Clinical Trials of Interferon-gamma in Treating Warts

Suk Woo Lee, M.D., Dong Houh, M.D., Hyung Ok Kim, M.D.,
Chung Won Kim, M.C., Tae Yoon Kim, M.D.*

Department of Dermatology, Catholic University Medical College, Seoul.
Department of Dermatology, Hyundae Haeseong Hospital, Ulsan, Korea*

This study was performed to investigate the clinical efficacy of intralesional recombinant interferon-γ (IFN-γ) in the treatments of warts, using a placebo comparison. Warts of each groups were injected with INF-γ containing 5×10^6 IU/ml (high dose), 1×10^6 IU/ml (low dose), or distilled water for injection as placebo, respectively, twice weekly for three weeks. The final therapeutic efficacy was determined on the fourth week after the beginning of therapy.

Among the 74 patients with periungual warts, plantar warts, or warts of other sites, complete clearing of the treated warts at week four occurred in 56% of the 36 patients receiving the high dose IFN-γ compared to 30% of the 53 receiving the low dose IFN-γ and 17% of the 36 receiving the placebo. Marked improvement showing 75% or greater regression of wart lesions was noted as 89% of patients receiving the high dose INF, compared with 55% receiving the low dose IFN and 50% receiving the placebo. The group of patients with warts of other sites showed the best response.

The group receiving the high dose IFN experienced some adverse effects more frequently or more severely than the group receiving low dose IFN. However, the effects were relatively tolerable to the patients. Therefore, intralesional injection of the high dose IFN-γ may be more useful in treating warts than a low dose IFN-γ.(Ann Dermatol 2:(2) 77-82, 1990)

Key Words: Intralesional injection, Recombinant interferon-γ, Wart.

Interferon (IFN) was first described as an antiviral agent composed of low molecular weight glycoprotein in 1957 by Isaacs and Lindenmann.[1] Apart from its known antiviral activity,[2,3] IFN also exerts antiproliferative,[4,5] antitumoral,[6,7] and immunomodulatory activities.[8,9] Recently, it has become possible to produce large amounts of pure IFN from bacteria by recombinant DNA technique.[10] Thus IFN is available for large scale clinical experiments and for the treatments of many diseases.

IFN is divided into three types by antigen specificity: 1) IFN-α, 2) IFN-β, and 3) IFN-γ. In comparison with a series of intralesional injections of IFN-α or IFN-β in the treatments of warts,[11-14] large scale clinical trial of IFN-γ has not been reported. This study, was performed in order to investigate the clinical efficacy of intralesional recombinant IFN-γ in the treatment of warts.

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Reprint request to: Dong Houh, M.D., Department of Dermatology, Catholic University Medical College, Kangnam St. Mary's Hospital, #505, Banpo-Dong, Seocho-Ku, Seoul, 137-040, Korea

MATERIALS AND METHODS

1. Patients and materials

This study enrolled 74 patients aged five or more years with warts of at least 3 month's duration. They visited the dermatologic clinic in Kang-Nam St. Mary's hospital, Seoul and Hyundae Haeseong hospital, Ulsan from July 1988 to March 1990. The patients had not received any specific anti-wart treatment for at least four weeks prior to entry into the study, and the majority of them had showed poor responses to previous applications of conventional treatments. Characteristics of the 74 patients are presented in Table 1. Of these patients, 40 were men and 34 were women; the mean age of the pa-

Table 1. The age and sex of 74 patients. Duration of warts and their distribution.

		No of patient	%	Age	No of patient	%	Distribution	No of patient
Sex	male	40	54	5-9	13	17	periungual	36
	female	34	46	10-19	35	47		
Duration	≤1 yr	29	39	20-29	13	18	plantar	17
of	≤3 yr	31	42	30-39	5	7	other	36
Warts	>3 yr	14	19	40-	8	11	sites	

tients was 20.

In this study, two different concentrations of recombinant IFN-γ preparations (Biotec institute, Lucky, Ltd.) produced from yeast by recombinant DNA technique were employed; one vial was 5×10^6 IU/ml in concentration (high dose IFN) and another was 1×10^6 IU/ml (low dose IFN). Each preparation showed 97% purification and $2\text{-}5\times10^7$ units/mg protein of specific activity by sodium dodecylsulfate polyacrylamide gel electrophoresis. Each preparation were preserved below -20°C, and warmed slowly at room temperature immediately before use. We used distilled water for injection contained in same vial as placebo.

2. Study design

Warts of the patients were largely classified as periungual, plantar, and warts of other sites.

In order to evaluate the relationship between the dose of IFN-γ and the clinical improvement of wart lesions, patients were randomly divided into two groups of high dose IFN-γ (group A) and low dose IFN-γ (group B).

In order to compare the clinical improvement between IFN-injected sites and placebo-injected ones, patients with multiple warts received IFN-γ injections into the warts on one side and placebo injections warts into warts on the matching site. The lesions receiving placebo injections were differently designated as control group (group C).

Warts of each groups were intralesionally injected twice weekly for three weeks (a total of six times) with 5×10^5 IU of IFN-γ per 50 mm^2 size (in group A), 1×10^5 IU of IFN-γ (in group B), or placebo (in group C) in a volume of 0.1 ml, respectively, using tuberculin syringes and 25 gauge needles. Also, the total amount of injected IFN-γ per patient on each injection did not exceed 5×10^6 IU.

Table 2. Assessment of clinical improvement

Effect	Reduction of lesion size	Scoring
Cured	complete clearing	3
Good	over 75%	2
Moderate	less than 75%	1
Poor	no change or increase	0

The injected warts were evaluated before injection at the onset of the study at every injection time for three weeks using a scale of 0 (poor) to 3 (cured) to measure change of size or flatness (Table 2). The final therapeutic efficacy was determined on the fourth week after therapy onset. On final assessment, patients showing clinical improvement above good were determined as IFN-responded group.

Potential local and systemic adverse effects of medication administration, manifested by the presence on absence of flulike symptons, pain or itching, were determined by questioning patients before and after injections. If present, the adverse effects were graded as mild, moderate, or severe, and duration were also recorded.

RESULTS

1. Effects of treatment

The three treatment groups were composed of 36 patients in group A, 53 in group B, and 36 in group C. Some patients had multiple warts on the different sites. The groups, composition were not significantly different from one another with regard to age or sex.

1) Periungual warts

The enrolled patients were 17 in group A, 19 in group B, and 15 in group C, respectively.

Among the 17 patients in group A, complete clearing of the treated warts at week four occurred in nine cases, compared with seven in the 19 patients of group B and three the 15 patients of group C. IFN-responded showing clinical improvement above good (INF-responded group) were 15 out of 17 patients in group A, compared to 11 out of

19 patients in group B and 8 out of 15 patients in group C (Table 3).

2) Plantar warts

The enrolled patients were seven in group A, ten in group B, and seven in group C, respectively.

Complete clearing of the lesions occurred in three cases in group A, in one case in group B, and in one case in group C. IFN-responded group was six of seven patients in group A compared with four of ten patients in group B and three of seven patients in group C (Table 4).

3) Warts of other sites

The enrolled patients were 12 in group A, 24 in group B, and 14 in group C, respectively. The warts, in order of frequency, were on the hands, forearms, lower legs, or faces.

Complete clearing of the lesions occurred in eight cases in group A, in eight cases in group B, and two cases in group C. IFN-responded group was 11 of 12 patients in group A compared with 14 of 24 patients in group B and 7 of 14 patients in group C (Table 5).

Among the total of 74 patients with warts on periungual, plantar, or other sites, complete clearing of the treated warts occurred in 56% of 36 patients receiving high dose IFN-γ (group A) compared to 30% of 53 receiving low dose IFN-γ (group B) and 17% of 36 receiving placebo (group C). Marked improvement, including complete clearing and good response, was noted in 89% of group A, compared to 55% in group B and 50% in group C (Table 6). Differences in rates of complete clearing of injected warts between group A and group B or group C were statistically very significant ($p<0.01$). Also, IFN-responders in group A (89%) were significantly different ($p<0.01$) than

Table 3. Evaluation of the therapeutic effect on periungual warts

Effect	Group A	Group B	Group C
cured	9	7	3
good	6	4	5
moderate	—	4	4
poor	2	4	3
Total	17	19	15

*Expressed as No. of patients

Table 4. Evaluation of the therapeutic effect on plantar warts

Effect	Group A	Group B	Group C
cured	3	1	1
good	3	3	2
moderate	1	3	2
poor	—	3	2
Total	7	10	7

*Expressed as No. of patients

Table 5. Evaluation of the therapeutic effect on warts of the other sites

Effect	Group A	Group B	Group C
cured	8	8	2
good	3	6	5
moderate	—	5	2
poor	1	5	5
Total	12	24	14

*Expressed as No. of patients

Table 6. Evaluation of the therapeutic effect on warts of all sites

Effect	Group A(%)	Group B(%)	Group C(%)
cured	56	30	17
good	33	25	33
moderate	3	23	22
poor	8	22	28

*Expressed as percent of patients

Table 7. Adverse effects of therapy

Effect	Group A (%)	Group B (%)
Local pain on injection	all	all
Flu-like symptoms		
fever	71	26
fatigue	45	—
chills	32	—
headache	26	4
myalgia	16	—
dizziness	3	7

*Expressed as percent of patients

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those in group B (55%) or in group C (50%); however, there was no significant difference between group B and group C. Moreover, clinical response in group A was noted earlier stage than in group B and group C (data not shown).

2. Adverse effects

The principal adverse effect associated with intralesional administration of medications was local pain on injection sites that lasting for several minutes, occurring in a almost all of the patients. In group A receiving high dose IFN, 71% of 36 patients reported flu-like symptoms including fever, chills, fatigue, or headache begining one or two after injection and subsided within six to eight hours, compared with 26% of 53 in group B receiving low dose IFN (Table 7). Also, the symptoms in the high dose IFN group were apt to last somewhat longer and were more severe compared with those in the low dose INF group.

DISCUSSION

Although the exact role of IFN in regression of viral skin diseases including warts, has not yet been identified, some mechanisms of action have been suggested. First, several cytoplasmic enzyme activities induced by IFN have been elucidated. IFN inhibits the synthesis of viral protein by oligoadenylic synthetase producing 2,5-oligoadenylates[2,15] and by protein kinase phosphorylating eIF-2,[3,16] and the both enzymes are activated by IFN. In addition, IFN inhibits the enzymes needed for synthesis of viral envelope.[3] Secondly, IFN exerts the antiproliferative effect by inhibiting glycosyl transferase and ornithine decarboxylase.[2] Thirdly, IFN enhances the cytotoxic activities of macrophages and natural killer cells against viral infected cells through interleukin-2 released by activated T lymphocytes.[17,18] Also, IFN activates immune responses by inducing the expression of HLA class II antigen or viral infected keratinocytes.[19-21] The series of pleomorphic effects on immune cells has been considered to be mediated almost exclusively by IFN-γ,[22] IFN-γ appears more likely to evoke cellular immune responses especially in resistant warts when compared with IFN-α and IFN-β.[23,24] Moreover, pure IFN-γ can be produced in large amounts from bacteria or yeast by recombinant DNA technique, consequently, IFN-γ is available in large scale clinical experiments and treatments.

Comparing a series of intralesional injections of IFN-α or IFN-β in the treatments of warts, a large scale clinical trial of IFN-γ has not yet been reported. Therefore, we performed the present study to investigate the efficacy of intralesional recombinant IFN-γ in the treatment warts and to evaluate the relationship of dosage of IFN-γ in the improvement of warts. Also, the difference in clinical improvement between IFN-γ injected warts and placebo-injected ones was compared. As a result, warts of other sites showed better response in IFN-γ therapy than warts of periungual or plantar region. In this group, complete clearing of high dose IFN-treated warts at week four was 67%, marked improvement showing 75% or more regression of wart lesions was 92%. Among the 74 patients with warts on all sites, the rate difference of complete clearing of treated warts between high dose IFN group (56%) and the low dose IFN group (30%) or the placebo group (17%) was statistically very significant. Marked improvement in the high dose IFN group (89%) was also significantly different from that in the low dose IFN group (55%) or placebo group (50%). There was no significant difference between the low dose IFN group and the placebo group. A clinical response in the high dose IFN group was noted earlier than in the low dose IFN group or placebo group. Therefore intralesional injection of high dose IFN-γ may be more useful in treating warts, than low dose IFN-γ.

Although it has been reported that multiple warts respond more slowly than single warts,[25] this was not the case in our study. Patients with multiple warts showed a response rate similar in comparison to that of the patients with single warts.

The relatively good response in placebo-injected warts may be induced by inflammation of injection sites[26] or by delayed effect through systemic absorption of IFN-γ simultancously injected on the other sites,[27,28] but the placebo-injected sites no inflammatory signs such as erythematous swelling or local heating. In other words, the therapeutic effect of IFN-γ may be systemic as well as local. This hypothesis is also supported by our observation that approximately 50 percent of uninjected

lesions resolved, if the IFN-injected lesions totally regressed.

Meanwhile, it is noted that linear thrombotic changes on healing process were observed in seven cases which showed complete clearing by IFN-γ. The change might be induced by IFN-γ itself or by vascular injury on injection.

In this study, it is encouraging that 89% of marked improvement of wart lesions occurred with 5×10^5 IU of IFN-γ injection six times for three weeks, compared with the previous results of Vance et al[13] reported 47% of treatment response of plantar warts with 1×10^6 IU of IFN-α injection nine times for three weeks and Niimura et al[14] reported 81% of marked response of common warts with 1×10^5 IU of IFN-β injection nine times for nine weeks.

It has been reported that almost all of the patients with intralesional injection of IFN had transient local pain on injection sites.[29] Another common adverse effect of IFN therapy is generalized flu-like symptoms including fever, chills, fatigue, headache, myalgia, or arthralgia.[8,13,30] In addition, transient bone marrow depression such as leukopenia and thrombocytopenia[31], hepatitis,[32] or reversible neurotoxicity[33] may occur. In our study, all of the IFN-injected patients had relatively tolerable local pain on injection sites for five to ten minutes. Also, 71% of high dose IFN-injected group showed more severe flu-like symptoms than those of low dose IFN group (26%).

CONCLUSION

We performed this study to determine the efficacy of intralesional IFN-γ therapy in 74 patients with warts. As a result, high dose IFN-γ showed significantly good response compared with low dose IFN-γ and the placebo, particularly in the patients with warts of other sites. But, the group receiving the high dose IFN-γ experienced more frequent adverse effects than those in the low dose IFN group. Thus additional studies should be needed to establish the optimal dose and treatment schedule that will maximize the convenience and effectiveness of IFN-γ injections while minimizing the adverse effects.

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