

Treatment of genital HPV-infections with natural alpha interferon from normal human leucocytes

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Summary: The antiviral action of Alpha Interferon is much more important than antiproliferous and immunomodulating actions.

In any case, all of them are required to resolve pre-neoplastic pathologies of the female genital tract, especially if they are at an initial stage or associated with virus cytopathic effects.

Key words: HPV-interferon.

INTRODUCTION

Interferons constitute a family of endogenous glycoproteins, classified as Alpha, Beta and Gamma Interferons in accordance with their physicochemical and antigenic properties.

Antiviral, antiproliferous and immunomodulating properties have been attributed to Interferon.

Interferon has been found to be very effective in the treatment of viral lesions, and its field of action has been extended to oncologic and immunologic fields too.

In the treatment of uterine cervix pathology, our aim is to use Interferon in

the field of CIN, a disease which strikes young women during the reproductive age, when ablative therapies could interfere with their fertility.

Natural Alpha Interferon (α IFN_N) from normal human leukocytes is a mixture of sublimes, each one probably having a different effect even though working synergetically.

Thanks to its natural properties, there is a lower risk of finding antibodies in circulation.

In this work data will be presented regarding the use of Natural Alpha Interferon from normal human leukocytes in the treatment of uterine cervix lesions associated with CIN.

MATERIALS AND METHODS

The research were carried out at the University of Naples - Faculty of Medicine and Surgery - Gynaecology and Obstetrics Department, where three groups of patients, presenting lesions at different stages, were examined.

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- 1) Group A: 5 patients presenting Condylomata Lata and/or virus cytophatic effects (VCE):

a) patients' age:

1) 48; 2) 25; 3) 37; 4) 35; 5) 34

b) range: from 25 to 48

c) average age: 36.

- 2) Group B: 6 patients presenting CIN 1-2 and/or VCE:

a) patients' age:

1) 23; 2) 22; 3) 54; 4) 35; 5) 30; 6) 34

b) range: from 22 to 54

c) average age: 33.

- 3) Group C: 5 patients presenting CIN 2-3 and/or VCE:

a) patients' age:

1) 43; 2) 32; 3) 41; 4) 47; 5) 36

b) range: from 32 to 47

c) average age: 40.

Diagnosis and therapeutic response were carried out by using both traditional methods such as Cytology, Vaginoscopy Biopsy, and a new method "In Situ" Hybridization on cervical smears.

Alpha Interferon from human leukocytes in a 1.000.000 I.U. soluble vial was used (Alfaferone by Alfa Wassermann).

Table 1. — *Group A: HPV.*

Cases	Age	HPV-DNA	Therapy	Results
1)	48	6/11	alfa IFNn	Complete recovery
2)	25	6/11	alfa IFNn	Complete recovery
3)	37	31/33/51	alfa IFNn	Complete recovery
4)	35	31/33/51	alfa IFNn	Complete recovery
5)	34	16/18	alfa IFNn	Persistent lesion

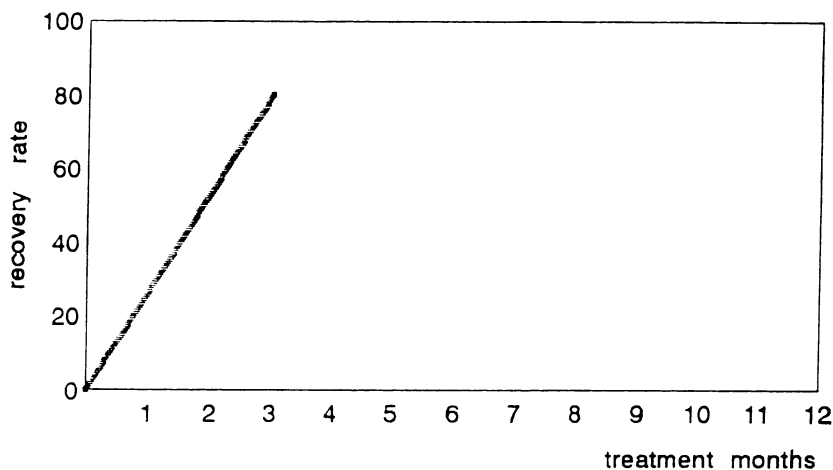
Interferon was used for intramuscular injections as follows:

Group A: one vial three times a week for three weeks.

Group B and Group C: a two-phase therapy was used:

1) induction therapy: 3×10^6 I.U. three times a week for three cycles;

2) maintenance therapy: 1×10^6 I.U. three times a week for three cycles.



Recovery of 4 out of 5 patients after a three months' therapy

picture 1

graphic by
A. Zarcone

Fig. 1. — Group A - Complete recovery. 80% of patients have tested negative at Probe-DNA after alfa IFNn treatment.

RESULTS

The response duration has been considered from the beginning of treatment.

Group A:

Four patients tested negative after three months from the conclusion of treatment.

In one patient presenting resistant lesions, the "In Situ" Hybridization revealed the presence 16/18 HPV (Table 1, Pecture 1).

Group B:

Three patients tested negative after a three months' two-phase therapy with Interferon.

– One patient was treated with Diathermocoagulation and successively with Interferon maintenance therapy because of persisting positivity at Probe DNA.

– Two patients were coned and were successively were treated with Interferon maintenance therapy.

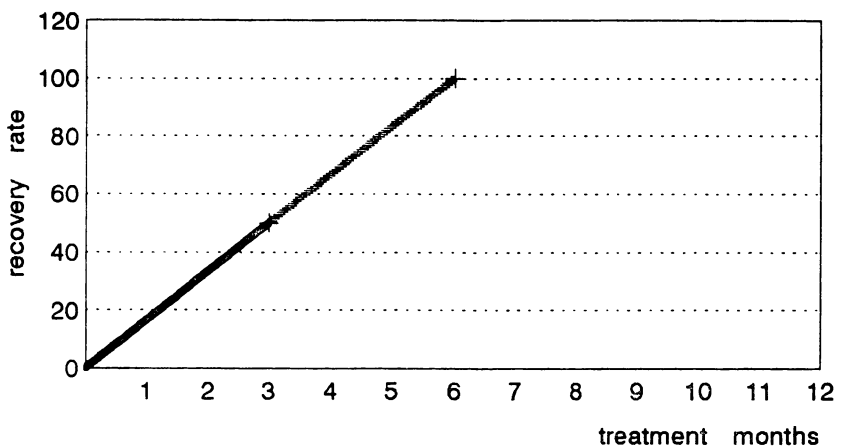
Table 2. – Group B: CIN 1-2 and/or VCE.

Cases	Age	HPV-DNA	Therapy	Results
1)	23	6/11	DCT	Subclinical infection
2)	22	16/18	Coniz.	Subclinical infection
3)	54	6/11	IFNn	Complete recovery
4)	35	31/33/51	IFNn	Complete recovery
5)	30	6/11	IFNn	Complete recovery
6)	34	16/18	Coniz.	Complete recovery

One of these patients tested positive at Probe DNA after conization and negative after Interferon therapy (Table 2, Picture 2).

Group C:

All five patients were coned because of lesions seriousness.



Recovery of 3 out of 6 patients using only Medical Therapy (50%)
Recovery of 3 out of 3 patients with integrated Therapy Surgical and Medical Therapy (100%)

picture 2

graphic by
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Fig. 2. — Group B - Complete recovery. 50% of patients have tested negative at Probe-DNA after alpha IFNn treatment.

Table 3. – Group C: CIN 2/3 and/or VCE.

Cases	Age	HPV-DNA	Therapy	Results
1)	43	Negative	Coniz.	Complete recovery
2)	32	31/33/51	Coniz.	Subclinical infection
3)	41	16/18	Coniz.	Subclinical infection
4)	47	Negative	Coniz.	Complete recovery
5)	36	16/18	Coniz.	Subclinical infection

– Three of these patients tested positive at Probe DNA after the operation and negative after a successive Interferon two-phase therapy (Table 3, Picture 3).

Collateral effects such as headache, myalgia and fever were recorded in five patients.

Alpha Interferon was the primary treatment for groups B and A.

Complete recovery was obtained in 4 out of 5 patients of group A and in 3 out of 6 patients in Group B (Picture 4).

DISCUSSION

Antiviral action is the principal action of Alpha Interferon, even if cytomodifying and cytoinhibiting actions are certainly present. In any case all these activities must be exploited to the utmost.

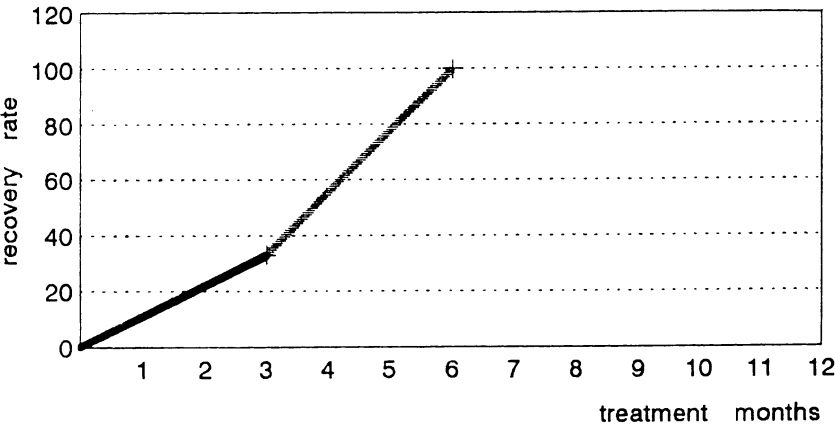
Immunomodulating action is integrated by antiproliferous action because a high dosage increases plasmatic concentration of immunoglobulins, cytotoxic activity of NK and the phagocytic activity the macrophages.

The results obtained with Alpha Interferon both as an antiviral and antineoplastic drug are encouraging, even if they have fallen short of our expectations.

Natural Alpha Interferon from normal human leukocytes, has an inhibiting action both on cell division and on oncogenic manifestations.

Alpha Interferon can probably affect cell differentiation, by modifying the manifestation of membrane antigens.

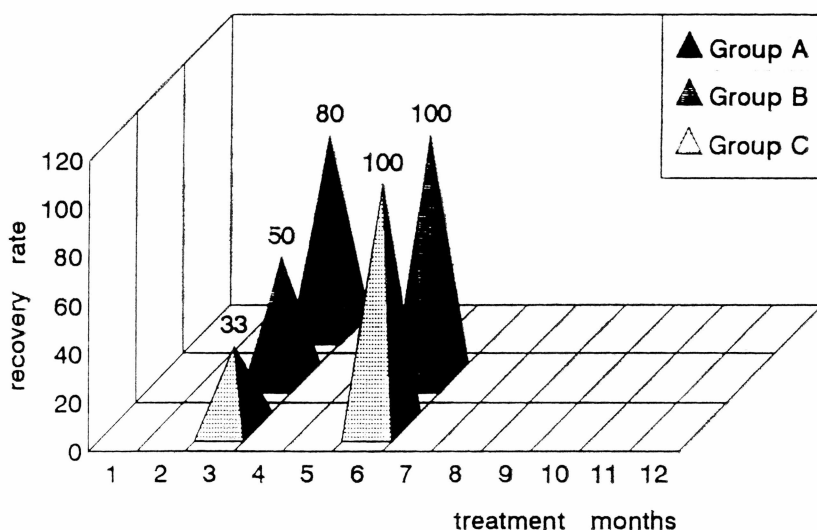
Prophylactic and/or therapeutic activity depends on the number of cell receptors.



Recovery of 2 out of 6 patients using only Medical Therapy (33%)
Recovery of 4 out of 4 patients with integrated Therapy Surgical and Medical therapy (100%)

picture 3graphic by
A.Zarcone

Fig. 3. — Group C - Complete recovery. 33% of patients have tested negative at Probe-DNA after Conization treatment.



picture 4

graphic by - A. Zarcone

Fig. 4. — Groups A-B-C.

In patients at risk, a higher dosage is necessary because Interferon has a limited half-life.

By using Alpha Interferon per intramuscular injections, plasmatic levels are less transitory and hepatic and renal catabolism is slower, than by using Alpha Interferon per intravenous injections.

The pharmacokinetics of beta and gamma Interferon are different because they are more hydrophobic and because they are mostly catalized at hepatic level.

Some researchers prefer to use Interferon per subcutaneous injections because the lymphatic flow would be involved.

The use of Alpha Interferon per intra and perilesional injections, even if advisable, has not been considered as it is tiresome, painful and expensive.

Finally, other research will be necessary in order to find out the most suitable way of administration and dosage for a complete recovery.

At the moment, Alpha Interferon cannot be considered as substitute therapy for

physical and surgical therapies in the treatment of CIN associated with HPV infections.

Thanks to its antiproliferous and immunomodulating action, Alpha Interferon is certainly useful as an adjuvant in trying to obtain a complete response and to prevent recidive lesions.

The use of new methods of discovering the presence of HPV subclinical infections should be introduced immediately in order to start supportive therapy, and to obtain more effective therapeutic results than those obtained with topic therapies.

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