Research Article

Dermatology Research

Therapy with Pegylated Interferon or Combined with Cryosurgery in Condyloma Acuminata. Phase III Clinical Trial

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Received: 04 January 2019; **Accepted**: 18 February 2019

Citation: Israel Alfonso Trujillo, Tomás Tabilo Bocic, Ángela Rosa Gutiérrez Rojas, et al. Therapy with Pegylated Interferon or Combined with Cryosurgery in Condyloma Acuminata. Phase III Clinical Trial. Dermatol Res. 2019; 1(1); 1-8.

ABSTRACT

Background: *The continuous recurrence of condyloma acuminata makes the constant search for necessary therapeutic alternatives.*

Patients and method: *To evaluate the therapeutic efficacy and safety of pegylated interferon, alone or adjuvant for cryosurgery, in the condyloma acuminata an open clinical trial was carried out on 30 patients of the "Hermanos Ameijeiras" hospital, who were randomized to receive for 6 weeks (group A) only fortnightly cryosurgery, (group B) subcutaneous pegylated interferon, once a week, associated with fortnightly cryosurgery application or (group C) only subcutaneous pegylated interferon, once a week. The main variable was the percentage of recurrence at one year of follow-up, evaluated quarterly. There was also a rigorous control of adverse events.*

Results: *At the end of the treatment 8/10 (80%) patients from group A, 10/10 (100%) from group B and 9/10 (90%) from group C were left without injuries. During the follow-up, none of the patients who received pegylated interferon, alone or adjuvant to cryosurgery, had recurrences; while 100% of patients who received cryosurgery as exclusive treatment relapsed ($p < 0.000$). The most frequent events were local burning (100%) due to cryosurgery and fever (6.6%), headache (6.6%), myalgia (3.3%) and malaise (3.3%) due to interferon.*

Conclusion: *Pegylated interferon alone or adjuvant to cryosurgery provides benefits for the quality of life of patients, with absolute and relative reduction of a 100% of the risk of recurrence.*

Keywords

Pegylated interferon, Cryosurgery, Condyloma acuminata.

Introduction

The need to find new therapeutic options that achieve a high percentage of cure or a low frequency of recurrences of condyloma acuminata (AC), with few or no adverse events, requires the development of controlled clinical trials that provide scientific evidence on these aspects [1].

The therapeutic combination of cryosurgery and recombinant human interferon (IFN) alpha 2b has been shown to be highly effective in AC, with mild or moderate adverse events [2].

Initiatives to improve the efficacy, tolerance and comfort of drugs are a constant within pharmacological therapy. Recombinant human interferon alpha 2b conjugated to polyethylene glycol (pegylated IFN), according to its pharmacodynamic characteristics, offers the possibility of distancing the doses administered with a greater potential antiviral effect and similar toxicity [3]. That is why this study was carried out, where for the first time in the world pegylated IFN was tested in the treatment of condyloma acuminata. Two study groups were formed (pegylated IFN alone and pegylated IFN adjuvant to cryosurgery) and a third group

that was the active control group (cryosurgery). The working hypothesis was as follows: the percentage of recurrences in the groups treated with pegylated interferon, alone and combined with cryosurgery, is significantly lower than that obtained with cryosurgery as exclusive treatment.

Objectives

General

To assess the therapeutic efficacy and safety of pegylated interferon, alone and combined with cryosurgery, in condyloma acuminata.

Specific

- To identify the occurrence of recurrences at one year of follow-up in the treatment groups, as well as patients free of disease at the different evaluation times.
- To evaluate the response of combination therapy, cryosurgery and pegylated IFN, applied in isolation in terms of the disappearance of the lesions at the end of the treatment.
- To establish the safety of the three therapeutic modalities in terms of the type and severity of adverse events.

Patients and Method

Design of the essay

A phase III, open, randomized and controlled clinical trial was carried out at the Clinical Surgical Hospital: "Hermanos Ameijeiras", in the period between January 18th, 2016 and May 2nd, 2018. The inclusion of 30 patients was planned which were assigned to three groups according to a random list. Each group was composed of 10 patients, treated for 6 weeks as appropriate and followed up for 1 post-treatment year. Three different therapeutic interventions were applied, cryosurgery as exclusive treatment, pegylated IFN associated with cryosurgery and pegylated IFN as exclusive treatment, as follows:

Group A: only application of cryosurgery of the lesions every 15 days.
Group B: subcutaneous administration once a week of pegylated interferon, associated with the application of cryosurgery of the lesions every 15 days.
Group C: Only subcutaneous administration once a week of pegylated interferon.

In all groups, the treatment was administered for 6 weeks.

Two weeks after the end of the treatment, the response to it was evaluated by comparing the initial and final stages of the lesions. In case of reaching the complete response, the patient was kept on post-treatment follow-up evaluations for 1 year. The intention was to detect recurrence of the disease and the criterion of therapeutic efficacy was issued at the end of the follow-up. The cases without complete response, concluded the study at the end of their 8 initial weeks and went on to use another conventional therapeutic scheme that provided the service.

Ethics

The protocol of the clinical trial was submitted to the consideration and approval of the Ethics Review Committee for Research (CEI) and the Scientific Council of the Hospital "Hermanos Ameijeiras" (HHA).

Selection of patients

Universe of the study

The universe was constituted by patients residing in Cuba, adults, of any sex and skin color, who attended the protocolized consultation of cutaneous virosis of the Dermatology Service of the HHA. The appropriate population was considered for the purposes of the trial, since this institution had the necessary equipment, instruments and interventions to confirm the following diagnostic criteria

Clinical: Any number of lesions in the form of isolated warts or plaques, with a raised and rough surface with the appearance of cauliflower, occupying an area equal to or bigger than 4 cm^2.

Anatomopathological by biopsy: Epidermal acanthosis with papillomatosis, hyperkeratosis and parakeratosis. The interpapillary processes appear elongated, tend to be oriented toward the center of the lesion, and visualization of enlarged keratinocytes with a picnotic and eccentric nucleus surrounded by a clear and eccentric halo surrounded by a clear halo, called coilocytes, is characteristic.

Inclusion criteria

- Patients of any sex and skin color who met the diagnostic criteria of condyloma acuminata, located in the external genitalia, perianal region, pubis and inner side of the thighs.
- Age between 18 and 60 years old, both inclusive.
- Not having received topical or systemic treatment with IFN or another antiviral drug one month before inclusion.
- Not having received treatment with levamisole or another immunomodulatory drug one month before inclusion.
- Voluntariness of the individual by signing the written consent.

Exclusion criteria

- Patients with a history of hypersensitivity to IFN alpha or any of the components of the formulation.
- Patients with a personal pathological history of cryoglobulinemia.
- Infection in lesions that need systemic antibiotic treatment.
- Other sexually transmitted diseases (syphilis, infectious urethritis, AIDS).
- Have received treatment with immunosuppressants (corticosteroids, cytostatics) three months before inclusion.
- Radiotherapy or chemotherapy received during the month prior to inclusion in the study.
- Patients with a confirmed diagnosis of malignant neoplasms.
- Decompensated acute or chronic hepatic disease: patients with total bilirubin>17 µmol/l, with hepatic transaminases 1.5 times the normal value, concomitantly with alkaline phosphatase 2.5 times over the upper normal limit (44-147 UI / L).
- Acute or chronic decompensated renal disease: patients with creatinine 1.5 times the normal value with other clinical and laboratory criteria.

- Decompensated cardiovascular disease confirmed by the clinical, electro and echocardiographic exam.
- Decompensated Diabetes Mellitus: glycemia >8 µmol/l.
- Women of childbearing age without safe contraception, pregnancy, lactation or with injuries in internal genitalia, evaluated by a gynecologist at their base hospital.
- Severe psychiatric disorder or other limitation that prevents the patient from giving consent or hinders their evaluation.

Evaluation variables

The patients were evaluated clinically, as recommended and usually proceeded with this disease. The response to treatment was defined by the initial – final comparison of the lesions. The effectiveness criteria used were defined according to the number and size of the lesions.

For the application of these evaluative criteria of efficacy, no statistical adjustment of the data was necessary. Both the main variable and the secondary variables were rational, since they are the usual variables in the diagnostic and evolutionary management of this disease.

Primary or principal efficacy variable

The occurrence of recurrence of the lesions was considered the main variable, consisting of the appearance of new lesions in the area treated in cases in which total response was obtained.

Secondary efficacy variables

Response 2 weeks after completing the treatment. It was evaluated taking into account the clinical examination of the patient, considering the following categories:

Total response: total disappearance of the injuries.

Partial response: decrease in the number of injuries by more than 50%.

Non-response: decrease in the number of injuries less than or equal to 50%, without the appearance of new injuries.

Progression: increase in the number or size of injuries.

Statistical methods used and sample size

Main variable

With the main variable, exploratory analyzes were carried out with the aim of knowing their overall behavior and assessing compliance with the necessary hypotheses for the application of the statistical tests in the evaluation stage.

The corresponding cross-classification table was constructed with the associated independence test (chi-square test or Fisher's exact test, depending on the fulfillment of the assumption on the expected frequencies of the table).

The 95% confidence intervals were estimated for the proportion of individuals with relapse in the three treatment groups.

The Kaplan-Meier curves for recurrence and for disease-free time were estimated and the log-rank test was used to compare the treatment groups.

Secondary variables

The corresponding cross-classification table was constructed with the associated independence test (chi-square test or Fisher's exact test, depending on the fulfillment of the assumption on the expected frequencies of the table) for the qualitative variables.

Measures of central tendency and dispersion were estimated. The corresponding comparisons between the groups were made for the quantitative variables.

Security variables

The frequency distributions and the 95% confidence interval were estimated for the proportion of patients with each of the adverse events that occurred. With each adverse event we estimated the frequency distributions of the parameters that characterize it (intensity, causality, outcome).

Control variables

The populations of the three treatment groups were characterized by estimates of central tendency and dispersion for the quantitative variables (for example: age, number of injuries, among others) and estimation of the corresponding proportions for the qualitative variables (for example: color of skin, sex, among others). The homogeneity between the treatment groups was not verified by statistical tests since it is considered that, as the randomized study, any difference that appears is due to chance, following the international recommendations expressed in the CONSORT 2010 guidelines [4].

Multiple logistic regression was carried out using relapse as the dependent variable and control variables as independent variables.

The following statistical programs were applied:

SPSS (version 20.0 for Windows): Estimation of frequency distributions, percentages, measures of central tendency and dispersion, analysis of Logistic Regression, analysis of the assumption of normality (Shapiro Wilk and Kolmogorov-Smírnov), analysis of variance or Kruskal test Wallis).

Determination of sample size. Number of subjects planned

The sample consisted of 30 patients from the universe of study who met the diagnostic criteria and inclusion criteria, in the period between January 18th, 2016 and May 2nd, 2018.

Results

Disposition of the subjects

We evaluated 58 patients with the diagnosis of condyloma acuminata. Thirty (51.72%) were included in the trial, 10 were randomized (33.33%) to receive cryosurgery only, 10 (33.33%) to receive pegylated IFN associated with cryosurgery and 10 (33.33%) remaining to receive pegylated IFN only.

There were 28 patients with exclusion criteria, which are detailed in Table 1.

Cause	Quantity	%
Condylomatous lesions in the internal genitalia	19	67.8
HIV positive serology	6	21.4
No voluntariness	1	3.6
Age over 60 years	2	7.14
Total	28	100

Table 1: Causes of exclusion.
Set of analyzed data.

The 30 patients included were considered for the analysis of the demographic, efficacy and safety results.

Demographic and basic characteristics

The male sex was the highest proportion (100%) in the study, with similar distribution among the three groups. There were 21 non-white skin patients, which was the majority globally (70%), in the cryosurgery group (80%), in the pegylated IFN + cryosurgery group (60%) and in the pegylated IFN group (70%). The age of the patients showed a global average of 24.6 years, with values between 18 and 60 years, where there were 18 (60%) under 20 years. 70% of patients denied having suffered any previous sexually transmitted infection. Only 2 (20%) patients from the group treated with cryosurgery, syphilis, 1 patient (10%) from the pegylated interferon group and herpes simplex 3 patients (2 from the group that received pegylated IFN and 1 from the group that received IFN + cryosurgery) reported. The overall mean was 17 injuries per individual, with no differences between the groups. The number of lesions> 5 mm in size had an overall average of 5 lesions, without differences between the groups. The average of the initial total area of the lesions oscillated around 20 cm^2, with a variation of 1 to 34 cm^2, being significantly lower in the group that received cryosurgery only (13.9 cm^2). The global average of the time of evolution of the lesions was 497 weeks, being higher in the group that received the combined therapy of pegylated IFN + cryosurgery (915.8), but without significant differences with respect to the rest of the groups.

Results of efficacy

Response to treatment

The final evaluation of efficacy was carried out in week 8. These results, corresponding to 2 weeks after the conclusion of the treatment, are shown in table 2. There were no significant differences between the groups in terms of response to treatment. The pegylated IFN associated with cryosurgery obtained 100% of total response, pegylated IFN as exclusive treatment achieved 90% of total response, while the application of cryosurgery led to 80% of total response.

Variables		Cryosurgery	IFN + Cryosurgery	IFN	Sig. Statistics
N		10	10	10	p= 0,32
Response evaluation	Total	8 (80)	10 (100)	9 (90)	
	Partial	2 (20)	0 (0)	1 (10)	

Table 2: Response to the end of treatment (week 8). * Chi square test.

Recurrences

Table 3 shows the results of the evaluations made in the follow-up of the treatment, ultimately the main variable of the trial.

It can be seen that 8/8 (100%) patients who received cryosurgery recurred as exclusive treatment, while patients with complete response from the groups that received treatment with pegylated IFN + cryosurgery and pegylated IFN as exclusive treatment remained without recurrence during the year of follow-up. This difference is significant, both from a statistical (p<0,000) and clinical point of view.

Group	Patients with relapse	Patients without recurrence	Total	Total Sig. Statistics *
Cryosurgery	8	0	8	p=0,000
Interferon + cryosurgery	0	10	10	
Interferon	0	9	9	
Total	8	19	27	

Table 3: Main efficacy variable (recurrence) at one year of follow-up.
Chi square test.

This absolute and relative reduction of 100% represents a high impact from the point of view of evidence-based medicine (Table 4).

Clinical relevance indicators	Value	IC (95 %)
Relative risk of recurrence (IFN + cryosurgery or IFN alone versus cryosurgery)	0,00	0,00 – 0,00
Absolute reduction of relapse risk	100 %	100 % - 100 %
Relative reduction of relapse risk	100 %	100 % - 100 %
Number of patients needed to treat to avoid a relapse	1	1- 2

Table 4: Treatment efficacy indices with IFN alone and IFN + cryosurgery compared with cryosurgery as an exclusive treatment from the point of view of evidence-based medicine.

From the point of view of clinical efficacy, it can be stated that 100% (19/19) of patients treated with pegylated IFN, either as exclusive treatment or as a combination treatment with cryosurgery, achieved long-term control of the disease (without relapse) in a clinically relevant way compared to the use of cryosurgery as exclusive treatment (p = 0000).

It was remarkable the speed with which they began to relapse the lesions in patients who received cryosurgery as exclusive treatment, at 3 months post-treatment they had already relapsed in 62.5% of the patients and at 9 months they had relapsed in the 100 % of them (Table 5).

Safety evaluation

Extension of the exhibition

For the evaluation and characterization of the safety profile of the trial, the 30 patients with evidence of having received at least one administration of any of the three therapeutic interventions used in the trial were considered.

Variables		Cryosurgery	IFN + Cryosurgery	IFN	Sig. Statistics*
N		**8**	**10**	**9**	
Recurrences	Month 3	3 (37,5)	-	-	**p=0,000**
	Month 6	4 (87,5)	-	-	
	Month 9	1 (100)	-	-	
	Month12	0 (0)	-	-	
	Total	**8 (100)**	**0 (0)**	**0 (0)**	
Patients free of injuries	Month 3	5 (62,5)	10 (100)	9 (100)	**p=0,000**
	Month 6	1 (12,5)	10 (100)	9 (100)	
	Month 9	0 (0)	10 (100)	9 (100)	
	Month12	0 (0)	10 (100)	9 (100)	
	Total	**0 (0)**	**10 (100)**	**9 (100)**	

Table 5: Response variables in the follow-up. * Chi square test.

Each patient treated with pegylated IFN was exposed for 6 consecutive weeks to a weekly administration of 0.18 mg, for a total of 6 administrations and of 1.08 mg. The cryosurgery exposure was every 15 days. All patients had 48 weeks of post-treatment observation.

Adverse events

An unfavorable medical event that occurred in the subject under clinical investigation to which the pharmaceutical product was administered, which did not necessarily have a causal relationship with that treatment, was considered an adverse event. It could be any involuntary unfavorable sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of the tested drugs, which may or may not be related to them.

Local burning was the only adverse event reported by 100% of the patients related to cryosurgery, which was of slight intensity and disappeared spontaneously between 10 and 15 minutes after its application. A patient in the group who received pegylated IFN + cryosurgery reported fever, headache and malaise four hours after the administration of the first dose of pegylated IFN; these symptoms disappeared 1 hour after the administration of two dipyrone tablets.

A patient in the group who received pegylated IFN as the exclusive treatment reported fever, headache and myalgias, six hours after the administration of the first dose of pegylated IFN; these symptoms disappeared 80 minutes after the administration of two dipyrone tablets (Table 6).

Type of adverse events		Cryosurgery	IFN + Cryosurgery	IFN	Total
Local burning by cryosurgery	N	10 (100)	10 (100)	-	20 (66,6)
	Lightweight	10 (100)	10 (100)	-	20 (66,6)
	Moderate	-	-	-	-
Fever	N	-	1 (10)	1 (10)	2 (6,66)
	Lightweight	-	-	-	-
	Moderate	-	1 (10)	1 (10)	2 (6,66)
Headache	N	-	1 (10)	1 (10)	2 (6,66)
	Lightweight	-	-	-	-
	Moderate	-	1 (10)	1 (10)	2 (6,66)
General malaise	N	-	1 (10)	-	1 (3,33)
	Lightweight	-	-	-	-
	Moderate	-	1 (10)	-	1 (3,33)
Myalgias					
	N	-	-	1 (10)	1 (3,33)
	Lightweight	-	-	-	-
	Moderate	-	-	-	1 (3,33)

Table 6: Type and severity of adverse events.

Discussion

To date it is considered that none of the therapeutic alternatives used achieves a total cure or the elimination of recurrences and the main virtue of the different products used is to extend as much as possible the injury-free interval in the individual.

The results shown in this report are totally consistent with the knowledge reported to date, regarding the response of the disease during treatment with cryosurgery or IFN alpha. Pegylated IFN has not been previously used in the treatment of condyloma acuminata.

Cryosurgery has demonstrated its high cytodestructive capacity in multiple trials. Among them, 3 studies stand out, with the following results: 91%, 100% and 30%, respectively [5-7]. Other authors have compared it with other topical modalities in the treatment of condyloma acuminatum, for example: 2 studies, cryosurgery against 95% trichloroacetic acid with variable response (86 and 50% against 70 and 10%, respectively) [8,9], one study, cryosurgery against 25% podophyllin resin with 30 and 20% response, respectively [10]; study, cryosurgery versus radiosurgery with 70 and 40% response, respectively [11], one study, cryosurgery against 5-fluorouracil in cream at 5% with 70 and 35% response,respectively [12].

The percentage of recurrence ranged between 10 and 65% [7,8,10-13]. The author of the present study and collaborators in 2014 compared two treatment groups: the first received cryosurgery only and the second received cryosurgery associated with recombinant human IFN alpha 2b with 68.6% and 92, 9% response tot and 83.1% and 2.6% of recurrences, respectively [2]. Now in the current study (2018) they compared cryosurgery as an exclusive treatment against cryosurgery associated with pegylated IFN and pegylated IFN as exclusive treatment, with 80%, 100% and 90% of total response and 100%, 0% and 0% of recurrences, respectively. The high percentages of recurrences with cryosurgery are due to the fact that liquid nitrogen does not stimulate the immune system or destroy HPV. Its action is exerted on the infected host cell, inducing the phenomena of inflammation, vasoconstriction and thrombosis, responsible for the destruction of the tumor mass and consequently the HPV that die therein die, without causing any effect on the HPVs that inhabit it adjacent sites and that are responsible for the recurrences [8,10,12].

IFN alpha has shown in several clinical trials, the short-term elimination of genital lesions, as well as systemic viral particles, which in some way prevents recurrence [14,15]. Several formulations with IFN alpha are registered for the treatment of this disease [16,17]. Other authors have used: IFN alpha intralesionally, three studies with variable results (therapeutic response: 100%, 62% and 62%, respectively) [18-20], IFN alfa 2a by subcutaneous route associated with isotretinoin orally at different doses (between 0.5 to 1 mg/kg/day), four studies with variable results (therapeutic response: 96%, 91%, 95% and 100%, respectively) [21,22]. IFN alpha 2a subcutaneously associated with CO_2 laser, 2 studies with variable results (therapeutic response: 81% and 90%, respectively) [23]. IFN alpha subcutaneously associated with surgical excision [24], a study with 100% response; IFN alpha 2a subcutaneously associated with topical 5-fluouracil (cream), two studies with variable results (therapeutic response: 96% and 81%, g) topical× 10^6 IU ×respectively): 17,25 IFN alpha (cream 2, six studies with variable results (therapeutic response: 52%, 80%, 90%, 90%, 90% and 73%, respectively [23-26-30]. The author of the present study and collaborators in 2014 conducted a trial Clinical trial where the therapeutic response found in the group that used the IFN alpha adjuvant to cryosurgery was 92.9% and the recurrence rate was 2.6%[2]; in the current clinical trial (2018) the therapeutic response was 80% , 100% and 90%, with recurrence percentages of 100%, 0% and 0%, in the groups that received cryosurgery as exclusive treatment, cryosurgery associated with pegylated IFN and pegylated IFN as exclusive treatment, respectively. The few studies that carried out an adequate follow-up to determine the recurrence rates report high figures that range between 6%, 41% [31,32], indicators that are very variable, some distant from ours and others similar to those reached by the present study in the there were no recurrences in the group that used pegylated IFN, either alone or associated with cryosurgery.

Few authors have used alpha IFN associated with cryosurgery. The doses and routes of administration of IFN in these studies have been variable: intralesional IFN alpha (1×10^6 IU) was used in a study with a response in 51% of the patients and no follow-up was done to determine the percentage of recurrence [33]; in 2 studies subcutaneous IFN alpha (3×10^6 IU) was used, 60.7% and 83% of patients responded, respectively, with the percentages of recurrences 50 and 69% at 3 and 6 months, respectively [34,35]; in another study IFN alpha (2×10^6 IU) subcutaneous against IFN alpha (4×10^6 IU) were compared by the same route of administration, 61 and 62% responded, respectively, the recurrence rates were 76 and 39% at 6 months post-treatment, respectively [36]. The author of the present study and collaborators in 2010 reported a case with condyloma acuminata lesions around the ileostomy where the lesions were completely eliminated with three biweekly sessions of cryosurgery with liquid nitrogen associated with subcutaneous administration three times a week of a bulb of recombinant interferon alpha (bulbs: 3×10^6 IU) for six weeks, without subsequent recurrence during one year of follow-up1; in 2014 they compared two treatment groups: the first received cryosurgery alone, which showed 68.6% of patients with a total response associated with a recurrence rate of 83.1% and the second received the combination of cryosurgery and interferon, which showed 92.9% of patients with a total response associated with a 2.6% recurrence rate, a result superior to that caused by cryosurgery alone, as the effect of interferon, a potent antiviral agent and inmunomodulador was added [2] and now in 2018, in the current study, compared cryosurgery as exclusive treatment against cryosurgery associated with pegylated IFN and pegylated IFN as exclusive treatment, with 80%, 100% and 90% of total response and 100%, 0% and 0% recurrence, respectively. The differences found between the percentages of recurrences may have been due to the fact that previous studies were carried out long ago, in different places, by different authors, which do not describe: the technique used to perform cryosurgery, the type of cryogen, the times of freezing and thawing, the time of exposure of the cells to freezing and the number of applications per session.

The work hypothesis was demonstrated, in which it was proposed that the percentage of recurrences in the groups treated with pegylated interferon, alone and combined with cryosurgery, would be significantly lower than that obtained with cryosurgery as exclusive treatment. The percentage of recurrence obtained in the group where pegylated IFN was used, alone and combined with cryosurgery, was null, while in the group that received treatment with cryosurgery as exclusive treatment, 100% of the patients recurred. The difference between the groups was 100%, in favor of the groups that used pegylated IFN, either alone or combined with cryosurgery, a result that also exceeded expectations.

The pegylated IFN has the main function to eradicate the lesions immediately and achieve control of long-term recurrences. In all the determinations, the active participation of the pegylated IFN in the reduction of the number and size of the lesions could be verified.

Given that it is a disease for which the usefulness and benefit provided by the IFN alpha is well established, it can be considered that the efficiency percentages and the safety profile of the pegylated IFN demonstrated in this test represent an alternative of choice available and possible benefit for the control of the disease.

In agreement with the above, the finding of a lower percentage of recurrences to treatment with pegylated IFN, alone and associated with cryosurgery, with respect to the exclusive use of cryosurgery, constitutes an element that supports the fulfillment of the hypothesis of the study and favors the use of the pegylated IFN as a favorable risk-benefit alternative.

As main conclusions regarding efficacy, the results show that treatment with pegylated IFN, alone and adjuvant to cryosurgery, reduced the proportion of patients with recurrence from 100 to 0%, which is highly significant, both from the point of view statistical as a clinician. This absolute and relative reduction of 100% represents a high impact from the point of view of evidence-based medicine. In addition, a response to the highly effective treatment was obtained in the three groups, with higher percentages in the groups where pegylated interferon was used, alone and associated

with cryosurgery, in comparison with the exclusive use of cryosurgery, without significant differences. Regarding safety in this study, there was no serious adverse event, there was no need for dose changes or frequency of administration of the medications and it was not necessary to interrupt treatment temporarily or permanently. No patient required additional medical attention or was in danger or risk of any kind. The totality of the events occurred with mild or moderate intensity and without causing any permanent consequence on the individual. The main adverse events reported were those included in the so-called flu-like syndrome, coinciding with what was described in any study with IFN and local heat, coinciding with what was described in any study with cryosurgery. For all the above, it is considered that the treatment was well tolerated and that an adequate safety profile was obtained for the product under study.

In conclusion, treatment with pegylated IFN, alone and adjuvant to cryosurgery, reduces the percentage of recurrences of condyloma acuminata significantly higher than cryosurgery by itself, and its therapeutic effectiveness is also high. All the adverse events were of mild or moderate intensity and without causing any permanent consequence on the individual.

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