

Adjuvant Treatment of Recalcitrant Genitoanal Warts with Systemic Recombinant Interferon-alpha-2c

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Seventeen male patients with recalcitrant genitoanal warts, who had been unsuccessfully treated with classical destructive modalities for 16 months on average, were included in an open uncontrolled trial. The treatment regimen consisted of caustic and/or surgical measures as judged optimally suited in the individual cases, combined with an intermittent systemic low-dose adjuvant interferon-alpha-2c regimen (3 or 6 5-day-courses with intervals of 2 weeks) followed by a 1-year-observation period. At the end of interferon treatment, no patient had clinically visible warts but 10 still had subclinical acetic acid positive lesions. At the end of the 1-year-observation period, clearance of both warts and acetowhite lesions was observed in 4 patients (23.5%), whereas acetowhite lesions persisted in 4 others (23.5%). Recurrence of clinically visible lesions, always within the acetowhite areas, was observed in 9 (53%) patients. Interferon may thus have been effective in suppressing clinical recurrences of genitoanal warts, but its potency to eradicate subclinical papillomavirus infection was disappointing. **Key words:** Human papillomavirus; Immunotherapy; Acetowhitening.

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Treatment of genital warts with classical therapy such as podophyllin or destructive methods - cryotherapy, electrodesiccation, laser surgery - is often frustrating for clinicians and patients alike. Clearance rates between 41% and 94% are reported, but relapses occur in at least 25% of patients thus treated within 3 months (1). After the clinical response of viral warts to interferon therapy was recognized (2), numerous treatment modalities have been designed using different interferons (alpha, beta, gamma). An early report claiming complete response rates of nearly 60% with interferon-alpha-2a alone and no recurrences within 7 months aroused great expectations (3), which were dampened by later studies with success rates below 50% and a mean recurrence rate of about 25% (4-6). Consequently, recent studies evaluated interferon as an adjuvant to destructive methods, using it either as gel (7), intralesionally (8) or systemically (9, 10). Such combination regimens were shown to reduce the recurrence rates as compared to laser treatment alone; a complete cure rate of 81% after an 8-month observation period has been reported (9). Likewise intralesional interferon was shown to enhance the effect of topical podophyllin (II).

Several factors render interpretation and comparison of the above data difficult. Two major problems are the difficulties of

Table I. Combined destructive/systemic interferon-alpha-2c treatment of recalcitrant genitoanal warts

Patient age (years)	Site	Duration (months)	Destruct. prior	Treatment present	INF cycles	Response at end of interferon	Status after one year observation
30	Periurethral	8	P	P	3	Total	Clearance
27	Anal penile shaft	11	surg.(3x)	surg.(1x) P	3	Total	Clearance
42	Perianal	12	P	surg.(1x)	3	Total	Clearance
24	Anal penile shaft	13	surg.(2x) P	surg.(1x) P	6	Partial	Subclinical Persistence
42	Anal penile shaft	12	surg.(2x) P	surg.(1x) P	6	Partial	Recurrence
22	Penile shaft	24	P	P	6	Partial	Recurrence
21	Penile shaft	13	P	P	6	Partial	Recurrence
42	Urethral prepuce	10	P TCA	surg.(1x) P	6	Partial	Recurrence
33	Anal	22	surg.(2x) P	surg.(1x) P	6	Partial	Recurrence
29	Prepuce penile shaft	24	P	P	6	Partial	Recurrence
44	Prepuce	72	P TCA	P TCA	6	Partial	Subclinical persistence
23	Urethral	10	surg.(2x)	surg.(1x)	3	Total	Clearance
26	Urethral	7	surg.(2x)	surg.(1x) P	3	Total	Reccurrence
25	Prepuce penile shaft	6	P	P TCA	6	Partial	Recurrence
26	Anal penile shaft	9	surg.(2x) P	surg.(1x) P	6	Partial	Subclinical persistence
26	Urethral	10	surg.(2x)	surg.(1x)	3	Total	Subclinical persistence
25	Anal penile shaft	9	surg.(2x) P	surg.(1x) P	3	Total	Recurrence (after 8 months)

INF = interferon

TCA = trichloroacetic acid

P = podophyllin

surg. = surgery

destruct. = destructive

Table II. Summary of the results of combined destructive/systemic interferon- α -2c treatment

No. of patients treated	Total response at end of combination therapy	Partial response at end of combination therapy	Status after 1-year observation		
			Clearance	Subclinical persistence	Recurrence
17	7 (41.2%)	10 (58.8%)	4 (23.5%)	4 (23.5%)	9 (53%)

objective measurement of disease extent and determination of its subclinical persistence after clinically successful treatment. Hohenleutner et al. (10), e.g., did not routinely use the acetic acid method to detect subclinical disease which consequently remained untreated, leading to a high recurrence rate (81%) after laser/placebo, and a lesser recurrence rate (42%) after laser/interferon- α -2b. Erpenbach et al. (9), in contrast, who performed acetic acid testing, registered relapses in only 19%, using a laser/interferon- α -2b combination therapy.

Obviously, persistent subclinical infection is the major factor leading to recurrences after destructive treatment of condylomata acuminata (CA). Since it has been claimed that interferon is capable of eradicating latent human papillomavirus (HPV) infection (12), we decided to combine optimal individual destructive treatment (except surgery) aimed at eliminating clinical lesions with adjuvant interferon aimed at prevention of relapses, in a series of cases who had previously proven extremely recalcitrant to classical treatment alone.

PATIENTS AND METHODS

Between September 1988 and June 1989, 18 male patients with exophytic genitoanal warts (4 with urethral, 7 with anal involvement) were recruited into the present cross-over study (Table I). They were all in good general health, over 18 years of age, and had been unsuccessfully treated with destructive methods in individual regimens for at least 6 months (median 16 months). Comparable classical therapy before and subsequently with interferon was our main strategy to draw conclusions about interferon treatment efficacy. The definitive resistance to therapy in our hands in the last 6 months was the criterion for additional interferon administration. Exclusion criteria were: positive HIV serology, signs of immunodeficiency and contraindications for surgical procedures or interferon. Laboratory tests performed prior to therapy included complete blood count with differential and platelets, serum electrolytes and iron, liver and renal function tests, electrophoresis and quantitative immunoglobulins. Blood counts and liver function tests were monitored at the end of each interferon cycle. Cell-mediated immunity was evaluated with the Mériex® "multitest" (skin test with several recall antigens). All patients were screened for concomitant sexually transmitted diseases including syphilis and HIV infection. Patients were advised to refrain from sexual intercourse or use condoms during therapy. Their partners were evaluated for HPV infection and treated if infected.

At the beginning of combination treatment, clinically visible CA were removed by such classical regimens judged to be best suited for the individual case. This included podophyllin alone in 4 patients (soft eruptive CA), podophyllin plus trichloroacetic acid in 2 (hyperkeratotic CA), podophyllin plus (electro)surgery in 8 (extensive exophytic CA or CA at specific locations, like intraurethral or intraanal), and surgical treatment alone in 3 cases (Table I). Acetic acid testing (5%, 5 minutes) was performed at the initial treatment and all follow-up examinations (see below). All acetowhite lesions were treated with podophyllin or trichloroacetic acid.

Recombinant interferon- α -2c (Berofor®, Bender) was given ac-

ording to the following low-dose interval regimen: 1.4×10^6 IU/d were administered subcutaneously into the upper thigh for 5 days, followed by an interval of 2 weeks. If necessary, podophyllin was continued at weekly intervals. Three such cycles of interferon were given in all cases; 10 patients who had persisting lesions thereafter received 3 additional cycles amounting to a total of 30 doses (42×10^6 IU) interferon at the end of therapy.

Follow-up examinations were performed at weekly intervals throughout interferon treatment, including acetic acid testing and, if necessary, topical treatment of CA and/or acetowhite lesions. Thereafter, patients were followed up in at least 3 monthly intervals for 1 year. 2/4 acetowhite lesions, which were finally judged as subclinical persistence, were examined histologically; both proved to be caused by HPV by the presence of koilocytes. The remaining 2 were clearly positive, considering the following clinical criteria: the presence of landscape-shaped acetowhite areas with slightly papillomatous surface in contrast to smooth and glossy surfaces seen in scars, the most likely differential diagnosis for acetowhite lesions in our patients.

Absence of both CA and subclinical acetowhite lesions after the last interferon cycle was classified as total response, and their sustained absence throughout the 1-year observation period as clearance. Absence of clinical lesions but presence of acetowhite lesions at the end of interferon treatment was classified as partial response; presence or reappearance of such lesions during the observation period as subclinical persistence; reappearance of CA as recurrence.

RESULTS

17/18 patients completed the combined local destructive/interferon treatment and the 1-year-follow-up period (Table I and II). One patient discontinued the treatment for unrelated reasons.

Defining the patients as their own control group during the 6 months before interferon with classical modalities alone, a 100% recurrence rate can be assumed and compared with the final success rate. None of the 17 patients had clinically discernible viral warts at the end of the last course of interferon. Only 7/17 (41.2%), all having received 3 interferon cycles only, were also acetic acid negative (total responses). The remaining 10 (58.5%), all having received 6 interferon cycles, were still acetic acid positive (partial responses). Judgement at this time might be influenced by the classical treatment modality used in addition to interferon. During the observation period, relapses of clinically visible lesions occurred in 9 patients (53%)-2 from the complete response and 7 from the partial response group. It is interesting to note that, in the latter group, clinically visible recurrences always arose within acetowhite lesions. If the term relapse is restricted to reappearance of condylomata in those who have achieved complete response, then the recurrence rate was only 2/7 (29%) or 3/7 (43%), if one considers the additional patient discovered to be HPV positive by acetowhiteness. Recurrences occurred within 3 months after the last course of interferon in 8 patients,

within 8 months in 1. At the end of the observation period, only 4 patients (23,5%) qualified as clearance. In 4 others (23,5%), acetowhite lesions had remained stable and resistant to podophyllin throughout the observation period (subclinical persistence).

Interferon side effects implying bio-availability were common, but mild or moderate. Fifteen patients had flulike symptoms at the beginning of therapy which declined after the first week. A reversible mild decrease in white blood cell count was noted in most patients. No local reactions were observed at the injection sites. One patient developed frontal sinusitis during interferon therapy, which responded promptly to appropriate antibiotics.

DISCUSSION

Prior to entering the present study, all of our patients had been unsuccessfully treated by destructive methods for 16 months on average. Since the response rate to interferon is supposed to be inversely related to the duration of clinical HPV infection (2), and men are thought to respond more poorly to interferon than women (6), their chances of being successfully treated with interferon alone was judged as equally minimal as the mere construction of treatment with destructive methods. Ethical considerations thus precluded the initiation of a controlled study, comparing classical destructive methods, interferon monotherapy and a combination of both. Instead, we decided to initiate a cross-over study combining those topical destructive measures which were felt to be best suited for the individual cases, with a constant interferon adjuvant regimen. Intralesional interferon was not feasible in our patients because of disease extent, and gel preparations with an exactly defined content of pharmacologically effective interferon were not available in Austria at this time. We thus chose a systemic intermittent low-dose interferon regimen modified from that of Gross et al. (3) (interferon-alpha-2c instead of interferon-alpha-2a, shorter intervals between treatment cycles). The rationale of this regimen is that both high doses and prolonged application of interferon may result in depressed activity of natural killer cells (13), which are expected to play a major role in controlling HPV infection (14).

After a 12-month observation period, the recurrence rate was 53% in our patient series and thus higher than that reported in trials using destructive measures alone (1). 47% of the patients were clinically symptom-free, but one half still had evidence of subclinically persistent HPV infection by the acetic acid technique, resulting in a total clearing rate of only 23,5%. In 3/4 of these patients surgery was the concomitant classical method, which probably contributed to the outcome. Like several other recent reports (4, 5, 15), we were thus unable to achieve as favorable results as Gross et al. (3) with interferon-alpha-2a monotherapy. In this pair-matched cross-over trial, comparing $1,5 \times 10^6$ IU versus 18×10^6 IU interferon-alpha-2a subcutaneously, complete remissions were observed in 8 of 14 subjects (57%) (3). The low-dose regimen with minimal toxicity was favored, since its efficacy appeared superior to that of high doses. In a later study these authors used the low-dose regimen successfully in 11 of 19 patients (57%) and

even demonstrated the absence of HPV-DNA from the sites of previous genital warts in 9 of 11 patients with complete remission by Southern blot hybridization (12). In contrast, Steinberg et al., using nonrecombinant alpha interferon 2×10^6 IU to 6×10^6 IU 3 times weekly for a minimum of 6 months, describe the failure of interferon therapy to eliminate latent virus (16).

Obviously, our disappointing results are consequently to the inclusion criterion of long standing, particularly therapy-resistant genital warts; conversely, they suggest that interferon-alpha-2c, which discloses minimal functional differences to other interferon-alpha 2 subvariants in vitro (17), at least in the regimen chosen by us, offers only moderate benefit in those circumstances where it would be most needed. In particular, elimination of subclinical HPV infection was not a prominent feature in our patient series, although it may be speculated that the recurrence rate in our patients would have been substantially higher without adjuvant interferon. Present data (8–10, 18) suggest that consequent destruction of subclinical lesions, preferably with laser surgery, is at least as efficient in the prevention of recurrences as interferon treatment.

Obviously, adjuvant interferon does not provide the final answer in the treatment of recalcitrant genitoanal warts. New strategies need to be developed, e.g. combinations of interferon with retinoids (15), immunomodulation (19–21) or vaccination (22).

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