

Genital Warts and Intralesional Injections of Interferon

J. C. Vance, B. J. Bart, and O. J. Rustad

Introduction

The incidence of condylomata acuminata has been found to be rapidly increasing over the past several decades. An increase of five times was documented by the Centers for Disease Control in the United States for consultations for condylomata between the years of 1966 and 1981 [1]. That warts may be sexually transmitted has been recognized by physicians for centuries, but the discovery of a possible role of wart virus in oncogenesis is much more recent, and the evidence is of necessity indirect. It is well demonstrated that human papillomavirus (HPV) can be detected in vulvar and cervical carcinoma in situ, bowenoid papulosis, verrucous carcinoma, and squamous cell carcinomas both on the genital areas and elsewhere [2-5]. Warts have been clinically observed to convert into squamous cell carcinomas in patients with epidermodysplasia verruciformis, and HPV has been detected in those malignancies [6, 7]. The conversion of viral warts into carcinomas has been documented in animal models [8].

The combination of a sexually transmitted disease with a potential for cancer development has resulted in a clinical problem having great emotional overlay. The demand by the affected individuals for successful treatment has at the same time revealed to us the weaknesses of our current modalities of therapy. Since there is no HPV-specific vaccine or therapy, we must rely on nonspecific destructive modalities such as trichloroacetic acid (TCA), podophyllum or podophyllotoxin, cryotherapy, surgical excision, and laser destruction; chemotherapy with agents such as 5-fluorouracil and bleomycin; or the use of the immune stimulators such as dinitrochlorobenzene (DNCB), BCG, or levamisole [9, 10]. Interferon was described in 1957 and was first tested in patients with warts in the 1970s [11, 12], but it did not become available for large, well-controlled studies until the early 1980s when recombinant DNA technology made large scale production possible [13]. The treatment of warts has been studied using a variety of interferon types and differing grades of purity, using variable dosages and schedules, and administered in forms varying from intravenous, intramuscular, subcutaneous, intralesional, and topically in ointments and creams. The types of warts and types of patients treated and their follow-up periods have also been variable, so comparisons among the various reports are difficult. Our studies at the Hennepin County Medical Center and the University of Minnesota in Minneapolis have been confined to intralesional injections of interferon, which will be reviewed here.

Interferon as a Single Agent

One-Wart Study

Beginning in 1983, we conducted a multicenter trial in which we demonstrated that intralesional injections of alfa-2b interferon (IFN) are safe and effective for the treatment of condylomata [14].

Methods

In that study, a single genital or perianal wart was treated, giving intralesional injections of IFN at a dose of 1 million units, 100 000 units, or placebo into the substance of the wart in a 0.1 ml volume. The schedule was three injections per week for 3 consecutive weeks. The response to therapy was followed for 12 weeks.

Results – Efficacy

Ninety-one of 114 patients completed the full 12-week study and qualified for analysis. By week 5 there was a difference among the groups, and by week 12 the high-dose group was significantly improved ($P < 0.01$). Complete clearing of the treated wart is the most important clinical criterion, and that occurred in 16 (53%) of 30 patients in the high-dose group as opposed to 6 (19%) of 32 receiving the lower dose of 100 000 IU per injection and 4 (14%) of 29 receiving placebo injections. The percent of treated condylomata that cleared over time is presented in Fig. 1.

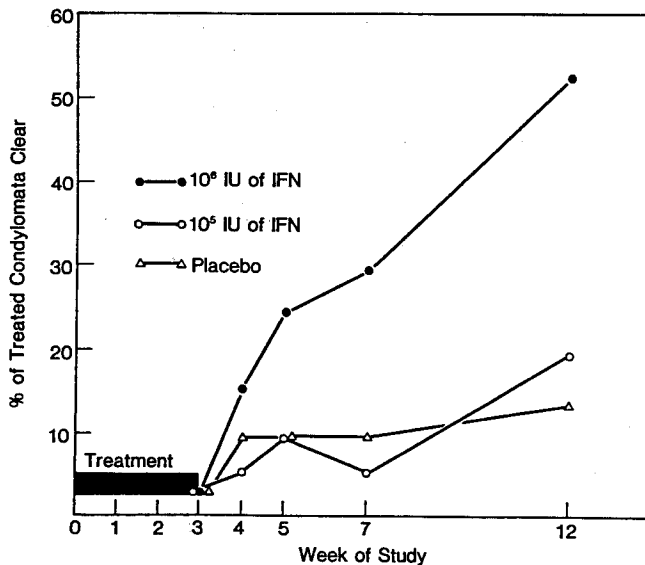


Fig. 1. Percent of treated condylomata that cleared over time (week of study), one-wart study

Results – Safety

The IFN injections were well tolerated. Among those in the high-dose IFN group 25 (68%) of 37 reported some type of side effects, compared with 19 (50%) of 38 in the low-dose IFN group and 17 (44%) of 39 receiving placebo. Only one patient receiving the high-dose IFN reported side effects judged to be severe (nausea), and that patient completed the study. Severe side effects were reported by three subjects in the placebo group (headache, genital pruritus, and urticaria). The most common mild symptom was the expected generalized flulike syndrome, consisting of a variable combination of fever, chills, myalgia, arthralgia, malaise, headache, and/or nausea. It occurred in 57% of patients receiving high-dose IFN, 29% receiving low-dose IFN, and 23% receiving placebo. Stinging, pain, or inflammation occurred at the injection site in 11% of patients receiving high-dose IFN, 18% receiving low-dose IFN, and 23% receiving placebo. Those local reactions did not present a therapeutic problem, since the patients felt they were mild enough to continue the study. No patient was dropped from the study because of laboratory abnormalities, although minor changes were commonly seen. Depression of the white blood cell count was seen in 15 (21%) of 70 patients receiving 1 million units, compared with none in the low-dose group and 4 (5%) of 74 in the placebo group. In the high-dose group, the depression was of approximately 1500 cells/ml and it returned to normal as soon as the therapy was completed. The group receiving 100 000 units showed a reduction of approximately 500 cells/ml. The hematocrit level was slightly reduced in the IFN-treated patients and the aspartate aminotransferase level was minimally elevated, but all other laboratory values showed infrequent and minor alterations not thought to be related to the IFN. The injections were thus safe as well as effective and well tolerated.

One- to Three-Wart Study (Eron et al.)

Our observations were confirmed and extended by Eron et al. [15] who injected 1 million units of IFN into one to three warts, and followed the warts for 16 weeks. Their randomized, double-blind trial enrolled 296 patients, of whom only 13 (4%) discontinued because of side effects.

Results – Efficacy

At 1 week after the completion of the 3 weeks of intralesional injections, IFN had produced a large reduction in mean wart area (62% decrease), as compared with placebo (1% increase; $p = 0.001$). At the completion of the 16-week follow-up, there was a 39.9% decrease in mean wart area in the IFN-treated group compared with a 46% increase in the placebo group. All treated warts had completely cleared in 36% of the IFN recipients and in 17% of the placebo recipients.

Results – Safety

Despite the higher dose of interferon given (up to 3 million units per treatment session), the injections were still well-tolerated clinically and only mild laboratory abnormalities were detected.

Five-Wart Study

In a double-blind, placebo-controlled study conducted in conjunction with Charles Welander, M.D. of Bowman Gray School of Medicine in Winston-Salem, North Carolina [16] we increased the number of warts treated to five per session.

Methods

The same dose of IFN per wart (1 million units or placebo) and schedule (three injections per week for 3 weeks) were used, but the patients were now followed for a total of 19 weeks. Eighty-two subjects were enrolled and evaluated for safety. Twelve were excluded from the efficacy analysis, primarily due to failure to return or to receive the complete course of injections, leaving 70 to be evaluated for efficacy; 32 in the IFN group and 38 in the placebo group. Dr. Welander enrolled 42 at Bowman Gray and 40 were enrolled at Minnesota. The patients at Bowman Gray differed in being primarily women,

Table 1. Demographic data on all efficacy subjects both centers, five-wart study

Characteristic	IFN	Placebo	Probability
Sex (male, female)	16/16	16/22	NS
Race (white/other)	28/4	34/4	NS
Age in years			
(mean)	29.7	28.4	NS
(range)	18–61	18–60	
Sexual preference (heterosexual/ homo-/bi-/NR)	30/0/1/1	32/1/0/5	
Lesion volume index in mm ³			
(mean)	79.9	53.5	NS
(range)	2.4–384	0.6–302	
Site, each lesion (penis/vulva/ perianal/other)	47/69/40/4	57/95/30/8	
Previous therapy (none/podophyllin/other)	8/20/4	11/23/4	NS

NR, not recorded; NS, not significant

in being about 7 years younger, and in having had more previous therapy than the patients at Minnesota, but the demographic factors of the two treatment groups pooled together showed no significant differences (see Table 1). Thirty-one subjects dropped out of the study for treatment failure, of whom 26 were in the placebo group and 5 in the IFN group. The greater number of dropouts in the placebo group produces a consistent bias when evaluating the data at each evaluation point, so the data has been calculated either as "end-point" which is the last valid visit in the study, regardless of the time, or "best response" which measures the best result while in the evaluation phase, regardless of the particular visit at which it occurred.

Results – Efficacy

At the endpoint the IFN-treated condylomata had decreased in mean volume by 40% while the placebo-treated warts had increased in mean volume by 56%, a significant difference ($P < 0.01$). The percentage change in patient target lesion volume index is shown in Table 2. As can be seen, only 9 (28%) of 32 patients were clear of all five lesions at the endpoint. In the placebo group, 22 (58%) of 38 patients had exacerbation of their wart volume index by endpoint. Table 3 shows the percentage change in the individual target lesions; 40% of all the 160 IFN-treated warts were clear at the endpoint while 23% of 190 warts treated with placebo were clear.

The response to IFN therapy was related to the initial size of the condylomata. This effect is shown in Table 4 which relates the pretreatment volume index of the warts to the number and percentage clear at the time of best response. It is a common finding with other treatment modalities that larger warts are more difficult to clear.

The time required for a wart to clear varied with whether IFN was used or placebo, as can be seen on Table 5.

Table 2. Percentage change in patient target lesion volume index at endpoint and best response, five-wart study

Patients with Degree of change	Endpoint		Best response	
	IFN	Placebo	IFN	Placebo
Increase	9 (28%)	22 (58%)	1 (3%)	8 (21%)
No Change	0	1	0	3
1%–25%	1	3	0	10
26%–50%	2	1	4	4
51%–75%	3	2	4	1
76%–99%	8	2	12	5
100% clear	9 (28%)	7 (18%)	11 (34%)	7 (18%)
No. of patients	32	38	32	38
Mean % change in volume	–40%	+56%	–80%	–28%
P value	<0.01		<0.01	

Table 3. Percentage change in individual wart volume index, at endpoint and best response, five-wart study

Warts with degree of change	Endpoint		Best response	
	IFN	Placebo	IFN	Placebo
Increase	27(17%)	84(44%)	2(1%)	23(12%)
No change	9	22	4	39
1%–25%	11	15	11	21
26%–50%	7	11	10	28
51%–75%	19	7	22	15
76%–99%	23	7	29	13
Clear	64(40%)	44(23%)	82(51%)	51(27%)
No. of warts	160	190	160	190

Table 4. Pretreatment size range (volume index) related to clearing by IFN at time of best response, five-wart study

Pretreatment, size volume index (mm ³)	No. clear	Percentage clear	No. of warts
< 1–5	23	77	30
6–10	16	64	25
11–20	11	41	27
21–30	6	40	15
31–50	10	55	18
51–100	8	44	18
>100 mm ³	8	29	27
Total	82	51	160

Table 5. Time of clearing of condylomata, five-wart study

Visit	IFN	Placebo
Week 1	0	1
Week 2	7	1
Week 3	13	4
Week 4	32	13
Week 7	15	5
Week 11	6	11
Week 15	4	10
Week 19	5	6
Total	82	51

Table 6. Response of untreated lesions to treatment, five-wart study

Improvement	IFN	Placebo
Exacerbation	0	1
No change	2	10
< 50%	6	4
> 50%–75%	1	0
> 75%–99%	3	0
Clear	7	6
Total	19	21

Nontreated condylomata were also measured in these subjects in order to determine if there was a systemic effect of IFN. As can be seen in Table 6, the effect of IFN on nontarget condylomata at the time of best response was modest. Clearing was seen in 7 (37%) of 19 warts in IFN-treated subjects, and at least moderate improvement (> 50%) in 4 (21%). Placebo-treated subjects had clearing of 6 (29%) of 21 warts but none had moderate or marked improvement. No change in or exacerbation of nontarget lesions was seen in only 2 (11%) of 19 IFN-treated subjects but in 11 (52%) of 21 placebo-treated patients.

Results—Safety

Only one IFN patient and no placebo patients dropped out of the study due to side effects, again showing that the drug is well tolerated even at 5 million units per treatment session. Forty (100%) of the IFN-treated patients developed at least one treatment-related adverse experience, and 28 (67%) of 42 placebo-treated patients also noted side effects, showing that the patients were being closely asked about such effects. The same flulike symptoms

Table 7. Percentages of IFN-treated patients reporting treatment-related adverse experiences, five-wart study

Symptom	Overall	Treatment period			Posttreatment Week 4
		Week 1	Week 2	Week 3	
Chills	75	70	28	11	3
Fever	70	60	31	17	6
Myalgia	70	50	36	36	6
Head- ache	55	50	23	11	0
Nausea	30	25	8	8	3
Fatigue	18	2	13	14	3

Table 8. Reports of intralesional IFN in condylomata

Study	Patients/ warts	IFN	Dose/ schedule	Response	Comments
Scott and Csonka 1979 [17]	11/11	Fibroblast	300 U/once	1 CR 9% 4 PR 33%	$P=0.045$ over con- trols
	11/?	Placebo			
Schonfeld et al. 1984 [18]	5/?	Beta IFN (Frone)	3 million U/ 4 ×, q.i.d.	5 CR 100%	Painful OR
	5/?	Placebo			
Geffen et al. 1984 [19]	10/32	Alfa IFN	0.8–35 million U/ 9–28 inj	21 CR 66%	
		(IFN Sciences)		7 PR 22%	
Gross et al. 1984 [20]	1/?	Beta IFN (Frone)	3 million U/ 4 ×, q.i.d.	1 PR	Recurred Ca in situ
Gall et al. 1985 [21]	4/?	Lymphoblasto- id (Wellfe- ron)	1 million U/ 2 × week- ly, × 4	3 CR 75%	After IM failed
Vance et al. 1986 [14]	30/30	Alfa-2b (Intron A)	1 million U/ 3 × week- ly, × 3	16 CR 53%	
	32/32	Alfa-2b (Intron A)	0.1 million U/3 × weekly, × 3	6 CR 19%	
	29/29	Placebo		4 CR 14%	
Eron et al. 1986 [15]	124/327	Alfa-2b (Intron A)	1–3 million U/3 × weekly, × 3	CR 36%	1–3 warts
	132/?	Placebo		CR 17%	1–3 warts
Vance et al. 1986 [16]	32/160	Alfa-2b (Intron A)	5 million U/ 3 × week- ly, × 3	64 CR 40%	
	38/190	Placebo		44 CR 23%	
Friedman- Kien et al. 1988 [22]	66/?	Alfa (Alferon N)	0.3–0.2.1 million U/ 2 × week- ly, × 8	CR 73%	
	66/?	Placebo		CR 36%	
Reichman et al. 1988 [23]	23/23	Alfa-2b (Intron A)	1 million U/ 3 × week- ly, × 4	11 CR 48%	
	15/15	Alfa-nl (Wellferon)	1 million U/ 3 × week- ly, × 4	6 CR 40%	
	20/20	Beta (Roswell Pk)	1 million U/ 3 × week- ly, × 4	10 CR 50%	
	18/18	Placebo		4 CR 22%	

CR, Complete Remission; PR, Partial Remission; IM, Ifosfamide

predominated, were mild or moderate, were of limited duration, and responded to oral acetomenophen. There was distinct tachyphylaxis of the side effects, with the incidence decreasing over the treatment period, and all were much improved by the fourth week. The most common treatment-related adverse experiences related to the week of the study are shown in Table 7.

Other Published Single-Agent Studies

Table 8 reviews the published reports of intralesional IFN use in condylomata. Several limited studies were done between 1979 and 1985 [17–21] which demonstrated that there was definite potential for intralesional IFN. Recently two well-controlled studies have been reported [22, 23] again confirming the usefulness of IFN given in this manner.

Friedman-Kien and his associates in Virginia and California [22] used natural (leukocyte) IFN (Alferon N) in a randomized, double-blind, placebo-controlled multicenter trial. The dose of IFN depended on the “wart area index,” but ranged from 0.3 to 2.1 million units (median, 1.2). The schedule was to give the IFN or placebo twice weekly for up to 8 weeks or until clearing occurred. The warts were completely eliminated in 62% of patients getting IFN and 21% of those getting placebo. Considering the warts individually, 73% were cleared by IFN and 36% by placebo. The patients were followed for up to 1½ years to evaluate for possible relapse, and 9 (25%) of 36 did so in the IFN group while 3 (23%) did so in the placebo group. The mean time until relapse was approximately 4 months for IFN-treated patients and 2 months for placebo-treated patients. Thus while relapse, which includes both recurrence and reinfection, was the same, IFN delayed the time to relapse.

Reichman et al. [23] carried out a double-blind, placebo-controlled, multicenter trial comparing the efficacy of three separate types of IFN; alfa-2b, alfa-n1, and beta. One wart was treated on each of the 76 patients, and the dose given was 1 million units or placebo at a schedule of three injections per week for 4 weeks. The three IFNs were approximately equal in efficacy, with clearing occurring in 48%, 40%, and 50% respectively. Placebo-treated subjects were cleared in 22%. Rates of relapse were similar among recipients of the three IFN preparations, being about one-third, and no significant difference was detected in comparison with placebo.

IFN Combined with Other Agents

Liquid Nitrogen VS Liquid Nitrogen and Interferon

In the clinical situation, everything possible is done to optimize the cure rate. In wart treatments that usually means combining two or more treatment modalities, and in Minneapolis we sometimes combine liquid nitrogen

cryotherapy to remove the bulk of the warts with podophyllin resin to help prevent recurrences.

We have recently completed a combination study designed to first remove the bulk of the virally infected tissue employing a widely used physically destructive method, liquid nitrogen cryotherapy [24]. Liquid nitrogen has the advantage of being inexpensive, and quick and easy to perform while producing minimal scarring [9]. Incomplete removal of the warts and recurrences are common, however. To that therapy we have added a course of interferon injections given into three selected warts to prevent recurrences. An equal number of subjects received the single liquid nitrogen treatment but did not receive the interferon injections.

Methods

The study was conducted in a randomized, parallel group, third-party blind fashion in which an investigator not acquainted with the treatment group of the patients did the wart measurements. Patients with the clinical diagnosis of genital or perianal condyloma acuminatum having three or more individual lesions greater than 3 mm but less than 16 mm in their largest diameter were enrolled.

Treatment

Human recombinant alfa-2b IFN (Intron-A) was used, giving 1 million units of IFN in 0.1 ml, the injection volume for each treated wart. One-half of the patients received a single treatment to all warts using liquid nitrogen, the other half were given the same treatment followed by thrice weekly injections of interferon at a dose of 1 million units per wart into each of three warts for 3 weeks. No placebo injections were given.

Results – Efficacy

Eighty-seven subjects were enrolled in the study, of whom 43 were randomized to receive liquid nitrogen alone (LN) and 44 to receive liquid nitrogen plus interferon injections (LN and IFN). Seventy-seven subjects were evaluated for efficacy, 38 in the LN group and 39 in the LN and IFN group. There were no statistically significant differences between the two treatment groups with respect to any of the demographic details (see Table 9). Looking first at the 3-week treatment period, 16 (42%) of the 38 patients receiving LN were cleared of all test site warts at some time-point. In the LN and IFN group, 19 (49%) of 29 subjects were cleared. The difference is not statistically different ($P=0.65$); see Table 10. The time to clearing was the same in both groups; see Fig. 2. This demonstrates that liquid nitrogen acts more quickly than IFN and so determines time to clearing.

By week 4, a significant difference between the groups was present. All 19 (49%) of the 39 subjects who cleared in the LN and IFN group were still clear, while only 9 (24%) of 38 subjects in the LN group were still clear ($P=0.03$). Subjects began dropping out of the study beginning at week 8, with only 10

Table 9. Demographic data on all randomized subjects: LN versus LN and IFN study

Characteristic	LN	LN and IFN	Probability
Sex (male/female)	31/12	32/12	> 0.99 ⁺
Race (white/other)	39/4	41/3	0.71 ⁺
Age in years (mean)	30.3	28.1	0.14*
(range)	18–61	18–50	
Weight in kg (mean)	73.7	73.4	0.87*
Sexual preference (heterosexual/ homo/bi-/NR)	32/2/1/8	35/4/1/4	0.62 ⁺
Total no. of warts (mean)	12.3	12.1	0.17*
(range)	3–40	3–60	
Wart volume index in mm ³ (mean)	49.7	44.6	0.25*
(range)	6.7–407	4.5–296	
Duration of warts in years (mean + STD)	2.2 + 3.8	1.9 + 3.2	0.43*
(range)	0.2–20	0.1–15	
Location of warts (vulva/perianal/ penile/other)	8/9/20/6	10/10/22/2	0.53 ⁺

* Wilcoxon's rank sum test

⁺ Fisher's exact test

subjects remaining in the LN group at week 24, while 23 remained in the LN and IFN group (see Table 11). A large number of patients discontinued the 6-month long study because of treatment failure, and the majority were in the LN group. Looking at the last visit or "endpoint" of each subject (independent of the study day) helps negate the effect of patient drop-out; 21 (54%) of 39 were clear at endpoint in the LN and IFN group while 9 (24%) of 38 were clear in the LN group, a significant difference ($P=0.01$).

The percentage of clearing of all treated sites was related to pretreatment mean wart size (volume index), as is shown on Table 12; 64% of the smallest warts (0 to 10 mm³) cleared under combination therapy, while 20% cleared with liquid nitrogen alone. Of the warts greater than 100 mm³, only 33% cleared with LN and IFN and 0% with LN.

Other demographic characteristics also correlated with clearing of all test sites (see Table 13). Gender, location of warts, lesion type and size all showed differences, which were the same for both treatment groups. Sexual preference was a factor primarily in the LN and IFN group. It is known that asymptomatic infection with human immunodeficiency virus (HIV) causes a marked reduction in the efficacy of IFN in the treatment of anogenital warts [25]. The duration of the warts did not appear to be an important factor in either group.

Table 10. Subjects having total clearing of all test sites: LN versus LN and IFN study

Visit	Treatment	Clear	Not clear	<i>n</i>	<i>P</i> value
Week 1	LN and IFN	0	39	39	>0.99
	LN	0	38	38	
Week 2	LN and IFN	6	33	39	0.43
	LN	9	29	38	
Week 3	LN and IFN	12	27	39	0.62
	LN	9	27	36	
Treatment phase best ^a	LN and IFN	19	20	39	0.65
	LN	16	22	38	
Week 4	LN and IFN	19	20	39	0.03
	LN	9	29	38	
Week 24	LN and IFN	18	5	23	0.21
	LN	5	5	10	
Last visit ^b	LN and IFN	21	18	39	0.01
	LN	9	29	38	

^a Treatment phase visit that had the best response (i.e., the lowest number of lesions present)

^b Independent of study day

Table 11. Subjects evaluable in study at each visit: LN versus LN and IFN study

Visit	LN	LN and IFN
Week 1	38	39
2	38	39
3	38	39
4	38	39
8	32	37
12	21	32
16	17	28
20	9	23
24	10	23

Table 12. Clearing of all treated warts at last visit as related to pretreatment wart size, LN vs LN and IFN study

Mean wart volume index (mm ³)	Liquid nitrogen + IFN			Liquid nitrogen alone		
	<i>n</i>	No. clear	Percentage clear	<i>n</i>	No. clear	Percentage clear
0-10	11	7	64	5	1	20
11-20	12	8	67	13	4	31
21-30	3	2	67	2	0	0
31-40	2	0	0	6	2	33
41-50	3	1	33	3	0	0
51-100	5	2	40	6	2	33
<100	3	1	33	3	0	0
Total	39	21	54	38	9	24

Table 13. Summary of demographic and baseline disease characteristics in subjects clearing all test site lesions at last visit, LN vs LN and IFN study

Risk factor		<i>n</i>	LN and IFN	(%)	<i>n</i>	LN	(%)
Gender	male	27	13	48	28	6	21
	female	12	8	67	10	3	30
Location	vulva	10	7	70	7	2	29
	perianal	8	2	25	7	1	14
	penis	19	11	58	18	5	28
	other	2	1	50	6	1	17
Sexual preference	heterosexual	32	18	56	29	7	24
	other	7	3	43	9	2	22
Mean target lesion size	≤ 20 mm ³	23	15	65	18	5	28
	> 20 mm ³	16	6	38	20	4	20
Duration of warts	≤ 1 year	27	15	56	23	6	26
	> 1 year	12	6	50	15	3	20
Skin site	not on mucosa	26	12	46	26	5	19
	On mucosa	13	9	69	12	4	33

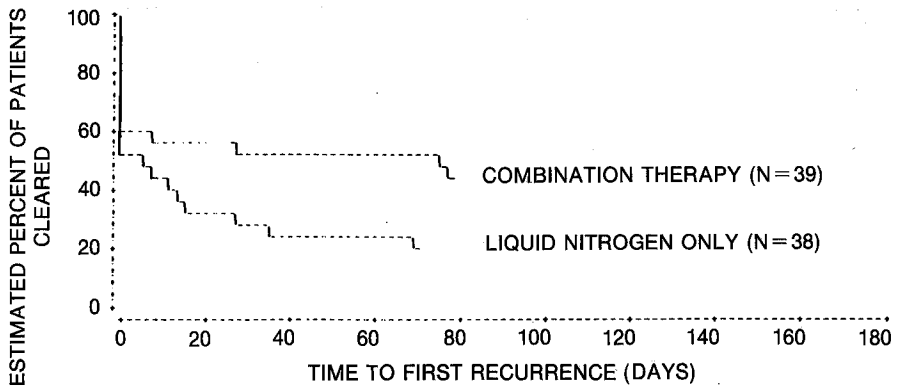


Fig. 2. Time to first recurrence, including all patients evaluated for efficacy, product limit survival estimate, LN vs LN and IFN study. Combination therapy means interferon alpha-2b and liquid nitrogen

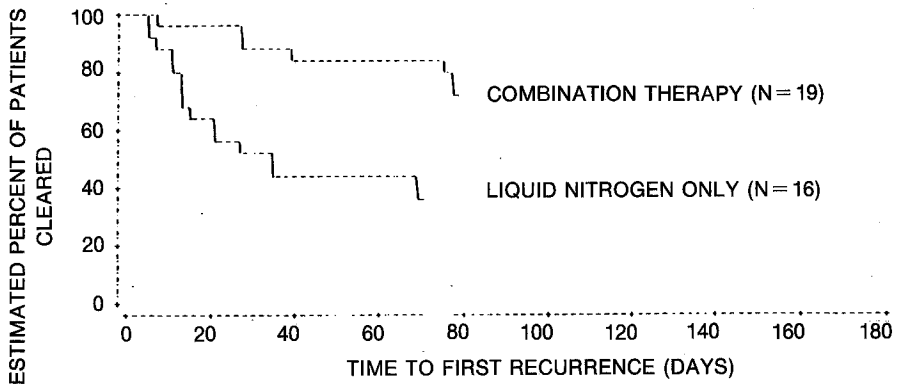


Fig. 3. Time to first recurrence, including only those who cleared by week 4, product limit survival estimate, LN vs LN and IFN study. Combination therapy means interferon alpha-2b and liquid nitrogen

An analysis of the time to first recurrence is demonstrated in Fig. 2, including all patients evaluated for efficacy. Thirty days after clearing of their lesions, approximately 54% of the LN and IFN and 28% of the LN patients remained clear of their lesions. At 60 days, the figures were 51% and 25% respectively. Limiting the analysis to those patients who cleared by week 4 is shown in Fig. 3; 89% of those in the LN and IFN group remained clear for 30 days, and 84% for 60 days. In the LN group, approximately 50% remained clear for 30 days, and 44% for 60 days.

Results – Safety

The adverse experiences encountered were similar to those previously reported for intralesional alpha interferon injections at similar dosages [14, 16].

40 (91%) of 44 subjects in the LN and IFN group reported at least one side effect. Flulike symptoms predominated. No treatment-related adverse experiences were encountered during the 6-month follow-up period, and no patients were dropped from the study for adverse experiences. The laboratory test results showed the treatments to be safe. The white blood cell counts temporarily decreased below normal values in 5 (11%) of the 44 in the LN and IFN group. Two (4%) of them had mild elevation of SGOT.

Conclusions

This study demonstrates that IFN given intralesionally can be of benefit as an adjunct to liquid nitrogen cryotherapy. It increases the number of condylomata which clear and also reduces the rate of recurrence. A weakness of this combination lies with the cryotherapy since it did not clear a high enough percentage of the warts. A useful combination which remains to be tested is repeated cryotherapy, as it is often given in practice, combined with IFN. That would increase the baseline rate of clearing before the IFN treatments. Destructive treatments which can clear 100% of the treated sites, such as electrocautery or laser vaporization, would also be effective since their cure rates and then prevention of recurrence should resemble those in Fig. 3.

Electrocautery Combined with IFN

Tiedemann and Ernst in Berlin have reported the results of their study using IFN as an adjuvant to electrocautery [26]. They enrolled patients with large condylomata, whose warts were of long duration, and with multiple recurrences, i.e., those who presented the most difficult clinical problems. Twenty-two were treated with electrocautery and then after allowing 5 to 10 days for healing, a course of IFN injections was given using alfa-2b (Intron A), at a dose of 5 million units, given intralesionally every 2 to 3 days to a total dose of 25 million units. They were compared with 11 patients who received electrocautery alone. There was a recurrence rate of 45% (5 of 11) within 6 weeks in the electrocautery group. In the combination group, only two patients (9%) developed a recurrence in a 6-month follow-up. Three others had transient recurrences which spontaneously resolved. Of importance is the observation that the injections of IFN caused delay in healing of the surgical sites if they were still open at the time the injections were started. It is probable that IFN delays wound healing.

Gerd Gross from Hamburg (F.R.G.) has also recorded the combination therapy of condylomata [27, 28]. He reported a case of a Buschke-Loewenstein-like condyloma in a woman with Hodgkin's disease who responded favorably to electrocautery followed by the topical application of recombinant alpha-2c in a hydrogel. It was applied four times daily for 8 weeks. The patient remains clear after 14 months follow-up.

Carbon Dioxide Laser Combined with IFN

Currently in Minnesota we are conducting a trial testing the combination of carbon dioxide laser vaporization of recalcitrant or large anogenital condylomata in conjunction with intralesional injections of alfa-2b interferon. The combination is being compared with laser treatment alone. The injections begin at the time of the surgery, and a mild delay of healing is noted (2 to 4 weeks to complete healing of erosions) but excessive pain or scarring have not been encountered. The IFN is started at 1 million units, and then is moved up to 5 million units per treatment as soon as it is tolerated, taking advantage of the tachyphylaxis phenomenon seen in IFN injections. The injections are given three times weekly for three weeks, and are placed adjacent to the treated sites, rotating the injections so that all adjacent areas receive some injections. To date 23 subjects have been enrolled in the combination group with as much as 18 months follow-up, and only two (9%) have experienced a recurrence. Both have elected to be re-treated with the combination. It is our preliminary impression that IFN injections add to a reduction in the recurrence rate of difficult cases of condylomata treated first with laser vaporization.

Discussion

Interferon given intralesionally is a safe and effective modality for the treatment of condylomata. It is similar to all other modalities of wart treatment in that not all warts clear up. The response rates for IFN-treated warts vary from 73% [22] to 36% [15]. The large differences probably relate to variations in the dose, duration of treatment, number of injections, type of IFN used, demographics of the treated individuals, types of warts treated, and the length of the follow-up period [14–23].

The mechanism by which IFN is effective in the treatment of warts remains unknown. Interferon does produce an antiviral state which limits the further spread of many viruses [29] but it also cause a reduction in cellular proliferation at the affected site, and changes in the host immune responses [30–33]. Since IFN has been shown to be capable of clearing cultured cells of their content of papilloma virus [34], it is hoped that *in vivo* treatment of affected sites using intralesional IFN may be capable of eradicating occult HPV in the skin thereby preventing recurrences of the condylomata and at the same time reducing risk of malignant proliferation.

Combinations of IFN with other treatment modalities will probably be the major way in which it is used for treating condylomata. Combinations with liquid nitrogen, electrocautery, laser vaporization, and others are currently being investigated and have been found to be useful adjuncts in the effort to control this difficult clinical problem.

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