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Treatment of Condylomata acuminata with Pegylated Interferon Alfa-2b in HIV-infected Patients*

N. H. Brockmeyer[1], A. Poffhoff[1], A. Bader[1], B. Hochdorfer[1], R. Schlottmann[1], H. Rasokat[2], P. Altmeyer[1], A. Kreuter[1], for the German Network of Competence HIV/AIDS

[1]Department of Dermatology, Ruhr-University, Bochum,
[2]Department of Dermatology, University of Köln, Germany

Abstract
Background: Interferon in a variety of topical, interlesional, and parenteral preparations has been used for condylomata acuminata (CA) in HIV negative patients.
Study goals: This open trial was initiated to determine the safety and efficacy of a new formulation of interferon, pegylated interferon-α2b (PEG-IFN, PegIntron®), in the treatment of recalcitrant CA in patients with HIV infection.
Study design: 22 HIV-1 infected patients in virologic steady state with clinically demonstrable anogenital CA were enrolled in this study (treatment group, n = 12; control group, n = 10). Patients in the treatment group received 80µg PEG-IFN s.c. once a week for 24 weeks. Follow-up period was 6 month. The effects were assessed by a clinical scoring system (complete response; major response; minor response; stable disease; progression of disease).
Results: 2 patients did not finish the study because of side effects. PEG-IFN was well accepted and completed by ten patients. Four patients revealed complete response, four patients had major response and two had minor response after PEG-IFN. In the control group, all patients showed progression of CA during the 24 weeks of this study ($p < 0.001$). 7/10 patients of the treatment group and 8/10 patients of the control received HAART.

While the differences of CD4 cell counts between treatment group and control group were not significant (increase of the mean CD4 cell count in the treatment group was 31.5 [75.33 without patient 1 with leucopenia under ribavirine], in the control group 69.75 CD4 cells), the HIV RNA decline in the PEG-IFN group was impressive (0.74 $\log_{10}$). Biological side effects of PEG-IFN treatment included flu-like symptoms, fatigue, local reaction, leucopenia, and increase of AST. This result makes an educated guess that PEG-IFN enhances the benefit of HAART.
Conclusion: PEG-IFN is an effective and safe therapy option in HIV infected individuals with CA with concomitant positive effects on the suppression of HIV-1 replication and CD4 cell count. It might be considered as an alternative in patients that have failed to standard therapies of CA and – at the same time –could improve the benefit of HAART to a great extent. This last hypothesis needs further research.

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Introduction

Condylomata acuminata (CA) is a genital infection caused by human papillomavirus (HPV). It is one of the most common sexually transmitted diseases that is increasing in prevalence. A variety of HPV subtypes, mostly HPV 6 and 11, have been identified in genital lesions [1]. Usually they produce benign lesions, but a few oncogenic subtypes such as HPV 16 and HPV 18 are associated with anogenital cancer [2]. The standard treatment modalities for CA include cryotherapy, electrosurgery, laser therapy, and application of podophyllotoxin or trichloracetic acid. Recently, imiquimod as the first immune response modifier to stimulate a localized immune response in CA has been added to the therapeutical armamentarium. Recurrence of CA due to the presence of HPV DNA in the clinically asymptomatic surrounding tissue is a major problem of ablative therapy. These recurrence rates reported in the literature range from 7.5% to 80% [3].

Human immunodeficiency virus (HIV) progressively destroys regulatory and effector cells of the (cutaneous) immune system, leaving patients highly vulnerable to bacterial, fungal, and viral infections, especially HPV [4]. Recombinant interferons (IFN) have been shown to be active agents in various viral infections. In several studies the efficacy of interferons in a variety of topical, interlesional, and parenteral preparations has been reported for CA in HIV negative patients [5, 6].

We initiated this trial to determine the safety and efficacy of a new formulation of interferon, pegylated interferon-α2b (PEG-IFN, PegIntron®), in the treatment of recalcitrant CA in patients with HIV infection.

Material and Methods

Patients

22 patients with documented laboratory diagnosis of HIV infection (two arms: treatment group (the PEG-

IFN-Group) and control group (no treatment for CA) in virologic steady state with clinically demonstrable anogenital CA were enrolled in the two following centres: the Department of Dermatology, Ruhr-University, Bochum; and the Department of Dermatology, University of Köln. One woman and eleven men (mean age 38.2 years, range 24 to 58 years) were included in the treatment group (Table 1); one woman and 9 men (mean age 41.3 years, range 30 to 62 years) were included in the control group (Table 2). Patient's stage of HIV infection was classified according to the WHO/CDC criteria. In the treatment group, seven patients received highly active antiretroviral therapy (HAART), three patients were naive to HAART. The diagnosis CA was established according to clinical and histopathological criteria, in this group mean duration of CA was 43.1 months (range 1 to 92 months). No other treatment (e.g. podophyllotoxin, topical or systemic viral therapy) had been given for at least four weeks before initiation of therapy. In the control group, eight patients received HAART, two patients were naive to HAART. Mean duration of CA in this group was 37.1 months (range 12 to 96 months). No treatment of CA (podophyllotoxin, topical and systemic viral therapy) was performed in the control group.

Woman of childbearing age had to have a negative pregnancy test at entry. All patients were advised to use condoms during the study to minimalize the risk of reinfection. Pregnancy, autoimmune disorders, psychiatric conditions, a history of cardiac, pulmonary, hepatic, or central nervous system disorders were exclusion criteria's. A history of an active opportunistic infection within the last twelve month before study entry was an exclusion criteria. We also excluded patients, who had a serum creatinine one and a half times the upper limit of normal, a white blood cell count less than 3000 cells/mm_3, a platelet count below 100000 elements/mm_3, or an aspartate aminotransferase serum concentration greater than twice the upper limit of normal.

Study Design

All patients had to give informed consent for participation. All of them had a history of previous treatments for CA. Before initiation of therapy, genitoanal region was clinically inspected. Additionally, all patients underwent anoscopic examination for CA. These examinations were repeated monthly until a follow-up period of six month. At study entry, all visible warts greater than 5 mm in diameter were electrosurgically removed in both PEG-IFN and control group. Smaller warts were not treated to document the effects of PEG-IFN. Patients in our treatment group received 80 microgram PEG-IFN (PegIntron®) once a week for 24 weeks. Each injection was given subcutaneously. Follow-up period was six month. Inspection of genitoanal region was repeated every other week. The effects on the number of lesions at each visit were assessed by a clinical scoring system (complete response; major response; minor response; stable disease; progression of disease), and photographic documentation was performed. Final clinical evaluation was performed at week 24 and after the six-month follow-up. We monitored local and systemic side effects at every visit during the treatment period and during follow-up period. We inquired the patients treated with PEG-IFN about the presence of fatigue, depressions, local reactions, and flu-like symptoms including fever chills, myalgia, malaise and headaches during therapy. The severity of adverse events was determined according to the National Cancer Institute (NCI) Toxicity Criteria. We collected complete blood counts, serum chemistries, HIV RNA testing and lymphocyte subpopulation determination at entry and every month during the 24 weeks of therapy. Patients were not allowed to use any kind of non-steroidal anti-inflammatory drug during treatment period except paracetamol, which was allowed to prevent flu-like symptoms after each PEG-IFN administration. Local discomfort and erythema at the injection site was relieved using topical corticosteroids and cold compresses. Patients were dropped out of the study in case of grossly abnormal blood counts or if they missed more than two consecutive visits.

Evaluation of Efficacy

Response to treatment was evaluated using the following criteria:
Complete response (CR): 100% clearance of CA
Major response (MR): at least 50% and less than 100% reduction of CA
Minor response (mR): at least 25% and less than 50% reduction of CA
Stable disease (SD): less than 25% reduction but less than 50% increase of CA
Progression of disease (PD): more than 25% increase of CA

Statistical Analysis

For distribution we used the Kolmogorov-Smirnov test; for comparison of paired samples by normal distribution we used the 2-tailed paired students t-test and Pearson's correlation (r); for comparison of paired samples by non-normal distribution: the Wilcoxon-test. If data were given on a nominal scale we used the McNemar Chi-Quadrat test. For comparison of two independent samples by normal distribution we applied the t-test for independent samples; for comparison of two independent samples by non-normal distribution, we used the Mann-Whitney U test (two-tailed). Data are given as mean and standard deviation (SD).

P values are two sided and are considered to be significant when $p < 0.05$, very significant when $p < 0.01$ and highly significant when $p < 0.001$.

Results

PEG-IFN was well accepted and completed by ten patients, two patients did not finish the study due to side effects. Response to PEG-IFN was assessed during the 24 weeks of therapy as well as up to six month after. Patient's characteristics, course of CD4 cell count, HIV RNA, and response to treatment are summarized in Table 1.

Table 1. Treatment grooup, demographic and clinical data.

Pat.-No.	Sex	Age	Diagnosis of HIV	Stage of HIV (CDC/ WHO)	HAART	Site of Disease	Duration of disease (month)	Prior treat-ment	Adverse events	CD4 at study entry/study end (ul)	HIV DNA at study entry/study end (copies/ml)	Response	CD4 at follow up (ul)	HIV RNA at follow up
1	F	30	10/91	B3	+	V, PA, IA	72	p, e	Leucopenia	512/159	<40/<40	CR	192	<40
2	M	31	05/00	A2	-	PA, IA	60	p, e	local reaction	525/725	14300/6520	CR	626	1520
3	M	41	09/85	C3	+	PA, IA	15	e	flu-like symptoms, high transaminases	506/519	<40/<40	MR	614	<40
4	M	57	09/99	C3	+	PA, IA	20	e	flu-like symptoms, fatigue	248/467	<40/<40	CR	530	<40
5	M	58	02/95	C3	+	P, PA, IA	75	p, e, i, g	depression	190/--	161/--	-	-	-
6	M	37	05/92	C3	+	P, PA, IA	55	p, e, i, g	flu-like symptoms	377/--	205/--	-	-	-
7	M	37	05/85	B3	+	PA, IA	92	e	-	588/551	<40/<40	CR	533	<40
8	M	34	03/01	A2	-	PA, IA	12	e	-	509/452	35700/5580	MR	539	20700
9	M	24	01/00	A2	-	PA, IA	24	e, p	-	743/944	34700/4940	mR	Lost	Lost
10	M	35	09/99	C3	+	PA, IA	6	e	flu-like symptoms, fatigue	222/269	<40/<40	mR	368	<40
11	M	36	10/92	C3	+	PA, IA	1	e	flu-like symptoms	120/232	<40/113	MR	333	<40
12	M	38	10/86	C3	+	PA	24	e	flu-like symptoms, erythema	414/394	<40/82	MR	370	<40

Table 2. Control group.

Pat.-No.	Sex	Age	Diagnosis of HIV	Stage of HIV (CDC/ WHO)	HAART	Site of Disease	Duration of disease (month)	Prior treat-ment	CD4 at study entry/study end (ul)	HIV RNA at study entry/study end (copies/ml)
1	M	41	02/85	B3	+	PA, IA	24	e	347/338	<40/<40
2	M	31	05/98	C2	+	PA, IA	96	e	642/823	<40/<40
3	M	62	05/92	C3	+	PA, IA	72	e	826/942	100/453
4	M	54	08/96	C3	+	PA, IA	36	e	253/235	220/850
5	M	33	10/97	A2	-	PA	28	e	449/518	28.700/6170
6	M	36	02/92	C3	+	PA, IA	14	e	135/173	65/88
7	M	39	10/99	B2	-	P,PA, IA	26	e	426/554	2860/6710
8	M	47	11/89	B3	+	PA, IA	12	p,i,e	126/110	<40/<40
9	M	30	10/98	C2	+	PA, IA	28	p,i,e	422/428	<40/<40
10	F	40	03/98	C3	+	V,PA, IA	35	e	303/505	<40/<40

CR, complete resp.; MR, major resp.; mR, minor resp.; SD, stable disease; PD, progression; V, vagina; P, Penis; PA, perianal; IA, intraanal; p, Podox; i, Imiquimod; e, electrosurgery; g, topical Interferon; +, yes; -, no

Biological side effects of PEG-IFN included typical flu-like symptoms, fatigue, local reaction, and increase of AST (Table 1.). Patient No. 1 showed leucopenia (2230 WBC/ml), but was also treated with ribavirine for hepatitis C coinfection. None of the side effects led to a reduction of dosage. No life-threatening side effects occurred, all side effects were of grade 1 (minimal). All of the above mentioned side effects and serologic changes resolved within a few days after completion of the 24-week PEG-IFN course. One patient was removed from the study because of beginning depression under PEG-IFN after three weeks of therapy (patient No. 5). One patient decided to finish study because of flu-like symptoms (patient No. 6).

Clinically, the results obtained were satisfactory for both the patients and the physicians. Four patients revealed complete response, four patients had major response and two had minor response after treatment with PEG-IFN.

In our control group, all patients showed progression of CA during the 24 weeks of the study. Comparing the two arms, we observed a highly significant reduction of the clinical score ($p < 0.001$) in the PEG-IFN group.

Additionally, nine of the twelve patients treated with PEG-IFN had an impressing increase of CD4 cell count until week 24 of treatment. The average increase of CD4 was 31.5. Only one patient with leucopenia revealed a decrease of CD4 cell count. Without her the increase was 75.33. In our control group increase of CD4 was 69.75 (therefore we did not find significance calculation both arms, Table 1). The benefit of Peg-IFN was even higher in patients without HAART. Their mean CD4 cell count was 592.23/μl before treatment and 700/μl after PEG-IFN (increase 114.77).

Additionally, we observed comparing the patients of our treatment group on HAART and naive to HAART: Patients naive to HAART (three patients) had a significant ($p < 0.01$) HIV RNA decline until week 24. The average viral decline was 0.74 $\log_{10}$.

Patients receiving HAART had no change of HIV RNA with levels below the limit of detection of ultrasensitive assay (40 copies/ml).

On follow-up, the treatment outcome remained stable for at least six month in all patients of the PEG-IFN group.

Discussion

Standard ablative treatments for CA mainly focus on the elimination of warts without being able to address to the residual HPV DNA in the asymptomatic surrounding tissue. IFNs have been demonstrated to be active agents in various viral infections due to their antiproliferative, antiviral and immunoregulatory properties [7]. They are mainly produced by peripheral blood mononuclear cells and have the potential to protect cells against HPV infection and to eliminate extrachromosomal viral DNA from HPV-transformed cells [8]. Accordingly, interferon-α has been reported to be effective in HIV negative patients with CA. In the present trial, the therapeutic effects of PEG-IFN for CA in HIV infected patients were evaluated and compared with an untreated control group.

PEG-IFN, a protein-conjugate containing a single straight-chain peg with a molecular weight of 12.000 Daltons and interferon-α2b in a 1:1 ratio, has an approximately 10-fold longer plasma half-life than regular interferon alfa-2b. The pegylated form intensifies interferon therapy by maintaining effective plasma drug concentrations over time. This delayed-clearance formulation allows for once-weekly dosing [9]. Additionally, the weekly dosing schedule positively affects patient's compliance and quality of life.

The parenteral administration of IFN theoretically treats all HPV-infected epithelial cells. The exact pathomechanism still remains unknown. Experiments in small animals have shown that after the injection there is an initial bolus in the circulation, which rapidly falls. The longer plasma half-life of PEG-IFN maintains constant pressure on HPV resulting in the good results obtained in this study. In addition to these antiviral effects, while there exists a direct effect of IFN to HPV infected cells, there exists an indirect effect on the cellular immune system [10].

The efficacy of intralesional IFN in CA has been demonstrated in various clinical trials [11-16]. These trials showed complete response rates between 13-60%. Nevertheless, intralesional application, especially in the genitoanal region, is painful, time spending, and unpleasant for the patient. This method is not practicable in patients with widespread lesions.

Topical IFN-α and IFN-γ is easy to applicate but has not provided consistent evidence for clinical benefit in anogenital CA [17, 18].

Recently, imiquimod, a member of a new family of immune response modifiers, has been introduced in the treatment of CA. It enhances innate and acquired immune responses via endogenous cytokine production [19]. Most patients under imiquimod experience a moderate to marked local reaction consisting of erythema, induration, erosions or ulcerations, which in some cases leads to discontinuation of therapy. Application of imiquimod by suppositories (anal tampons) has been reported for CA. However, its intraanal application remains difficult [20].

Other results so far observed under imiquimod treatment should also be considered subject to further investigation, i.e. the prognostic factors of gender and immune status to therapeutic response. Sauder et al. report an overall clearance rate of 50% (54/109) for external genital and perianal warts in immunocompetent patients treated with imiquimod 5% cream 3 times weekly until wart clearance up to 16 weeks, with clearance rates in females (72%) significantly higher than in males (33%) [21]. In another study including 74 patients, of whom the majority suffered from recurrences of genital warts, the complete clearance rate under imiquimod was 33% with 37% complete clearance within the subgroup of immunocompetent patients [22]. A randomized trial in HIV-infected patients with anogenital warts came out with only 13% (7/53) total clearance in the imiquimod treated group vs. 8% (2/25) in the vehicle group (PP-analysis, $p = 0.710$, not significant) and partial remission (> 50% reduction in total wart area) rates of 47% in the imiquimod group versus 20% in the vehicle group (PP-analysis, $p = 0.013$), respectively [23]. For those of the

patients who were previously treated, the three most common wart therapies reported were podophyllotoxin, cryotherapy, and electrocautery. There were no effects reported on the underlying HIV-disease except the fact that no exacerbation of any patient's HIV/AIDS disease was attributed to treatment with imiquimod.

Systemic IFN-α alone or in combination with standard therapeutic options or retinoids has been shown to be safe and effective in the management of genital warts [24-30]. To our knowledge, most previous studies included immunocompetent individuals. The present study is the first report about PEG-IFN for recalcitrant CA in HIV infected individuals, without any serious adverse events.

According to HAART, there was an increase of CD4 cell count in almost all patients of both arms. While HAART suppressed HIV RNA significantly in both groups, we yet did find significancy in our patients not on HAART compared to patients on HAART receiving PEG-IFN. So as an additional positive effect, PEG-IFN shows potent and significant anti-HIV-1 activity. These findings are consistent with previous observations showing that IFN-α exerts potent suppression of HIV-1 replication in patients naive to HAART with CD4 cell count >200/mm_3 at baseline [31]. The antiviral actions of IFN include inhibition of reverse transcription, inhibition of viral assembly and virion release [32, 33]. There is evidence that CD4 and CCR5 receptor positive IFN-producing cells raise the susceptibility to HIV infection and subsequent destruction [34].

In regard of CD4 cell count, our findings differ from the observations of Hatzakis et al. They reported no change in CD4 levels during IFN-α treatment.31 However, the authors hypothesized that a four week cycle of IFN-α was too short to assess the kinetics of CD4. Additionally, the application of 5 MIO I.E. of nonpegylated IFN daily is according to a higher dosage than 80mg and may therefore have a suppressive effect on CD4 cell count.

In conclusion, our results show that PEG-IFN is an effective and safe treatment modality in HIV infected individuals with CA with positive effects on the suppression of HIV-1 replication and increase of CD4 cell count. Because of the encouraging results of this trial, an open prospective, non-randomized pilot-study with PEG-IFN in HIV-infected individuals naive to HAART was performed and will soon be evaluated.

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Address for correspondence:
Prof. Dr. N. H. Brockmeyer
Department of Dermatology
Ruhr-University Bochum
Gudrunstrasse 56
D-44791 Bochum, Germany
Tel.: ++49-234-509-3474
Fax: ++49-234-509-3475
E-mail: N.Brockmeyer@derma.de