condylomatosis, in the Colposcopic Unit of the Department of Obstetrics and Gynaecology of the II Medical Faculty of Naples.

Requirements for inclusion in the trial were: disease diagnosed more than 2 months previously by colposcopic, cytological and histological examination, and age ranging from 18 to 60 years.

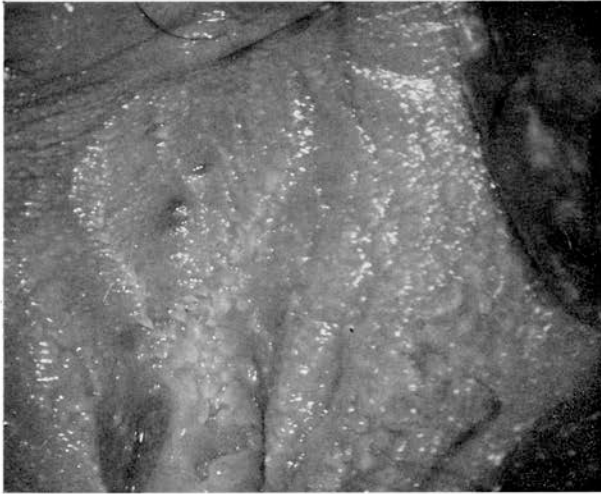


Fig. 1. — Microcondylomatosis.

natural killers (NK) and macrophages. Its antiviral activity is particularly due to the activation of cellular immunity^(7, 8).

In this study, we aim to confirm the results reported by other Authors^(9, 10, 11), addressing our interest particularly towards the treatment of relapsing condylomatosis which seems to be a critical point of therapeutical protocol.

The aim of our study which started in February 1985 and was completed in July 1987, was to evaluate:

1) the therapeutical effectiveness of beta-IFN;

2) the possibility of decreasing the incidence of relapses.

Factors of exclusion were: pregnancy, therapy with cytostatics, immunostimulators and steroids; hepatic, renal or cardiac insufficiency.

Three forms of condylomatosis were recognized: micro-condylomatosis (early condylomata) in 10 patients (fig. 1); condylomata acuminata (young condylomata) in 25 patients (fig. 2); florid condylomatosis (old condylomata) in 25 patients.

We differentiated florid condylomatosis from condylomata acuminata both by colposcopic features and by the extent of the damaged area: condylomata acuminata shows in area less than 30 mm² while florid condylomatosis presents a surface larger than 20 mm².

Colposcopy was performed by using a Leisegang photocolposcope allowing magnification up to $\times 15$ and cleaning the vulva with a solution of acetic acid 5%, vagina with acetic acid 3% and then with Lugol solution.

Micro-condylomatosis, difficult to diagnosed inspectively, is evidenced by colposcopy as small circular outgrowths with a white apex. Condylomata acuminata are intensely white, finger-like projections with a vascular axis that appears clear only at the apex of the condyloma.

Finally, florid condylomatosis, a generally multi-focal form, consists of clusters of condylomata acuminata more easily demonstrated with acetic acid.

Cytologic smears, processed and stained by using Papanicolaou's procedure showed cellular changes produced by HPV, consisting of koilocy-

the condyloma's area); absence of response (AR- when the condyloma's area did not change).

The high infectivity of HPV and the possibility of a re-infection in the couple justified our attention in researching condylomatous lesions in partners. They were submitted to accurate anamneses, examinations of genitalia, colposcopic examinations of the penis, urinary cytology and cytologic examination of the meatus urinarius and, if necessary, to a histocological drawing, with modality and results similar to those obtained in female patients.



Fig. 2. — Microcondylomatosis and condylomata acuminata.

tosis and VCE (viral cytopathic effect). Aimed biopsy was performed with Schumacher biopsy forceps.

Histology showed elongation of papillae covered with parakeratotic and acanthotic squamous epithelium including a connective-vascular axis, the site of chronic phlogosis and cellular koilocytosis.

All patients were treated indifferently with beta-IFN (Frone-Serono) i.m. according of the following scheme:

- 1) first week: 3 000 000 I.U. \times 5 days + 2 days' interval;
- 2) second week: 2 000 000 I.U. \times 5 days + 2 days' interval;
- 3) third week: 2 000 000 I.U. \times 5 days + 2 days' interval.

The therapeutic effect was evaluated as follows: complete response (CR- disappearance of disease); partial response (PR- reduction of

Male patients were treated with local beta-IFN 4 times a day for 10 days. Prominent condylomata were treated with cryo-coagulation combined with beta-IFN.

As regards our second aim: "possibility of decreasing the incidence of relapse", we selected two groups of patients adopting the same criteria of inclusion and exclusion.

The patients of the first group (ten cases) were treated only with bipolar biactive aimed diathermocoagulation (DTC) (Diacut Wipamed equipment) under colposcopic control in narcosis.

After the therapy, we biopsied the normal tissue peripherally to the lesion, then stained it by using the indirect immunoperoxidase technique (12).

Bioptical specimens were fixed in 10% neutral formalin, embedded in paraffin, and stained

with hematoxylin-eosin. The deparaffinized sections were sequentially incubated with normal goat serum, guinea pig anti-HPV serum, rabbit anti-guinea pig whole serum, goat anti-rabbit whole serum, and rabbit peroxidase-antiperoxidase soluble complex (13).

Positive reaction for detection of HPV-antigens was represented by brown intranuclear precipitates in koilocytical superficial cells.

The second group (ten cases) was treated combining DTC and therapy with beta-IFN, according to the following schema:

1) first week: 3 000 000 I.U. \times 5 days + 2 days' interval;

2) second week: 2 000 000 I.U. \times 5 days + 2 days' interval, after four months, this cycle was repeated.

We performed bioptical drawing for immunoperoxidase stain before beta-IFN therapy and after second cycle.

A follow-up of 3-6-12 months was carried out in all patients.

RESULTS

Beta-IFN showed different effectiveness in the three forms of the condylomatosis we studied.

During follow-up, we obtained a complete disappearance of microcondylomatosis, corresponding to 100% of CR.

Only in ten cases (40%) of condylomata acuminata we observed a CR; in seven cases (28%) a PR and in 8 cases (32%) not only an AR but, on the con-

trary, an increased propagation of disease. In 25 cases of florid condylomatosis, we did not have CR, while we had a PR in seven cases (28%) and an AR in the remaining 18 cases (72%).

Analysing the incidence of relapse in two groups of patients submitted to different treatments (only DTC, or DTC with beta-IFN) we noticed a different response. In the first group of ten patients treated with DTC only, indirect immunoperoxidase on the zones near the lesions revealed, in 3 cases (30%), the presence of HPV-antigens, confirming the location of the virus in normal tissue (fig. 3).

During the follow-up, only two of these three cases developed a relapse (within 6-7 months), while the remaining one resulted completely undamaged, perhaps because of a spontaneous remission of the disease.

In the second group of 10 patients treated afterwards, we combined DTC

Table 1. - Effectiveness of beta-IFN treatment *i.m.* (Frone Serono) in 60 patients with vulvo-vaginal condylomatosis.

	No. of cases	CR	PR	AR
Micro-condylomatosis	10	10 (100%)	0	0
Condylomata acuminata <30 mm ²	25	10 (40%)	7 (28%)	8 (32%)
Florid condylomata >30 mm ²	25	0	7 (28%)	18 (72%)
	60	20 (34%)	14 (23%)	26 (43%)

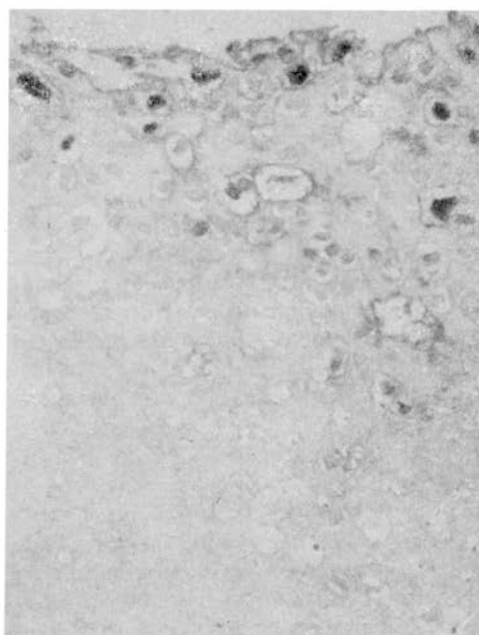


Fig. 3. — Positive immunoperoxidase on normal tissue.

with beta-IFN therapy. Immunoperoxidase on the adjacent normal tissue, soon after DTC, showed active replication of HPV in 4 cases out of 10 (40%); then was reduced, after the second cycle of beta-IFN treatment, to one case with subsequent relapse.

Table 2. - Treatment immunoperoxidase positivity (impo+) and incidence of relapses in two different groups of patients.

	Treat- ment	No. cases	Impo +	Impo --
I group	DTC	10	3	7
	Relapses		2 (66.7%)	0
II group	DTC	10	4	6
	Relapses post 2 cycles beta-IFN		1 (25%)	0

DISCUSSION

Analysing our results, we can draw two conclusions:

1) Therapy with beta-IFN provides complete recovery from the disease in a great number of cases (34%), and partial remission in 23.3% cases. It is the treatment of choice for microcondylomatosis whereas it is only moderately effective with condylomata acuminata and patients with florid condylomatosis hardly recover. Florid condylomatosis presents enhanced viral infectiousness, and is more resistant to the action of beta-IFN which, nevertheless, seems to have a partial effect that other medical treatments have not had in these cases.

2) Our second observation concerns the incidence of relapses and the excellent results we obtained by combining beta-IFN with DTC. We started from a retrospective analysis which showed that condylomatosis recurred especially in patients with a florid form, and in those treated

only with physical therapy (DTC, Cryotherapy, Laser).

Moreover, in 1985, Ferenczy⁽¹⁴⁾ pointed out the possibility of a latent sub-clinical phase of the disease after Laser treatment. These observations induced us to analyse the different effectiveness of DTC alone or combined with beta-IFN.

In fact, our study confirmed a higher incidence of relapses in the first group of patients treated with DTC alone, and the presence of an active HPV infection in normal tissue identified by the immunoperoxidase technique.

On these bases, we can define the "sub-clinical state of the disease" by pointing out the difference between "clinical" and "biological" recovery. HPV can persist despite physical therapy: probably, its presence is due to dismissal of viral DNA during cellular lysis or to periodical falls of infected cells onto adjacent normal tissue.

The "beta-IFN system" plays an essential role in the treatment of "latent" HPV infection, determining with its antiviral and immunostimulating activity, a "biological recovery" which physical treatment alone cannot probably provide.

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