A comparison of interferon alfa-2a and podophyllin in the treatment of primary condylomata acuminata

The Condylomata International Collaborative Study Group

Abstract

***Objectives*—to compare the response to treatment and recurrence rate of condylomata accuminata using subcutaneous injection of interferon alfa 2a 1·5 million units three times weekly for four weeks, or podophyllin resin 25% applied to lesions twice weekly for up to six weeks.**

***Design*—Randomised open study.**

***Setting*—Multicentre European study in genitourinary medicine, dermatovenereology, and gynaecology departments.**

***Patients*—87 males and 67 females with condylomata acuminata for less than six months and no history of previous treatment.**

***Main outcome measures*—Complete clearance of lesions and evidence of recurrence at three months and nine months after treatment commenced.**

***Results*—A complete response was achieved at three months in 15 of 64 (23%) in the interferon treated group, and 31 of 69 (45%) in the podophyllin treated group (p = 0·003). At nine months 10 of 13 patients in the interferon group and 22 of 30 patients in the podophyllin group remained completely clear of lesions.**

***Conclusions*—At the dose regimen used interferon alfa 2a monotherapy was not as effective a therapy as the standard therapy of podophyllin 25% application.**

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Introduction

The reported incidence of condylomata acuminata has been increasing in developed countries, illustrated by a rise from 21,959 new cases per year in 1976 to 67,078 in 1986 in genitourinary clinics in England.[1] Although a number of treatment modalities are available for the management of condylomata acuminata, incomplete responses and relapses are common.[2,3] In addition, treatment is often associated with considerable discomfort and unpredictability of systemic side effects.

One of the most common first-line therapies in European genitourinary medicine, gynaecology and dermatology clinics is local application of podophyllin resin. Cure rates of 32% to 100% have been reported using various dose regimens[4,5] but relapses are frequent. The most common side effects of this treatment are local irritation and skin ulceration, but more serious side effects, including death, have been reported when podophyllin has been used in high doses.[6,7]

The antiviral and antiproliferative properties of interferons may be useful in the treatment of condylomata acuminata.[8,9] By stimulating the immune system, systemically administered interferon may enable the body to clear papillomavirus infection. Interferon therapy has been used both locally (topical applications or intralesional injections) and systemically (subcutaneous or intramuscular injections) with some encouraging results.[10-14] One report has suggested that there may be a difference in response depending on the human papillomavirus (HPV) type involved.[15]

The aim of this study was to compare the lasting response between interferon alfa-2a and podophyllin treatment in patients with previously untreated condylomata.

Patients and methods

Patient selection

The study took place in five countries (United Kingdom, Finland, Italy, Belgium and Denmark). One hundred and fifty-four male and female patients

aged between 18 and 65 years were recruited from nine centres. All were Caucasian and were included on the basis of the following inclusion and exclusion criteria. The inclusion criteria were clinical evidence of previously untreated condylomata on the external genitalia and/or perianally, which had been present for less than 6 months. Patients had to be willing to conform to the requirements of the study including a biopsy, an HIV antibody test and to give their witnessed oral or written informed consent. Patients were excluded if they had internal genital or anal lesions exclusively, if they had ever received any other immunomodulatory drugs (including interferon), were pregnant, lactating or not using adequate contraception, had evidence of malignant neoplastic disease (except intraepithelial neoplasia of the cervix, or localised basal cell cancer), had an acute sexually transmitted disease or a positive HIV antibody test.

Patients were withdrawn from the study if they had an interruption or change of treatment regimen, if they had any adverse event severe enough to warrant discontinuation, if they became pregnant, if they missed one week's therapy of interferon alfa-2a, if they failed to return for follow-up visits or if they had progressive disease.

Study design

Patients were randomised to one of the two treatment regimens, either interferon alfa-2a 1·5 million international units (MIU) (ROFERON®-A, F. Hoffmann-La Roche, Ltd, Basle, Switzerland) subcutaneously three times weekly for 4 weeks or podophyllin resin 25% application twice weekly for up to 6 weeks. Podophyllin resin was supplied to all centres from a central source and was reconstituted each day of the study as a 25% solution for local application to the warts. The treatment period was followed by a treatment-free follow-up period of 2 months. Complete responders at month 3 were followed up to 9 months or until they had recurrence which ever occurred first.

Collection of data

Biopsy On entry into the study, a scissor biopsy was taken of one of the lesions under local anaesthetic. Formalin-fixed, biopsy specimens were processed in a single laboratory and analysed for histology and detection of human papilloma virus (HPV) DNA (HPV 6,11,16,18,31 and 33) by the same histopathologist[16,17] (Dr Kari Syrjänen, Department of Pathology, University of Kuopio, Finland).

Lesions The number and distribution of lesions were determined at entry to the trial and recorded on a scale diagram of the genitalia. Note was taken of whether lesions were isolated, confluent or both. Patients were examined for the presence of internal lesions ie warts seen in the vaginal barrel, on the cervix, in the anal canal or in the urethral meatus.

Adverse events Patients were questioned about possible local or general adverse events at each assessment. These were graded as mild, moderate, severe or life-threatening, and an evaluation of whether they were related to treatment or not was made by the investigator. Adverse events were recorded at the end of each week for the first 8 weeks of the study and then at 12 weeks.

Laboratory Haemoglobin, white cell count, platelet count, aspartate aminotransferase (ASAT) and serum creatinine were determined during the 2 weeks before the start of therapy and were repeated after 4 weeks and at 12 weeks. HIV-1 antibody tests were performed during the 2 weeks before entry into the study and after 3 months by use of fully evaluated and licensed ELISA kits (Abbott Laboratories, Chicago: Organon, Sydney).

Treatment acceptability An acceptability card was completed at the end of treatment by the patient at home using free text, independently of the investigator. In addition a standardised questionnaire was completed in the investigator's office.

Assessment of response Responses were graded as complete response (clearance of all lesions), major incomplete response (over 75% clearance), minor incomplete response (between 25% and 75% clearance), no change and progression (new lesions and/or increase of more than 25% in size of existing lesions). A relapse was recorded if lesions reappeared after a complete response.

Statistical methods Homogeneity of the demographic and pre-treatment disease characteristics in the treatment groups was determined descriptively. Descriptive statistics were employed for the response and recurrence rate and for the safety data. Survival methods were used to test time (days) to complete response (log rank test). Identification of pre-treatment characteristics predictive of response to trial treatment was performed using a logistic regression analysis. Response to trial treatment was considered as the dependent variable, with age, sex, weight, overall duration of disease, number of lesions at baseline, type of lesion, presence of internal lesions, histology and HPV type, incorporated as explanatory variables.

Recommendations It was strongly recommended that the patients or their partner(s) always use condoms during the study if and when they had sexual intercourse.

Results

Patient population and baseline characteristics

A total of 154 patients with primary condylomata were entered into this study, 50 from the UK, 92 from Finland and the remaining 12 patients from Italy, Belgium and Denmark. Eighty-one patients

were randomised to the podophyllin group and 73 to the interferon alfa-2a group. The two groups were comparable for age (median 23 years), weight and height. A description of the lesions at entry is summarised in table 1. Most patients (about 65%) in both groups had papillary type of lesions (condylomata acuminata) and all of these showed no or a mild intraepithelial neoplasia (data not shown). About 90% of the papillary type of lesions were associated with HPV DNA type 6 and/or 11 (data not shown).

Response to treatment at 3 months and recurrence free interval at 9 months

Of the 154 patients recruited for the trial, 133 of these were eligible for the analysis of outcome at 3 months after entry (64 and 69 patients in the interferon and podophyllin groups, respectively). Nine patients in the interferon alfa-2a treatment group, and 12 patients in the podophyllin treated group were not evaluable because they were lost to follow-up or withdrawn because of protocol violations.

Of the 133 evaluable patients a complete response at any time during the first 3 months was seen in 19 of 64 (30%) in the interferon alfa-2a group and 52 of 69 (75%) in the podophyllin group. Table 2 shows that at the end of 3 months (approximately 2 months after completion of the treatment), 15 of 64 (23%) patients in the interferon group still remained completely clear of lesions and 4 patients had relapsed. In the podophyllin group, 31 of 69 (45%) patients had a complete response and 21 patients had suffered a recurrence. Those patients with a complete response and 21 patients had suffered a recurrence. Those patients with a complete response at 3 months were further followed until month 9 of the study. Of the 15 patients in the interferon group, 2 were lost to follow-up. Of the 13 evaluable patients 10 (77%) were still completely clear and 3 (23%) had suffered a recurrence. In the podophyllin treatment group, 1 of 31 patients was lost to follow up. Of the 30 evaluable patients, 22 (73%) still had a complete response, and 8 (27%) had had a recurrence. The cumulative recurrence rate at 9 months, of patients who had had a complete response at any time, was 7 of 19 (37%) patients in the interferon group, and 29 of 52 (56%) patients in the podophyllin group.

Table 1 Pre-treatment characteristics of the 154 patients enrolled in the trial

Parameter	*Interferon Alfa-2a*	*Podophyllin*
Number of patients	73 (45 M, 28 F)	81 (42 M, 39 F)
Number of lesions		
Median (range)	8·0 (1–95)	9·0 (1–60)
Type of lesions		
Isolate	48 (66%)	44 (54%)
Confluent	4 (6%)	8 (10%)
Both	21 (29%)	29 (36%)
Internal lesions		
Present	19 (26%)	19 (24%)
Not present	54 (74%)	62 (77%)
Duration of disease (months)		
Median (range)	2·0 (1–6)	1·0 (1–6)
Microscopic morphology		
Papillary	46 (63%)	51 (66%)
Papular (+pigmented)	12 (16%)	8 (10%)
Flat	11 (15%)	15 (19%)
Other	4 (5%)	7 (9%)
Grade of intraepithelial neoplasia		
None	54 (74%)	60 (74%)
Mild	12 (16%)	16 (20%)
Moderate/Severe	5 (7%)	1 (1%)
Not assessable*	2 (3%)	4 (5%)
HPV type		
6, 11, 6 + 11	48 (66%)	56 (69%)
16, 18, 6/11 + 16/18	6 (8%)	4 (5%)
31, 33	0 (0%)	3 (4%)
Negative	18 (25%)	14 (17%)
Not assessable*	1 (1%)	4 (5%)

*biopsy lost or inadequate for processing.
M = male, F = female.

Figure 1 shows complete responses at different time points in both treatment groups. The maximum complete response rate in the interferon group was seen at about week 5, that is, one week after cessation of treatment. The time to complete response was 4 to 5 weeks in the podophyllin group. The median time to complete response was shorter in the podophyllin group (23, range 4–85 days) than in the interferon alfa-2a treatment group (44, range 8–148, days). A log-rank test was highly significant ($p < 0.001$) in favour of podophyllin.

These results were not affected by the possibility of reinfection during the study since the number of times patients had sexual intercourse was equally distributed over time and treatment group (a total of approximately 80% of patients in both groups) and in both treatment groups, about 85% of patients having sexual intercourse used condoms.

Analysis of factors affecting outcome

The impact of prognostic factors on the complete response rate at the 3 months assessment was identified by analysing the pre-treatment characteristics of all evaluable patients as described in the methods. The results for specific subgroups of patients are presented in table 3. Considering all patients, a complete response was favoured in patients who received podophyllin treatment ($p = 0.003$), had a negative result for the HPV typing ($p = 0.001$), had small numbers of lesions (≤ 10) at baseline ($p = 0.015$) and were female ($p = 0.035$). Other parameters tested did not affect the complete response rate ($p > 0.1$). Considering the patients in the interferon group only, a complete response was more likely in female patients. The complete response rate of males treated with interferon (11%, see table 3) differs significantly from the 42% response rate of interferon-treated females ($p = 0.007$) and also from males treated with podophyllin (response rate of

Table 2 Overall assessment of the response to treatment

Treatment	*Assessment times*	*Complete response n (%)*	*Major Inc response n (%)*	*Major Inc response n (%)*	*No change n (%)*	*Progression n (%)*	*Recurrence n (%)**
INTERFERON ALFA-2A							
n = 64	3 M final†	15 (23)	6 (9)	9 (14)	10 (16)	20 (31)	4 (21)
	95% CI:	14–36					2–15
n = 13	9 M***	10 (77)					3 (23)
	5% CI:	46–95					5–54
PODOPHYLLIN							
n = 69	3 M final†	31 (45)	3 (4)	3 (4)	3 (4)	8 (12)	21 (40)
	95% CI:	33–57					20–43
n = 30	9 M‡	22 (73)					8 (27)
	95% CI:	54–88					12–46

*% is calculated from the number of complete responders.
†3 month final: patients who withdrew because of progressive disease are included as progression and patients who had a recurrence before the 3 month assessment are included as recurrence.
‡9 month: only patients with a complete response in the 3 month final assessment were included in the assessment at 9 months.

56%, $p < 0.001$). The low response rate of males to interferon treatment mainly accounted for the difference in complete response rates between the two treatment groups.

Treatment acceptability

Equal numbers of patients in both treatment groups returned the acceptability card and a similar percentage found the treatment acceptable (approximately 80%). The content of the free text did not vary substantially between the two treatment groups. The most frequent comments concerned the effectiveness of the treatment, the amount of pain experienced, the convenience of the treatment and treatment schedule and the helpfulness and concern of the medical staff. Belief that the treatment was effective was the most important parameter in making the treatment acceptable: 62% of the patients treated with podophyllin believed that the treatment was effective compared with only 35% of the interferon-treated patients. At 4 weeks (the end of treatment for most patients), 45% of the podophyllin treated patients already had complete clearance of all lesions while only 10% of the patients in the interferon group had a complete response at this time (fig 1). More patients

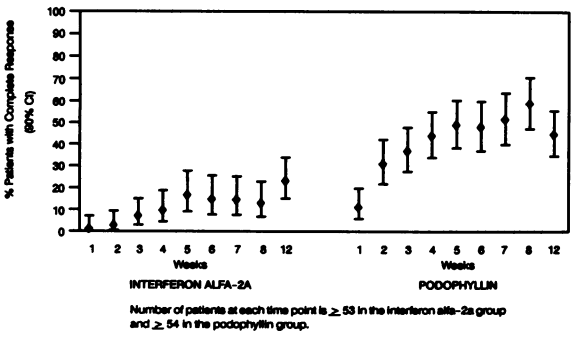

Fig 1 Complete response at different time points.

in the interferon group found the treatment convenient than in the podophyllin group (50% and 20%, respectively). The frequency of all other comments was similar in both treatment groups.

Figure 2 summarises the data collected by the investigators using a standard questionnaire. Data were collected for 67 and 74 patients in the interferon and podophyllin groups respectively. More patients treated with podophyllin regarded the treatment as painful and as affecting their sex life (12% and 32% of patients found the treatment painful in the interferon and podophyllin groups, respectively, and 25% and 51% of patients, respectively, found the treatment affected their sex life). All other responses were similar in both treatment groups. Most patients in both treatment groups would be prepared to continue treatment in the case of a partial response and would be retreated in the case of a relapse.

Adverse events

The type of adverse events reported was characteristic of the treatment received. The majority of adverse events reported by interferon-treated patients were those synonymous with a "flu-like" syndrome. This syndrome was defined as one or more of the following symptoms; fatigue, myalgia, chills, fever and flu-like symptoms, with headache included if it was accompanied by another flu-like event. Flu-like syndrome was reported by 41% of the patients in the interferon group and 1% of patients in the podophyllin group. Local skin reactions at the application site were seen in 50% of patients in the podophyllin group and 11% of patients in the interferon group and included general local reactions, skin ulceration, irritation and pain. No patient was withdrawn because of adverse events. All adverse events were reversible upon discontinuation of the trial drug.

In the interferon alfa-2a treatment group, a median transient fall of 1·5 giga/l in leukocyte count was recorded at the end of the treatment period which

*Table 3 Complete response rates at month 3 in specific subgroups of patients**

Subgroup	Interferon Alfa-2a n = 64	Podophyllin n = 69	Total n = 133
Total†	15/61 (25%)	31/51 (61%)	46/112 (41%)
Sex:			
Male	4/35 (11%)	15/27 (56%)	19/62 (31%)
Female	11/26 (42%)	16/24 (67%)	27/50 (54%)
Number of lesions at pre-study:			
0–4	6/17 (35%)	4/7 (54%)	10/24 (42%)
5–10	4/15 (27%)	18/23 (78%)	22/38 (58%)
11–20	5/29 (17%)	9/21 (43%)	14/50 (28%)
Microscopic morphology:			
papillary	7/38 (18%)	17/28 (61%)	24/66 (37%)
papular (+ pigm.)	3/10 (30%)	5/7 (71%)	8/17 (47%)
Flat	4/10 (40%)	7/12 (58%)	11/22 (50%)
HPV type:			
negative;	11/14 (79%)	6/10 (60%)	17/24 (71%)
6	0/15 (0%)	13/20 (65%)	13/35 (27%)
11	4/23 (17%)	7/10 (70%)	11/33 (33%)
Grade of intraepithelial neoplasia			
None	11/46 (24%)	22/36 (61%)	33/82 (40%)
Mild	2/10 (20%)	8/12 (67%)	10/22 (45%)

*only groups with more than 15 patients in total included.
†total numbers = no of patients with a 3 months assessment. Patients withdrawn before month 3 for progressive diseases or recurrence are not included.

was not clinically relevant and had returned to the pretreatment levels by 2 months after discontinuation of therapy. No patient developed a total leukocyte count less than 3·6 giga/l. The podophyllin group did not show relevant changes in leukocyte counts throughout the study.

No relevant changes in median platelet, ASAT, haemoglobin and creatinine values were observed throughout the study in either treatment group.

Discussion

Current treatments for condylomata acuminata are largely unsatisfactory. In the case of chemical ablative therapy, using either podophyllin or trichloroacetic acid, the response rates are unacceptable and there is a high rate of recurrence and new lesion formation.[1] Chemical treatments may fail because of poor tissue penetration, particularly with keratinised warts.[18] In the present study up to 60% of subjects

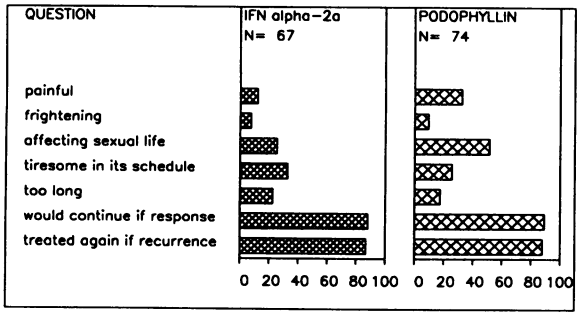

Fig 2 Percentage of YES answers in the acceptability assessment at the end of treatment.

with previously untreated condylomata treated with podophyllin had relapsed by 9 months after commencement of the study.

The present study showed that a lower clearance of previously untreated lesions was obtained at 3 months when interferon alfa-2a was used (23%) than when podophyllin was used (45%). There was also a higher incidence of progression of the disease with interferon treatment, but a lower relapse rate was noted in those who had a total clearance. Observations of extragenital cutaneous warts in small series of patients treated with placebo have shown remission rates between 17% and 30%.[12 19 20] Therefore, the 23% cure rate obtained at 3 months after treatment with 1·5 MIU interferon alfa-2a given three times a week for 4 weeks is consistent with the rates reported for spontaneous remission and interferon must be considered as ineffectual as single agent therapy for previously untreated anogenital warts. Several groups have reported the successful use of α- and β-interferon in the primary management of genital warts. In these studies, total clearance of warts was reported for up to 82% of patients after subcutaneous or intramuscular interferon in doses of 1 to 18 MIU for up to 51 patients.[15 21–25] The favourable outcome in some of these studies may be due to larger doses of interferon and/or longer duration of therapy. However, it should be noted that these studies were conducted with a smaller sample of patients than reported here.

A favourable outcome from interferon therapy was noted in females as previously reported by Kirby *et al.*[26] Stratification of patients by number of lesions showed that the smaller the number of lesions on initial assessment, the better the prognosis after

treatment with both podophyllin and interferon alfa-2a. The HPV type contained in the lesions of the lower genital tract has been suggested as having a bearing on response to interferon therapy.[15] This was not confirmed in this study, but, interestingly, a significantly better response of HPV-negative lesions which had the microscopic appearance of warty tissue was apparent. It is possible that lesions with fewer copies of HPV are more responsive to interferon, although the therapeutic relevance of this finding is questionable.

The most frequently reported adverse events were characteristic; local skin reactions at the application site after podophyllin application, and flu-like symptoms after interferon therapy. These adverse events have been well-documented in other studies.[15 22 24]

In conclusion, monotherapy with interferon alfa-2a three times a week for 4 weeks at a dose of 1·5 MIU, was not shown to be an effective treatment for primary condylomata when compared with local applications of podophyllin. Additional dose finding studies are required to establish the potential role of interferon alfa-2a in the treatment of condylomata. Perhaps its role in the treatment of condylomata will be in combination with other therapies; this may warrant future investigation.

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1 Anonymous. *New Cases Seen at NHS Genito-urinary Medicine Clinics in England 1976–1986*. Statistical Bulletin, DHSS Bulletin 2/7/88.
2 Margoli S. Therapy for condylomata acuminata: A review. *Rev Infect Dis* 1982;**4(suppl)**:S–829–36.
3 Dinsmore WW. The therapy of genital warts. *J Clinical Hospital Pharmacology*. 1986;**11**:381–8.
4 Gabriel G, Thin RNT. Treatment of anogenital warts—comparison of trichloracetic acid and podophyllin versus podophyllin alone. *Br J Venereal Dis* 1983;**59**:124–6.
5 Kaplan IW. Condylomata acuminata. *New Orleans Med Surg J* 1941/42;**94**:388.
6 Ward JW, Clifford WS, Monaco AR, Bickerstaff HJ. Fatal systemic poisoning following podophyllin treatment of condylomata acuminata. *South Med J* 1954;**47**:1204–6.
7 Slater GE, Rumack BH, Peterson RG, Podophyllin poisoning, systemic toxicity following cutaneous application. *Obstet Gynecol* 1978;**52**:94–6.
8 Kimchi A. Increased levels of interferon induced 2-5 oligoadenylate synthetase in mature T lymphocytes and in differentiated friend erythroleukaemic cells. *J Interferon Res* 1981;**1**:559–69.
9 Rubenstein M, Orchansky P. The interferon receptors. CRC *Crit Rev Biochem* 1986;**21**:249–75.
10 Scott GM, Csonka GW. Effect of injections of small doses of human fibroblast interferon into genital warts. *Br J Venereal Dis* 1979;**55**:442–5.
11 Geffen JR, Klein RJ, Friedman-Kien AE. Intralesional administration of large doses of human leukocyte interferons for the treatment of condylomata acuminata. *J Infect Dis* 1984;**150**:612–5.
12 Eron LJ, Judson F, Tucker S, *et al.* Interferon therapy for condylomata acuminata. *N Engl J Med* 1986;**315**:1059–4.
13 Friedman-Kien E, Eron LJ, Conant M, *et al.* Natural interferon alpha for treatment of condylomata acuminata. *JAMA* 1988;**259**:533–8.
14 Reichman RC, Oakes D, Bonnez W, *et al.* Treatment of condylomata acuminata with three different interferons administered intralesionally. *Ann Intern Med* 1988;**108**:675–9.
15 Schneider A, Papendick U, Gissmann L, De Villiers E. Interferon treatment of human genital papillomavirus infection: importance of viral type. *Int Cancer* 1987;**40**:610–4.
16 Syrjänen S, Syrjänen K. An improved in situ DNA hybridization protocol for detection of human papillomavirus (HPV) DNA sequences in paraffin-embedded biopsies. *J Virol Methods* 1986;**14**:293–304.
17 Syrjänen K. Biology of human papillomavirus (HPV) infections and their role in squamous cell carcinogenesis. *Med Biol* 1987;**5**:21–39.
18 Oriel JD. Genital warts. In: Holmes KK, Mardh P-A, Sparling PF, Weisner PJ, eds. *Sexually Transmitted Diseases, 1st ed.* New York, McGraw Hill, 1983:504.
19 Schonfeld A, Nitke , Schattner A, *et al.* Intramuscular human interferon β injections in treatment of condylomata acuminata. *Lancet* 1984;**i**:1038–41.
20 Ikic D, Bosnic N, Smerdel S, *et al.* Double blind clinical study with human leukocyte interferon in the therapy of condylomata acuminata. In: Ikic D, ed. *9th International Immunobiological Symposium Yugoslav Academy of Sciences and Arts*, 1975, Zagreb, Yugoslavia.
21 Gall SA, Hughes CE, Trofatter K. Interferon for the therapy of condylomata acuminatum. *Am J Obstet Gynecol* 1985;**153**:157–63.
22 Gross G, Ikenberg H, Roussaki A, *et al.* Systemic treatment of condylomata acuminata with recombinant interferon-alpha-2a: low dose superior to the high-dose regimen. *Chemotherapy* 1986;**32**:537–41.
23 Dinsmore WW, Maw RD. Treatment of resistant condylomata acuminata with interferons. *Interferons Today and Tomorrow* 1987;**5**:30–1.
24 Gross G, Roussaki A, Schopf E, *et al.* Successful treatment of condylomata acuminata and Bowenoid papulosis with subcutaneous injections of low-dose recombinant alpha. *Arch Dermatol* 1986;**122**:749–50.
25 Gall SA, Hughes CE, Mounts P. Efficacy of human lymphoblastoid interferon in the therapy of resistant condylomata acuminata. *Obstet Gynecol* 1986;**67**:643–51.
26 Kirby PK, Kiviat N, Beckman A, Wells D, Sherwin S, Corey L. Tolerance and efficacy of recombinant human interferon gamma in the treatment of refractory genital warts. *Am J Med* 1988;**85**:183–8.