Intralesional Recombinant Alpha-2a Interferon for the Treatment of Patients With Verruca

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Background **: Interferon alpha-2a has already been shown to be effective in clinical use of virus-originated diseases such as hairy cell leukemia, condyloma acuminatum, and AIDS-related Kaposi's sarcoma. The use of recombinant alpha-interferon may allow common warts to be treated relatively atraumatically and with less incidence of recurrence.**

Objective **: We tried to determine the safety and effectiveness of intralesional injections of recombinant alpha-2a interferon in the treatment of patients with common warts.**

Methods **: A single wart on each patient was weekly injected with 0.75 to 1.5×10^5 IU/25mm^2 of interferon for 8 weeks, and the response to treatment was followed up-to 6 months.**

Results **: Clearing of the treated wart at the end of treatment occurred in 5(71%) out of 7 patients and the rest showed no improvement. With evaluation for relapses up-to 6 months after treatment, warts relapsed in 2(40%) out of 5 patients. Therefore, 3(43%) out of 7 patients were completely free of warts 6 months after treatment.**

Conclusion **: Intralesional recombinant interferon alpha-2a has a limited therapeutic effect, but may be considered as a therapeutic modality of recalcitrant verruca or when it can be anticipated that destructive techniques or blistering agents will not be tolerated.**

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Key Words : Interferon alpha-2a, Intralesional therapy, Verruca

Warts have been mainly treated by locally destructive methods, up to now, such as surgical excision, electrocautery, cryosurgery and more recently, laser vaporization, all of which may result in scarring and be associated with recurrence[1]. Chemical destructive methods using various acids, such as salicylic and/or lactic acid, can be applied by the patient, but may cause local irritation and not be uniformly effective. Podophyllum resin application has also variable effectiveness and must be used with caution. Antimitotic agents, such as bleomycin[2] and fluorouracil[3] have been tried, but side effects of those agents limit their usefulness. Dinitrochlorobenzene immunotherapy[4,5] for warts has recently been questioned because of its mutagenicity[6].

Antiviral activity of interferon(IFN) makes it a reasonable possibility as a treatment modality for warts because of its antiproliferative, antitumor, and immunomodulatory activities that may also play a role in clearing the wart virus from skin and mucous membranes[7,8].

This study was performed to evaluate the safety and effectiveness of intralesional injections of recombinant alpha-2a IFN in the treatment of patients with verruca.

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MATERIALS AND METHODS

Subjects and Materials

7 patients with the clinical and histological diag-

Table 1. Demographic characteristics

No. of patients enrolled	7
Sex	
Male/Female 6/1	
Median age, years	31
Location of warts, No.	
Sole	6
Hand	4
Neck	1
Lip	1
Clinical status at enrollment	
Median duration of disease(y)	3.1
Wart-area index (mm^2)	
Median	164
Range	35-400

Table 2. Clinical features of patients

Case	Sex/Age	Sites	Duration (y)	Tx. history
1	M/27	Sole, Rt.	6	none
2	M/37	Neck, Post	1	none
3	M/26	Lip, Upper	2	none
4	M/30	Finger, Index	4	cryotherapy laser Tx.
5	M/33	Sole, Left Hand, Dorsum Finger, Thumb	1	cryotherapy
6	M/37	Finger, Index Toe, 4th	5	E/D*
7	F/27	Sole (× 3)	2	DNCB*

E/D*:Electrodessication, DNCB*: Dinitrochlorobezene

nosis with verruca vulgaris or verruca plantaris were selected for this study (September, 1997 - January, 1999). All of the patients did not have a history of cardiac diseases, pulmonary embolism, thrombophlebitis and any medications affecting the activity of IFN. Informed consents were obtained following a thorough discussion of our study with each patient. Human recombinant alpha-2a IFN (Alphaferon, Cheil-Jedang Co., Seoul, Korea) was prepared as freeze-dried material and supplied in vials. IFNα-2a was diluted with 2 ml of sterile water to the 1.5×10^5 IU/0.1 ml.

Methods

Each wart was measured (maximum length, width, and maximum height) with a caliper and the wart-area index (product of length × width) was recorded. The wart-area index has been used to adjust the doses of IFN.

The injection volume was approximately 0.05 to 0.10 ml/25mm^2 of wart-area index, which was sufficient to saturate the lesions[9] and the initial injection dose of IFNα-2a was approximately 0.75 to 1.5 × 105 IU/25mm^2 of wart-area index. The injections were done using a 26-gauge needle at the edge of and directly underneath the wart.

Injections were performed weekly either for 8 weeks or until all the treated warts completely disappeared, whichever came first.

Evaluation of Efficacy

Patients were examined weekly during treatment for 8 weeks and 6 months after the end of treatment to evaluate safety and efficacy. The treated warts were evaluated for therapeutic response by measurement of wart-area index and photography. Complete response was defined as complete disappearance of the treated lesions for up-to 6 months after treatment.

RESULTS

Clinical characteristics

Six men and one woman were enrolled in this study. The mean age of the patients was 31 years old, and the median duration of disease was 3.1 years. 4 out of the 7 patients had a history of treatment with other modalities in the past. The mean wart-area index was 164 mm^2 before treatment. Table 1 and Table 2 summarize the demographic characteristics and the clinical features of the patients.

Efficacy and Course

In the present trial, clearing of the wart at the end of treatment occurred in 5(71%) out of 7 patients. During evaluations for relapses up-to 6 months after treatment, we found relapses in 2(40%) out of 5 patients who were treated initially. Therefore, 3(43%) out of 7 patients were completely free of warts at 6 months after treatment. Table 3 summarizes the treatment data.

Adverse reactions

All the patients never experienced fever or flu-like syndrome (including at least two of the following : fever or chills, myalgias or other pains, or

Table 3. Response to intralesional recombinant alpha-2a interferon in 7 patients with verruca.

Patient	Sex /Age	Sites	W.A.I.* (mm^2)	Dose* (1-4wks)	W.A.I.** (mm^2)	Dose* (5-8wks)	Total Dose*	Response(at the end of Tx. /6 months after Tx.)
1	M/27	Sole	120	70	80	50(5-6)	380	Clear/Clear
2	M/37	Neck	120	70	80	50(5-8)	480	Clear/Recur
3	M/26	Lip	60	30	60	30(5-8)	420	Stationary/Stationary
4	M/30	Finger	35	20	35	20(5-8)	160	Stationary/Stationary
5	M/33	Sole	120	70	100	60(5-7)	460	Clear/Clear
		Hand	60	30	33	20(5-7)	180	Clear/Clear
		Finger	60	30	Clear	-	120	Clear/Clear
6	M/37	Finger	50	30	50	30(5-8)	240	Clear/Recur
		Toe	140	80	140	80(5-8)	640	Clear/Recur
7	F/27	Sole(1)	400	120	200	60(5-8)	720	Clear/Clear
		(2)	400	120	200	60(5-8)	720	Clear/Clear
		(3)	400	120	200	60(5-8)	720	Clear/Clear

W.A.I.* : Wart-area index, at first visit, W.A.I.** : Wart-area index, at the end of 4 wks Tx., Dose* : × 10,000I.U./week

malaise), but every patient complained of local pain at the time of the injection.

DISCUSSION

There are many effective therapeutic options available for the treatment of a verruca. The treatment of choice is based on the size, location of lesions, patient's tolerance, compliance, effectiveness of previous treatments, and cost considerations. First-line therapies include cytotoxic agents, vesicants, cryotherapy, dessication and currettage, and more recently laser vaporization, and there have been different reports about the cure rates of each modalities[1].

Cryotherapy with liquid nitrogen have the advantages of no need for anesthesia, minimal discomfort and scarring. Disadvantages of cryotherapy include localized burning and pain and decreased effectiveness. Cryotherapy is recommended to be performed on children because it is easily tolerated and effective for lesions in children and adolescents, which tend to be more superficial than those in adults. CO2 laser ablation have ranged from 62% cure rates for multiple recalcitrant lesions[13] to 94.7% cure rates for isolated lesions[14]. This method has the advantages of minimal discomfort, minimal postoperative complications and a high success rate, but have disadvantages and possible complications of scar tissue formation, recurrence, sterile abscess formation and infection. Horwitz and Marker[15] reported a success rate of 65% with electrodessication. A major benefit of this method is that one treatment is usually effective, but side effects, such as moderate-to-severe pain, difficulty in controlling depth and recurrence of larger or recalcitrant warts may preclude its use. Immunotherapy with dinitrochlorobenzene had 50% to 70% cure rates[4,5]. This method has the advantages of no anesthesia, no discomfort and pain, no risk of scarring. Obvious disadvantages include the need for multiple treatments, varying cure rates, and recurrences. DNCB should be used with caution as it has been implicated as cross-reacting with other chemicals and causing contact dermatitis as well as having possible mutagenic and carcinogenic effects[6]. Injection therapy with bleomycin advocated by Sollitto and co-workers[16] had a 32.2% cure rate, and by Bremner[18] showed 63% success rate. Scarring is rare but local tissue destruction, microthrombosis and pain are common side effects in this method.

The introduction of IFN was a welcome addition to this therapeutic arsenals. There are several types of IFN: α-, ß,-, and γ-, as well as the more recently described acid labile, δ-, and amniotic membrane IFNs[10]. All are classified according to the cell from which they are derived, their structure,

and their differing biochemical characteristics. Alpha is induced by Sendai virus in leukocytes or lymphoblasts. The alpha family now has 20 subtypes that differ in amino acid compositions. Of them, the alpha-2a has a lysine at position 23[11]. IFNα-2a has already been shown to be effective in clinical use of virus-originated diseases such as hairy cell leukemia, condyloma acuminatum and AIDS-related Kaposi's sarcoma[11]. We have previously reported successfully treating five patients with basal cell carcinoma and two patients with actinic keratosis with the intralesional injection of recombinant alpha-2 IFN[12].

Antiviral activity of IFN makes it a reasonable possibility as a treatment modality for warts because of its antiproliferative, antitumor, and immunomodulatory activities that may also play a role in clearing the wart virus from the skin and mucous membranes[7,8]. When Vance and co-workers[18] compared the efficacy of 10^6 IU of IFNα-2a, 10^5 IU of IFNα-2a, or placebo, clearing occurred in 13%, 22% and 21% of patients with plantar verruca, respectively, which did not have any statistical differences between IFN and placebo. However, in the case of condyloma acuminatum, a dose of 1×10^6 IU given three times per week was a safe and effective treatment. The absence of clinical improvement with recombinant α-interferon as the treatment modality on plantar verruca may be caused by several factors, such as infected HPV types, skin architecture, and turn over rates of different sites of the skin.

In our study, we used wart-area index to calculate and adjust IFNα-2a dosing. With dose of 0.75 to 1.5×10^5 IU/25mm^2, 3(43%) out of 7 patients were completely free of warts at 6 months after treatment. Two of 4 patients with recalcitrant verruca could achieve complete clearing of warts. Overall results are not so satisfactory, and intralesional recombinant IFNα-2a may not be suitable for initial treatment modality, but may be considered as a substitutive treatment of recalcitrant verruca. Since the number of patients in our study was small and there was no other controlled study at the same time during this study, a long-term case-controlled study would be required to determine the optimal dose and treatment schedule that will maximize the convenience and effectiveness while minimizing the side effects.

REFERENCES

1. Bunney MH: Viral warts: Their biology and treatment. Oxford, Egland, Oxford University Press, 1982.
2. Shumer SM, O'Keefe EJ: Bleomycin in the treatment of recalcitrant warts. J Am Acad Dermatol 9:91-96, 1983.
3. Hursthouse MW: A controlled trial on the use of topical 5-fluorouracil on viral warts. Br J Dermatol 92:93-96, 1975.
4. Bucker D, Price N: Immunotherapy of verrucae vulgaris with dinitrochlorobenzene. Br J Dermatol 98:451-455, 1978.
5. Dunagin WG, Millikan LE: Dinitrochlorobenzene immunotherapy for verrucae resistant to standard treatment modalities. J Am Acad Dermatol 6:40-45, 1982.
6. Black HS, Castrow FF, Gerguis J: The mutagenicity of dinitrochlorobenzene. Arch Dermatol 121:348-349, 1985.
7. Krim M: Towards tumor therapy with interferons: I. Interferons: production and properties. Blood 55:711-721, 1980.
8. Krim M: Towards tumor therapy with interferons: I. Interferons: production and properties. Blood 55:875-884, 1980.
9. Getten JR, Klein RJ, Friedmankien AE: Intralesional administration of large doses of human leukocyte interferon for the treatment of condyloma acuminata. J Infect Dis 150:612-615, 1984.
10. Johnson RE, Johnson JC, Kloberdanz ST, et al: Recombinant α-interferon and verruca plantaris. J Am Podiatr Med Assoc 81:253-257, 1991.
11. Rudolf Stadler, Augusto Mayer-da-Silva, Burkhard Bratzke, et al: Interferons in dermatology. J AM Acad Dermatol 20:650-656, 1989.
12. Sung In Cho, Yoon Whoa Cho, Chang Kwun Hong, et al: Basal cell carcinoma and actinic keratosis treated with intralesional injection of recombinant alpha-2 interferon. Annal of Dermatology 7(2):116-120, 1995.
13. Mancuso JM, Abramow SP, DiMichino B, et al: Carbon dioxide laser management of plantar verrucae: A six-year follow-up survey. J Foot Surg 30:238, 1991
14. Mueller TJ, Carlson BA, Lindy MP: The use of the carbon dioxide surgical laser for the treatment of verrucae. J Am Podiatr Med Assoc 70:136, 1980.
15. Horwitz O, Marker T: The efficacy of electrocaus-

tic, keratolytic and placebo treatment in patients with single warts. Dermatologica 40:127, 1960.
16. Sollitto RJ, Napoli RC, Gazivoda PL, et al: A perspective study using bleomycin sulfate in the treatment of plantar verrucae. J Foot Surg 28:141, 1989.
17. Bremner RM: Warts: Tretment with intalesional bleomycin. Cutis 18:264-266, 1976.
18. Vance JC, Bart BJ, Hansen RC, et al: Intralesional recombinant alpha-2 interferon for the treatment of patients with condyloma acuminatum or verruca plantaris. Arch Deramtol 122:272, 1976.