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Interferon alpha-n1 (Wellferon) for refractory genital warts: efficacy and tolerance of low dose systemic therapy

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Summary

This multi-center trial compared two doses of parenterally administered interferon alpha-n1 (Wellferon) in men and women with recurrent/resistant genital warts. Patients received either 1 or 3 MU/m^2 daily for 14 days, then 3 times weekly for 4 weeks; non-responders could receive an additional four weeks of treatment. A total of 107 patients were enrolled, and 102 were evaluable after six weeks of study. The principal dose comparison was in 57 women assigned alternately to the two doses. Median lesion measurements were reduced significantly from baseline at weeks 2, 4 and 6 in both groups. Statistical analysis showed no difference in response to 1 versus 3 MU/m^2. The overall complete response (CR) plus partial response (PR) rate at week 6 was 69% for the two doses. Two additional groups of 21 women and 24 men were treated at the higher dose with CR plus PR rates of 75 and 50%, respectively. Week 10 disease evaluations for all groups showed 19 of 77 patients to be completely cleared. Of these 19, only one had recurrent disease at the end of the 6-month study period. Analysis of the incidence of symptomatic side effects showed a significantly higher frequency among women treated with 3 MU/m^2 than among women treated with 1 MU/m^2. Five dose reductions

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and two withdrawals for toxicity occurred, all in the high dose group. This study demonstrates that parenterally administered Wellferon produces clearance of resistant genital warts in many patients, and that rates of clearance do not appear to vary between groups receiving moderate or low dose therapy.

Interferon alpha-n1; Genital wart; Human papillomavirus

Introduction

Condyloma acuminatum, or ano-genital warts, is a sexually transmitted disease of the skin and mucous membranes that is caused by certain human papillomavirus (HPV) types (Gissmann et al., 1980, 1982). Recent evidence suggesting that closely related HPV are strongly associated with the development of cervical carcinoma and other genital tract neoplasias has led to an increased interest in the appropriate management of these infections (Macnab et al., 1986). In addition, ano-genital warts are increasing rapidly in incidence, and the disease represents a major uncontrolled public health problem (Centers for Disease Control, 1983). Although a variety of treatment modalities for these infections is available, not one is completely satisfactory. Most traditional methods of treatment have utilized either physical or chemical destruction (VonKrogh, 1981; Shumer et al., 1983; Hasumi et al., 1984), or surgical removal (Hahn, 1981; Krebs et al., 1985). However, both local and systemic complications have been associated with these methods, and disease frequently recurs following therapy. Development of recurrent disease may be related to the inability of the initial therapy to inactivate infectious virus completely, or to remove all infected tissue. In addition, it is now known that genital HPV disease is frequently multifocal, and may be difficult to diagnose by physical examination alone. In fact, tissue biopsies of histologically normal epithelium may contain HPV DNA (Ferenczy et al., 1985). Thus, the development of an effective form of systemic antiviral therapy will probably be necessary to treat these infections successfully.

Data from anecdotal observations (Strander et al., 1974), open studies (Geffen et al., 1984), one in vitro system (Turek et al., 1982), and recently completed placebo-controlled trials (Eron et al., 1986; Vance et al., 1986; Reichman et al., 1988) indicate that interferon represents a potentially useful treatment modality. Parenteral administration of beta-interferon has been associated with significant regression of genital warts (Schonfield et al., 1984) and intralesionally administered alpha-2a, alpha-2b, alpha-n1, and beta interferons have produced significant rates of lesion regression of interferon-injected warts. Although this route of administration may also produce beneficial effects on non-injected lesions (Reichman et al., 1988), this observation needs to be confirmed. In addition, intralesional injections are uncomfortable, and impractical for patients with multiple, highly keratinized, or extensive lesions.

Previous trials of parenterally administered interferon alpha-n1 (Wellferon) have

been associated with significant rates of lesion regression. A pilot study employing intramuscularly administered alpha-n1 in doses of 4–6 megaunits (MU) per day appeared to benefit patients who had disease which was refractory to conventional therapy (Alawattegama et al., 1984). An additional study demonstrated that 5 MU/m^2 given daily for a period of six weeks was associated with significant regression of lesion areas in 15 of 16 patients (Gall et al., 1986). However, all patients in the study developed side effects of interferon therapy or abnormalities of laboratory tests, and required reduction of dose or interruption of therapy. A blinded placebo-controlled trial demonstrated that a non-steroidal anti-inflammatory agent given concomitantly reduced interferon alpha-n1 side effects without affecting rates of disease response (Trofatter et al., 1985). The present report presents the results of a study designed to determine the comparative efficacy and toxicity of doses of 1 or 3 MU/m^2 of interferon alpha-n1 administered parenterally to patients with biopsy proven, refractory condyloma acuminatum.

Materials and Methods

Patient population

Patients who participated in this study were enrolled in clinics at the Duke University Medical Center, Durham, North Carolina; the University of California, Irvine, California; or the University of Rochester, Rochester, New York. All patients had a diagnosis of condyloma acuminatum established by histologic examination of lesion biopsies. In addition, all patients had disease of at least three months' duration, and had failed a course of conventional therapy. All studies were approved by human experimentation committees at each institution, and written informed consent was obtained from each patient prior to study entry. Except for condyloma acuminatum, all patients were in good health as determined by medical history, physical examination, and routine laboratory tests. Patients were excluded from participation if they had received a form of immunological therapy in the previous eight months, were pregnant, practiced inadequate methods of birth control or were nursing mothers. Patients were not permitted to participate either if evidence of malignancy was present in tissue biopsy specimens, or if they were receiving corticosteroids, cytotoxic, or other immunosuppressive drugs.

Study design

A diagram of the study design is presented in Fig. 1. Prior to study entry, blood was obtained for determination of complete blood counts including differential and platelet counts, creatinine, SGOT, SGPT, total bilirubin, blood urea nitrogen, and alkaline phosphatase. Blood tests were performed weekly during the period of daily administration of study medications, and every two weeks thereafter. Serum specimens were obtained on day one at 0, 4, 8, and 24 h for determination of serum interferon titers following initial injections. Follow-up serum samples were obtained at the end of weeks 2, 4, 6, 8, 10, and 24 to monitor blood levels of interferon and for detection of anti-interferon antibodies.

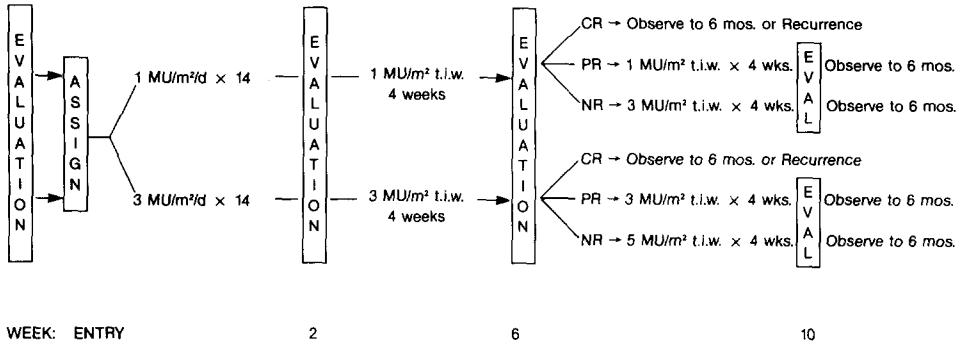

Fig. 1. Schematic diagram of study design for comparison of 1 MU/m^2 and 3 MU/m^2 doses of Wellferon for resistant genital warts.

Treatment with interferon alpha-n1 (Wellferon) was initiated at one of two different doses. Women were assigned alternately to receive either 1 MU/m^2 or 3 MU/m^2. Men began at the higher dose, as did an additional group of women who were not enrolled in the dose comparison study. Injections were administered either intramuscularly or subcutaneously for two weeks, followed by the same dose given three times per week for an additional four weeks. Modifications of dosage were made according to a standardized dosage modification schedule if patients encountered unacceptable side effects or developed interferon induced abnormalities of laboratory tests.

Disease evaluation

Evaluations of lesions were made at the time of enrollment and at two-week intervals. Bidimensional measurements of lesions were recorded on a grid superimposed upon detailed anatomic diagrams. Total lesion area was calculated as the sum of products of these measurements. Complete response (CR) was defined as total clearance of all measurable lesions. Partial response (PR) was defined as greater than or equal to 50% but less than total clearance of disease, and no response (NR) was defined as less than 50% reduction or increase in lesion area as compared to area of disease at study entry.

After the initial six weeks of therapy, a decision was made to continue or stop interferon treatment based on patients' responses. In general, patients obtaining complete clearance were taken off drug and observed until recurrence or month six of study. Partial responders were maintained at their starting doses three times weekly for four weeks. Non-responding patients had doses escalated from 1 to 3 or 3 to 5 MU/m^2 administered three times per week for an additional four weeks. Following ten weeks of therapy, patients were observed monthly for changes in disease status.

Interferon

Interferon alpha-n1 (Wellferon) is a highly purified preparation of alpha interferons derived from a human lymphoblastoid cell line, Namalwa, by viral induction (Finter et al., 1980). Wellferon was supplied as a frozen solution in Tris-glycine buffered saline with human serum albumin added as stabilizer. This preparation contains no preservatives. Wellferon is greater than 95% pure interferon and has a specific activity of $1–2 \times 10^8$ IU/ml of protein prior to the addition of stabilizer. The material for this clinical trial was supplied by Wellcome Biotech, Beckenham, United Kingdom, through Burroughs Wellcome Co., Research Triangle Park, North Carolina.

Virus typing

HPV DNA was extracted from biopsy specimens removed from patients at the time of entry to the clinical trial and the viral genome was analyzed using Southern transfer and hybridization (Mounts et al., 1982, 1984). Papillomavirus subtypes were determined on the basis of hybridization patterns obtained under moderately stringent hybridization conditions (T_m −28°C) with radioactively labeled HPV-6 DNA. Restriction enzyme mapping was performed with DNA samples digested with endonucleases *Hin*dIII, *Hpa*I, *Eco*R1 and *Pst*I.

Interferon levels and serum neutralizing titers

Assays for determination of serum interferon titers were performed in a standard viral cytopathic effects (CPE) inhibition assay in 96-well microtiter trays. The assay utilized human foreskin fibroblasts, FS-7 cells, grown in monolayer culture and challenged with vesicular stomatitis virus. Standardization of each assay was performed with the NIH reference standard (G023-901-527) for human leukocyte interferon. Titers were determined in duplicate for each sample and expressed in IU/ml as the reciprocal of the dilution resulting in 50% inhibition of CPE as corrected to the standard. Results were reported as averages of duplicate values.

Serum interferon concentration-time data were subjected to model-independent pharmacokinetic analysis for patient data. Because of the limited number of samples per patient and the high degree of inter-patient variability, these analyses were limited. Parameters calculated included the observed peak concentration and the area under the interferon concentration-time curve (AUC as h × IU/ml).

Serum neutralizing activity to Wellferon was determined in a biological assay according to the WHO Guidelines (WHO, 1985). Briefly, a fixed dilution of serum (1:10) was tested against varying concentrations of Wellferon in a standard antiviral assay similar to that described above. Results were reported in U/ml of neutralizing activity based on the reduction in titer of a standard Wellferon preparation. All specimens were assayed in duplicate and results calculated as the average of these duplicate values. Serum samples were scored as positive if the neutralizing activity was 18 U/ml.

Data management

The composite database for this study was compiled by the Clinical Data Processing Department of Burroughs Wellcome Co. Standardized data collection forms were used at all centers. Databases for each center were quality assured through a character-by-character comparison of a ten percent sample of forms to a computerized printout. All errors found during quality assurance were corrected and data were released for statistical analysis. Data were analyzed using the Statistical Analysis System (SAS). All P values are two-tailed.

TABLE 1

Wellferon in condylomata acuminata: demographic and patient characteristics

	Dose comparison groups (women)		Additional treatment groups (3 MU/m^2)	
	1 MU/m^2	3 MU/m^2	Women	Men
	N = 30	N = 27	N = 21	N = 24
Age (years)				
Mean	27.8	29.1	30.5	29.0
Race (%)				
White	83	89	81	92
Black	13	7	19	8
Hispanic	3	0	0	0
Oriental	0	6	0	0
Body surface area (m^2)				
Mean	1.8	1.7	1.7	2.0
Range	1.4–3.1	1.4–2.3	1.0–2.2	1.7–2.6
Duration of disease (years)				
Median	0.90	0.83	1.08	0.50
Lesion area (cm^2)				
Median	1.7	2.2	11.0	2.6[a]
Range	(0.02–121.57)	(0.06–43.7)	(1.0–96.0)	(0.06–143.0)
Previous treatment				
Podophyllin	27	21	18	14
Cryotherapy	13	7	11	10
Cautery	6	3	0	6
Laser	1	2	1	2
Surgery	4	3	6	6
Other	6	5	8	0

[a] At entry 20/24 men had perianal lesions.

Results

Patient characteristics

A total of 107 patients was enrolled in this study. After 6 weeks, 5 patients were considered not evaluable because of protocol violations or lack of adequate follow-up. Characteristics of the remaining 102 patients are presented in Table 1. After 10 weeks of study, lack of adequate follow-up made an additional 13 patients not evaluable. Thus, a total of 89 patients were available for analysis at week 10. Patients who were not evaluable were distributed similarly among the 4 treatment groups. The principal dose comparison was conducted in two groups of women; 30 assigned to 1 MU/m^2 and 27 assigned to 3 MU/m^2. Two additional treatment groups were included in this study and consisted of 21 women who received 3 MU/m^2 outside the alternate treatment design and a group of 24 men who also received 3 MU/m^2 as initial therapy.

Patients were of similar age, were predominantly white, and had had disease for similar periods of time prior to study entry. The two dose comparison groups were remarkably similar, although the 3 MU/m^2 group had a slightly greater median lesion area. The additional treatment group of women at 3 MU/m^2 had a greater median lesion area than the dose comparison groups. This measurement is probably indicative of more extensive infection. Most patients had received at least one conventional treatment modality prior to study enrollment. Many had received multiple therapies, the most common being podophyllin. Extent of disease at different anatomic sites did not differ significantly among the three different groups of women. However, it is noteworthy that 20 out of 24 men had perianal lesions at entry.

Evaluation of efficacy

The principal dose comparison analysis of this study was conducted in the two groups of women assigned to either 1 MU/m^2 or 3 MU/m^2 as outlined in Table 1 (Dose Comparison Groups (Women)). The median lesion areas at different time points for these dose comparison groups and numbers of paired values for each

TABLE 2

Median lesion area measurements: dose comparison groups of women

Week of study	1 MU/m^2		3 MU/m^2	
	N	cm^2	*N*	cm^2
Baseline	30	1.70	27	2.19
2	28	0.38[a]	25	0.52[a]
4	29	0.36[a]	25	0.29[a]
6	28	0.35[a]	23	0.19[a]
8	22	0.25[a]	19	0.23[a]
10	25	0.36[a]	16	0.27[a]

[a] Median lesion areas significantly less than baseline. $P \leq 0.002$ by one-sided Wilcoxon Signed Rank Test.

evaluation are summarized in Table 2. Comparison of each week's median area to baseline area demonstrated highly significant decreases at all weeks for both groups ($P \leq 0.002$). However, no statistically significant differences between the two groups were observed when week six areas were compared ($P = 0.47$ by two-sided Wilcoxon Rank Sum Test). In addition to these similar decreases in lesion areas, overall response rates at week six were similar. Among 28 patients treated at 1 MU/m^2, four (14%) had complete clearance, 15 (54%) had partial clearance, and nine (32%) had no response. Responses were similar for the 3 MU/m^2 group; 4 (17%) had complete resolution, 12 (52%) had partial resolution, and 7 (30%) had no response. Percentage changes from baseline were tested also (data not shown). As with absolute changes in lesion areas, each group showed significant reductions from baseline at all weeks tested, but there was no significant difference between the two groups.

Table 3 presents the median lesion areas for the two additional treatment groups. Significant regression of lesions as compared to baseline was demonstrated for each group at weeks 2, 4, 6, and 8 and, for women, at week 10 also. Median values continued to decline for the group of women treated at 3 MU/m^2 throughout the 10 week period. In contrast, median lesion areas increased after week 6 for the group of men. This observation suggests that men do not respond as well as women to interferon therapy. A difference in response according to sex is suggested also by the overall response rates of the additional treatment groups at week six (Table 4). Of 20 evaluable women, one (5%) had a complete response, 14 (70%) partial responses, and 5 (25%) no response. Responses were somewhat different for the men treated at 3 MU/m^2. One patient (6%) had complete clearance, 8 patients (44%) partial clearance and 9 (50%) patients had no response. It is interesting to note that the baseline lesion area for the women was approximately four-fold greater than that for the men. However, after four weeks of therapy, the median value was less for the women than for the men.

Evaluation of secondary therapy period

The purpose of the secondary treatment period was to determine if additional therapy for partial responders or escalation to a higher dose for non-responders

TABLE 3

Median lesion area measurements: additional treatment groups of 3 MU/m^2

Week of study	Women		Men	
	N	cm^2	*N*	cm^2
Baseline	21	11.03	24	2.58
2	20	3.17[a]	22	2.03[a]
4	17	1.29[a]	20	1.79[a]
6	20	1.17[a]	18	0.73[a]
8	18	1.12[a]	16	1.38[a]
10	15	0.40[a]	14	1.41

[a] Median lesion areas significantly less than baseline. $P \leq 0.002$ by one-sided Wilcoxon Signed Rank Test.

TABLE 4

Summary of overall responses by treatment group

Dose comparison (women)	Week 6		Week 10	
	1 MU/m^2	3 MU/m^2	1 MU/m^2	3 MU/m^2
Complete clearance	4	4	6	6
50% clearance	15	12	13	8
50% clearance	8	1	6	2
No response	1	6	2	3
Additional treatment (3 MU/m^2)	Women	Men	Women	Men
Complete clearance	1	1	4	3
50% clearance	14	8	10	2
50% clearance	3	5	2	6
No response	2	4	0	4

enhanced disease clearance. In addition, duration of clearance in complete responders was monitored. In the dose comparison groups, 16 patients started at 1 MU/m^2 had doses escalated, whereas seven started at 3 MU/m^2 had doses increased. In the additional treatment groups, five women and nine men who initiated therapy at 3 MU/m^2 had doses escalated to 5 MU/m^2 following the week six evaluation. Examination of individual patient data did not show an advantage for escalation. The original treatment groups were not subdivided for analysis based on dose escalations; however, all groups were tested for a difference in changes in total lesion areas during the secondary treatment period.

The overall responses for the four treatment groups at weeks 6 and 10 are summarized in Table 4. All four groups had increases in the proportion of patients exhibiting complete clearance of disease. Although significant differences in lesion areas between weeks 6 and 10 were not demonstrated, additional patients became complete responders during this period in each group. The most striking change was in the additional treatment group of women at 3 MU/m^2. Fourteen of 16 (88%) evaluable patients at week 10 had complete or partial responses. In contrast, the group of men at this dose had only five of 15 (33%) evaluable patients with these responses. In general, the combined response rate was greater for all three groups of women. Nineteen of 27 women (70%) originally started at 1 MU/m^2 and 14 of 19 (74%) started at 3 MU/m^2 had complete or partial clearances at the end of 10 weeks of therapy.

Recurrence of disease

Monthly follow-up of patients for recurrence of disease was conducted for 6 months. Table 5 presents the data for the 19 patients considered complete responders at week 10. As indicated, only two of these 19 had disease recurrences during follow-up. However, one patient with recurrent disease and one additional patient in the lower dose group were considered disease-free at month 6 without further therapy. The recurring patient in the 3 MU/m^2 group still had measurable

TABLE 5

Recurrence of disease in complete responders (CR) by treatment group

	Response at week 10	Disease recurrence (month)	Response at end of study (6 months)
Dose comparison groups			
1 MU/m^2	6 CR	1[a] (4)	7 CR
3 MU/m^2	6 CR	1 (4)	5 CR
Additional treatment groups			
Women	4 CR	0	6 CR
Men	3 CR	0	3 CR

[a] Patient considered CR at month 6.

lesions at month 6. Two patients in the additional treatment group of women continued to respond off drug and were considered complete responders at month 6. Thus, the number of patients with complete clearance was 21 at the end of study and only one of the original 19 (5%) complete responders had regrowth of lesions.

Clinical laboratory results

Alterations of clinical laboratory values often associated with interferon therapy were commonly observed in patients who participated in this study. Quartile plots for three of these measurements are presented in Fig. 2. Frequently observed changes included decreases in total white blood cell counts and total platelet counts. Increases in SGOT and SGPT levels also were observed. As depicted in Fig. 2, these alterations tended to be greater for the higher dose group, although most were not significantly different statistically. The most profound changes occurred within the first two weeks, probably as the result of daily administration of Wellferon. These alterations were usually transient and returned toward normal ranges during weeks 4 and 6.

Reductions of doses due to abnormal laboratory values were not common. No patients treated at 1 MU/m^2 required dose modification. Six patients in the 3 MU/m^2 group had doses reduced; five for total white blood cell counts below 4000/mm^3 and one for platelets less than 100 000/mm^3.

Systemic side effects

Interferon-associated side effects were observed in the majority of patients treated in this study. The overall incidence of four of the most common side effects for the dose comparison groups are depicted graphically in Fig. 3. In addition to fever, headache, fatigue, and flu-syndrome, chills, nausea, and vomiting were reported also but at much lower incidences. Grade 3 or severe symptoms were reported rarely. For the six symptoms listed above, the number reported by patients on the higher dose was statistically significantly greater ($P \leq 0.05$) for all weeks tested. For example, 39% of the 1 MU/m^2 group versus 79% of the 3 MU/m^2 group reported headaches during the initial week on study. Fever and headache were acute symptoms that occurred most frequently during the first week of injections with marked reduction during weeks 2 and 6. In contrast, fatigue persisted

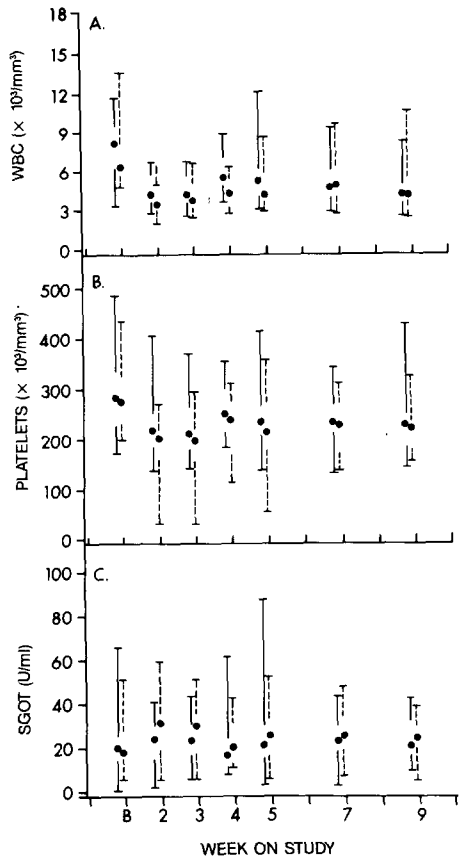

Fig. 2. Quartile plots of values for total white blood cell counts, platelet counts, and serum glutamic oxaloacetic transaminase values for the dose comparison groups. Data are expressed as median values with upper and lower quartiles indicated by vertical bars. The solid vertical bars represent the 1 MU/m^2 group and the dashed vertical bars the 3 MU/m^2 group.

throughout the treatment period. It is important to note that less than 10% of the patients treated at 1 MU/m^2 experienced these latter two symptoms by the second week of therapy.

Withdrawals from study due to intolerable side effects were rare and dose-related. Seven patients from the high dose group withdrew, whereas no one from the 1 MU/m^2 group cited side effects as the reason for stopping injections. There were no serious adverse side effects or life-threatening events reported. All side effects resolved when Wellferon administration was stopped.

Serum interferon levels

Determination of serum interferon titers following the initial dose of Wellferon allowed calculation of areas under concentration curves (AUC) for the two doses employed (see Fig. 4). Peak serum interferon titers varied considerably from pa-

tient to patient with a range of 11 to 402 U/ml for the lower dose and 32 to 654 U/ml for the higher dose; mean peak titers were 118 and 179 U/ml, respectively. The mean AUC values with ranges presented in Fig. 4 are for women treated at 1 and 3 MU/m^2 and men treated at the higher dose. Mean AUCs were 1607 and 3311 for women treated at 1 and 3 MU/m^2, respectively. The mean AUC for men administered 3 MU/m^2 was 1468. These results reflect the marked patient to patient variability for clearance of Wellferon and suggest a difference between women and men administered the 3 MU/m^2 dose. AUC data were not predictive of disease response.

Serum neutralizing titers

A total of 99 of the 107 patients enrolled in this study had pre- and post-therapy serum specimens assayed for neutralizing activity to Wellferon. No patient had detectable activity prior to receiving interferon therapy. One patient developed a positive neutralizing titer following treatment. This twenty-year-old woman received a dose of 3 MU/m^2 during both the primary and secondary treatment periods. A

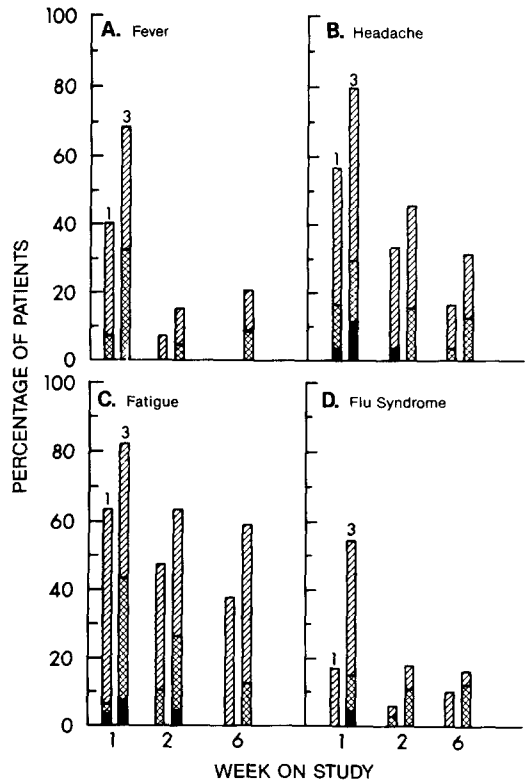

Fig. 3. Incidence of symptomatic side effects for the dose comparison groups of women treated at 1 MU/m^2 or 3 MU/m^2. Data are presented as the percentage of patients reporting mild (▨), moderate (▩), or severe (■) side effects; N = 30 for the 1 MU/m^2 groups and N = 27 for the 3 MU/m^2 group.

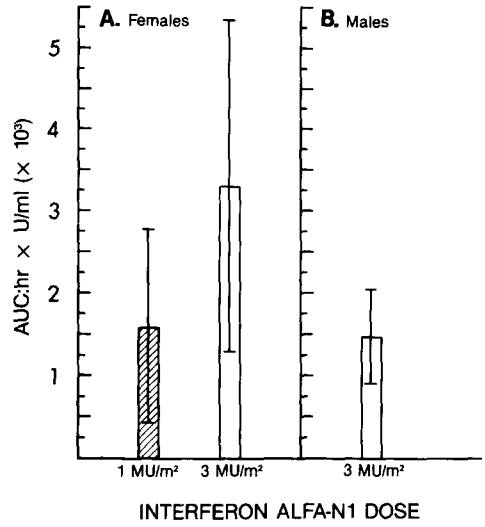

Fig. 4. Mean AUC values for women (A) treated at 1 ( ) or 3 MU/m^2 ( ) and men (B) treated at 3 MU/m^2. Data are presented as the mean values for these groups and vertical bars represent standard deviations.

positive titer of 47 U/ml was detected in the week 11 serum sample. She had the anticipated side effects of fever, chills, and some myalgia on initial dosing; these were mild and ameliorated with repeated injections. After six weeks of therapy, she had a 95% clearance of visible lesions. She completed a second course of therapy and was considered a complete responder at the final study evaluation.

HPV typing of tissue biopsies

Wart tissue biopsies obtained at entry were analyzed for presence of HPV DNA by Southern blot techniques. The results of these analyses are presented in Table 6. The use of this technique also enabled the identification of subtypes of HPV-6.

TABLE 6

Human papillomavirus typing/subtyping of tissue biopsies

HPV subtype	Number of patients	Disease responses		
		CR	PR	NR
6c	9	3	3	3
6d	10	2	8	0
6e	17	3	12	2
6e/f	4	1	2	1
6f	4	0	2	0 (2 NE)
6h	6	3	3	0
6 (uncharacterized)	7	3	3	1
Total	57	15	33	7 (2 NE)

Of 57 available specimens, sufficient quantities of DNA were obtained from 50 for subtyping purposes. The most prevalent subtypes were HPV-6e and 6d. Only two of the 57 patients typed for HPV were considered non-evaluable for response. Comparison of HPV subtype to disease response showed no distinct pattern between the subtype present and response to Wellferon therapy. This lack of correlation was evident for both the low and high dose groups of patients (data not shown).

Discussion

This study examined the effects of two different dosage regimens of Wellferon in the treatment of women with condyloma acuminatum. Patients were assigned alternately to receive 1 MU/m^2 or 3 MU/m^2, each administered daily for two weeks and then three times weekly for four weeks. Two additional treatment groups, consisting of women with extensive disease and men, also received the higher dose. All patients in the study had a history of disease which was refractory to conventional modes of therapy, and all patients had histological confirmation of HPV infection. Rates of complete and partial responses to therapy were similar at 6 and 10 weeks between the two dose comparison groups. Side effects typical of systemic interferon administration occurred more commonly in the recipients of the higher dose, as did abnormalities of routine laboratory tests. In addition, dose reductions and withdrawal from the study occurred primarily in the high dose group. Among the 19 patients whose disease had completely cleared after 10 weeks of study, only one (5%) had recurrent disease at the conclusion of the 6-month observation period. Peak serum interferon levels and area under the curve measurements were not predictive of response to treatment in this study. HPV subtype determinations did not appear to be helpful in predicting response to Wellferon either.

These efficacy results are similar to those which have been previously reported in patients with genital warts who received Wellferon treatment. In the present study, however, we were able to demonstrate that lower doses of Wellferon produce similar rates of lesion regression as do higher doses. This observation is consistent with our finding that peak serum levels of interferon and area under the curve measurements did not predict response to Wellferon. In addition, low dose Wellferon was tolerated significantly better than high dose therapy, and also produced fewer abnormalities of routine laboratory tests.

Intralesionally administered interferons have been shown in recent studies to produce significant rates of regression of injected lesions. In addition, one study indicated possible beneficial effects on uninjected lesions (Reichman et al., 1988). The results of intralesional investigations are difficult to compare with results of this study and previous investigations of parenterally administered Wellferon. Parenteral studies have generally employed higher doses and have focused on the effects of treatment on all measurable disease rather than on individual lesions. Parenteral administration offers the advantage of ease of administration and better patient acceptance. Intralesional injections are comparatively difficult to admin-

ister, and relatively few lesions can be treated at any one clinic visit. In addition, the overall incidence of interferon-associated side effects which was observed in the present study of the 1 MU/m^2 dose, was actually lower than the incidence of similar side effects which was reported following intralesional injection of alpha-2b interferon (Vance et al., 1986).

In the present study, less than 5% of the participants who experienced complete resolution of disease developed recurrent lesions during the 6 month follow-up period. This observation differs from the 33% rate of recurrence observed in a recently completed study of intralesional administration (Reichman et al., 1988). Reasons for this discrepancy are not clear, but may reflect the longer and more intensive treatment regimen that was employed in the present study, or possibly differences in the patient populations which were studied.

Of interest in the present study is the comparatively poor response of the men to interferon treatment. One recent report demonstrated that patients who were seropositive to human immunodeficiency virus (HIV) were less likely to experience resolution of interferon alpha-2b-injected genital warts than were patients who were seronegative (Douglas et al., 1986). Although the serological status to HIV in our patient population is not known, the vast majority of men who participated in the study had perianal warts, which are known to be more commom among homosexual than among heterosexual men (Judson et al., 1980). Because of the high rates of HIV seropositivity among homosexual men, it is possible that HIV infection could be responsible for the comparatively poor rate of lesion regression which was observed in our male study group.

Studies of another HPV disease, recurrent respiratory papillomatosis, suggested that certain virus subtypes may be associated with severe or more aggressive forms of disease that did not respond well to conventional laser therapy (Mounts et al., 1982). To examine the possibility that HPV subtype might predict response to interferon in the present study, HPV subtyping using Southern hybridization techniques was performed on tissue biopsies obtained prior to treatment. No correlation between HPV subtype and disease response was observed, suggesting that HPV subtype may not be a useful predictor of response to interferon. However, more extensive studies of virus type and subtype, including examination of tissue specimens taken during and after therapy, will be necessary to determine the potential importance of virus type in the natural history of genital warts and response to therapy.

In summary, parenteral administration of Wellferon produces resolution of genital warts in many patients with severe refractory disease, and low dose therapy appears to be as effective as high dose therapy. In addition, low dose therapy is much less toxic than high dose therapy, and is well tolerated by most patients. Following complete resolution of all lesions in the present study, recurrent disease was rarely observed and appears to be less common than that which has been reported following conventional modes of therapy (VonKrogh, 1981; Krebs et al., 1985). Additional studies will be required to determine optimal dosage regimens for the use of Wellferon in the treatment of genital warts.

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