ß-interferon topical treatment in low and high risk cervical lesions

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Summary: In a series of 131 patients we evaluated the effects of medical therapy with β-Interferon cream in patients with cervical Human Papilloma Virus (HPV) infection, which in some cases, was associated with CIN. Treatment consisted of the direct daily application of 1,000,000 IU β-Interferon cream to colposcopically positive areas over a period of 15 days.

At intervals of 1, 6, 12 and 24 months following treatment, cytohistological tests were carried out to assess the effects of treatment. At the 24-month control, the overall percentage for regression was 79.57% of cases. Regression was observed in 58.33% of patients with cytohistological changes associated with HPV without atypia, and in 69.85% of patients with HPV with atypia (38.9% total regression).

The regression pattern for CIN lesions was as follows: in CIN lesions, regression occurred in 85.36%, in CIN II in 84.20%, and 37.5% of CIN III cases showed total regression.

INTRODUCTION

In genital HPV infections, both medical and surgical approaches have been used ([2, 6]) depending on each particular case, the site and size of lesions and the grade of any associated CIN lesions ([1, 8]).

Over recent years, progress made in immunology and molecular biology has opened up new horizons in the diagnosis and treatment of HPV genital infections. Different methods have been studied with a view to stimulating the organism's own defence mechanisms, and to averting viral replication and spread when the infection is already in course.

Interferon production is a natural defence mechanism against viral infection, and currently it is considered particularly important in the treatment of HPV genital infections whether associated with CIN lesions or not ([3, 4, 12, 13, 15, 16, 17]).

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MATERIALS AND METHODS

At this Institute from January 1987 to December 1989, 131 women (age range, 18 to 60 years, mean age 39 years) were treated with local β-Interferon cream for cervical HPV, associated with CIN in 82 cases, to assess the efficacy of this type of treatment against HPV cervical infections whether or not associated with CIN lesions. The diagnosis of viral infection had been made on the basis of cytohistological tests using Meisels' cytologic and Reid's histological criteria ([9, 10, 11, 14]); the diagnosis of CIN was made using Ferenczy's criteria ([7]).

Treatment consisted of a direct daily application of 1,000,000 IU β-Interferon cream to colposcopically positive areas over a period of 15 days.

At intervals of 1, 6, 12 and 24 months, cytohistological tests were made to ascertain the therapeutical effects. On the basis of the initial lesions, seven groups were identified:

– Group I: cytohistological changes associated with HPV (HPV);

– Group II: cytohistological changes associated with HPV and with CIN I (HPV + CIN I);

– Group III: cytohistological changes associated with HPV and with CIN II (HPV + CIN II);

– Group IV: cytohistological changes associated with HPV with atypia (HPVa);

– Group V: cytohistological changes associated with HPV with atypia and CIN I (HPVa + CIN I);

– Group VI: cytohistological changes associated with HPV with atypia and CIN II (HPVa+CIN II);

– Group VII: cytohistological changes associated with HPV with atypia and CIN III (HPVa + CIN III). These lesions were also divided into two categories following the Bethesda System [18];

– low-grade squamous intraepithelial lesions, groups I and II;

– high-grade squamous intraepithelial lesions, groups III to VII.

Once the treatment had been completed, the results were described as:

– *Total Regression*: complete disappearance of HPV and CIN lesions.

– *Partial Regression*:

a) regression of atypia in the viral lesions;

b) downgrading of CIN lesion with persistence or not of HPV alterations;

c) complete disappearance of CIN with persistence of HPV cytohistological changes.

– *Persistence*: unchanged HPV and CIN lesions with respect to the initial diagnosis.

– *Progression*: appearance of CIN in HPV lesions; or appearance of atypical viral lesions; or upgrading of CIN lesions.

RESULTS

Follow-up data are as yet available only for 71% of patients treated with β-Interferon cream. Although the number of patients attending follow-up diminished over the year following treatment (at one month all 131, at six months 127, at twelve months 114 and at twenty-four months 93) the distribution of cases with respect to diagnosis before treatment is constant ($p=0.99$ n.s.).

Of the patients with cytohistological changes associated with HPV and diagnosed before therapy, 24.43% had no atypia, while 12.98% had associated atypia (Table 1). In the remaining cases, HPV alterations and CIN lesions were associated as follows: CIN lesions and HPV alterations with atypia in 23.66% of cases; CIN lesions and HPV alterations without atypia in 38.93% of cases (the CIN I and HPV group made up 30.53% of cases). After treatment, a progressive cytohistological regression was observed in HPV cervical uterine changes, whether or not associated with CIN (Table 2).

Following treatment, the lesions showed the following course: total regression,

Table 1. – *Distribution of patients according to the initial diagnosis (before therapy).*

	1 month		6 months		12 months		24 months	
	no.	%	no.	%	no.	%	no.	%
HPV	32	24.43	32	25.20	29	25.44	23	24.73
HPV + CIN I	40	30.53	40	31.50	35	30.70	28	30.11
HPV + CIN II	11	8.40	9	7.90	8	7.02	7	7.53
HPVa	17	12.98	17	13.39	17	14.91	15	16.13
HPVa + CIN I	8	6.11	8	6.30	6	5.26	5	5.38
HPVa + CIN II	13	9.92	12	9.45	11	9.65	8	8.60
HPVa + CIN III	10	7.63	9	7.09	8	7.02	7	7.53
	131		127		114		93	

Table 2. – *Course of the lesions after therapy (all cases).*

	1 month		6 months		12 months		24 months	
	no.	%	no.	%	no.	%	no.	%
TR	41	31.30	49	38.58	56	49.12	47	50.54
PR	52	39.69	40	31.50	31	27.19	27	29.03
Pers.	32	24.43	31	24.41	19	16.67	12	12.90
Progr.	6	4.58	7	5.51	8	7.02	7	7.53
	131		127		114		93	

Legend – TR: Total Regression; PR: Partial Regression; Pers.: Persistence; Progr.: Progression.

31.30% of cases (41 patients) and partial regression in 39.69% of cases (52 patients), the overall percentage of regression being 70.99%. At the first control persistence was 24.43% (32 patients) and progression 4.58% of cases (6 patients).

Six months after therapy, the percentages were comparable: regression (total and partial) 70.8%; persistence 24.41%; and progression 5.51%.

One year after therapy an improvement in regression (76.31%) was observed. Total regression, in particular, was 49.12%, persistence reduced to 16.67%. Two years after therapy, the regression percentage was higher: 79.57% (p: 0.1 n.s.), persistence was 12.9% and progression 7.53%. Later, an inversion of the total and partial progression ratio was obtained with an improvement in the total regression (Fig. 1).

At one year, the data on the effects of therapy on HPV alteration (without considering CIN associated lesions) were as follows: 58.33% of the 72 HPV patients without atypia presented total regression, 40.27% showed persistence, and only one patient showed progression (nuclear atypia). One year after therapy data for CIN lesions (without considering HPV alterations) were as follows: total regression in 85.36% of cases of CIN I, and persistence in 14.63%. Of CIN II lesions, in 47.36% of cases total regression was observed, partial regression occurred in 36.84%, and persistence in 5.26%. Only two patients were upgraded to CIN III.

Only eight of our patients presented CIN III lesions: in three total regression of CIN occurred; in one there was a regression to CIN II and in four persistence (Table 3).

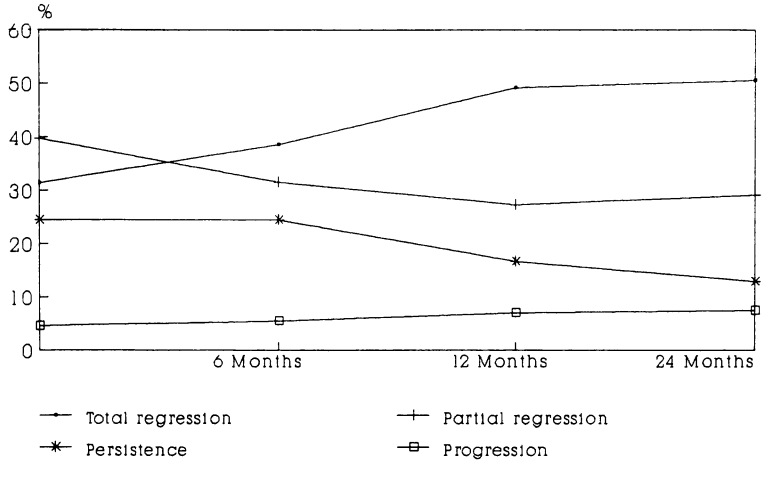

Fig. 1. — Course of the lesions after therapy (all cases).

Table 3. – *Course of HPV alterations of associated CIN; and course of CIN alterations irrespective of HPV associated changes at one year.*

	HPV		HPVa		CIN I		CIN II		CIN III	
	no.	%	no.	%	no.	%	no.	%	no.	%
TR	42	58.33	16	38.9	35	85.36	9	47.36	3	37.5
PR	0	0	14	30.95	0	0	7	36.84	1	12.5
Pers.	29	40.27	12	28.57	6	14.63	1	5.26	4	50.00
Progr.	1	1.38	0	0	0	0	2	10.52	0	0
Total	72		42	0	41		19		8	

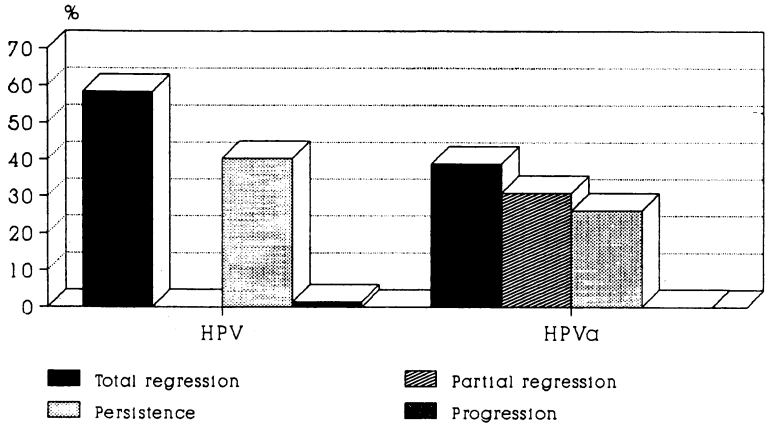

Fig. 2*a*. — Course of HPV alterations irrespective of CIN associated lesions after one year.

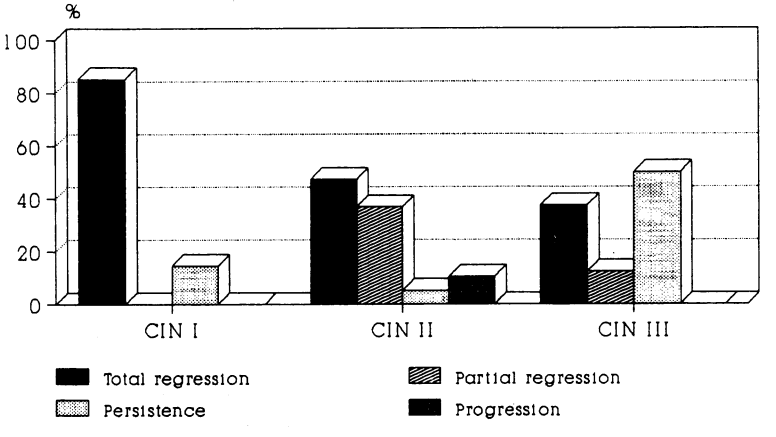

Fig. 2*b*. — Course of CIN lesions irrespective of HPV associated changes after one year.

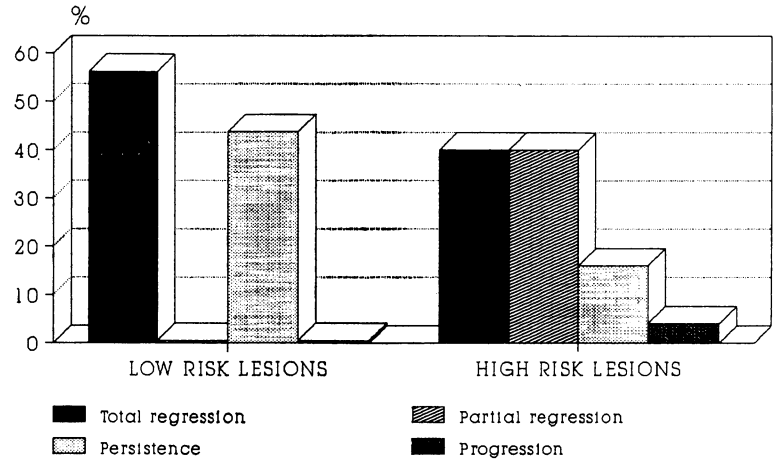

Fig. 3. — Course after one year of the low and high risk lesions.

If we consider the effect of therapy on lesions by distinguishing between two categories of lesions (high-grade and low-grade) (Table 4, Figs. 3 and 4) it emerges that at one year, total regression had occurred in 36 patients (56.25%), and this outcome had not changed two years after treatment. Persistence was found in 43.75% of cases.

In the 50 patients with high-grade lesions a different type of evolution was observed: at one year regression was observed in 80% of cases, total regression occurring in 40%; 20% of the high-grade lesions persisted. Two years after treatment, regression was found in 83.32% of cases: 59.52% of these regressions were total and 23.80% partial. In 14.28% of these cases the lesions persisted.

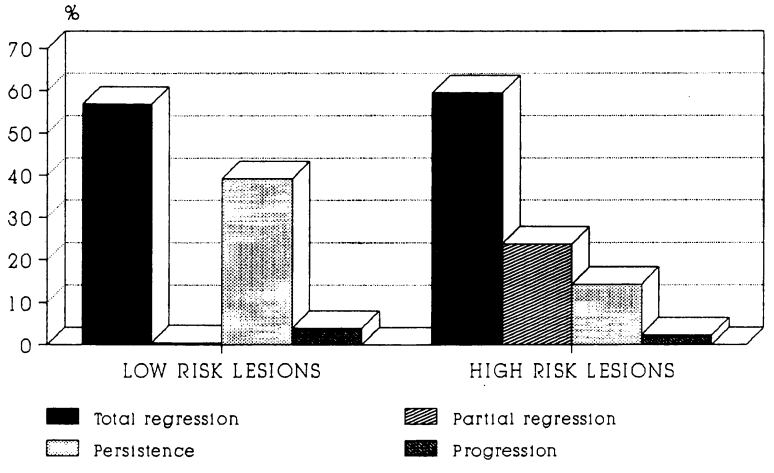

Fig. 4. — Course after two years of the low and high risk lesions.

Table 4. – *Course of low and high risk lesions after one and two years according to the Bethesda System.*

	1 year				2 years			
	low risk		high risk		low risk		high risk	
	no.	%	no.	%	no.	%	no.	%
TR	36	56.25	20	40	29	56.86	25	59.52
PR	0	0	20	40	0	0	20	23.80
Pers.	28	43.75	8	16	20	39.21	6	14.28
Progr.	0	0	2	4	2	3.92	1	2.3
Total	64		50		51		42	

DISCUSSION

Follow-up results from our 131 patients treated with local β-Interferon cream for HPV lesions, whether or not associated with CIN, showed that this treatment was successful. One year after therapy regression was observed in 76.31% (Table 2) of cases although it must be kept in mind that in 27.19% of cases regressions were partial.

An important finding was the improvement in the percentage of regressions: at two years, the highest percentage was reached. The number of partial regressions also decreased, thus increasing the final percentage of total regressions.

The results obtained demonstrate that β-Interferon therapy is effective against HPV infections, also in the presence of CIN.

The improvement observed in the regressions at the two-years follow-up examination can be explained by immunitary factors: the defence system is activated and the lesions heal.

During the one year follow-up, colposcopic, cytological and histological signs of HPV alterations were found in 13 patients who had completely recovered, although the lesions were different from those observed before treatment. It should here be established whether these lesions are due to a "new" infection or are recurrences.

Moreover, the finding that 9.92% of cases lesions reappeared after a regression time of from 12 to 24 months suggests that immunological defences play a very important role.

Persistence was found in 19 patients (16.67%) :16 with cytologically, histologically and colposcopically evidenced persistence of lesions after 6-12 months were treated by Diathermic Loop Excision. In five of these cases the histological examination of surgical samples revealed lower-grade lesions; in only one CIN II patient was there an upgrading (CIN III). In ten patients the preoperative histological diagnosis was confirmed.

Surgery can always resolve an HPV if prior medical therapy is unsuccessful. It therefore appears advisable to integrate the two therapies, as this leads to recovery in most cases ([5]). Surgery seems to be more appropriate therapy for HPV lesions with important epithelial and stromal changes, whereas medical therapy is very useful when HPV infection is diffused.

An integration of medical and surgical therapies appears particularly valuable in cases of longstanding epithelial-stromal lesions, that are localized and associated with diffused epithelial HPV infection.

In 62.59% of our cases, HPV alterations were associated with CIN (Table 1). β-Interferon cream therapy was useful also against CIN lesions. In a high percentage of CIN I cases, lesions regressed, whereas the percentage of regressions in CIN II and CIN III cases was lower.

Moreover, the response to therapy appears to indicate a category of low grade lesions (HPV and CIN I) and a category of high grade lesions (CIN II and CIN III), categories already identified in the Bethesda System ([18]).

Topical β-Interferon cream administration had no collateral effects. It should, however, be borne in mind that our pa-

tients were required to attend the out patients were required to attend the out-patients' clinic every day for fifteen days and

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