

Immunotherapy of Gynaecological High-Risk Human Papilloma Virus Infection With Human Leukocyte Ultrafiltrate

H. Spitzbart* and U.B. Hoyme

Department of Obstetrics and Gynaecology, Frauenklinik, Erfurt, Germany

ABSTRACT

Objective: In this preliminary presentation the outcome of women following systemic treatment of cervical human papilloma virus (HPV) with a leukocyte ultrafiltrate is reported.

Methods: Cervical brush specimens of 819 women with low-grade CIN-1 were evaluated for HPV infection. HPV-positive patients were treated either by cone biopsy because of suspicious colposcopy or by antibiotics for symptoms of bacterial cervicitis. The remaining women were considered as asymptomatic carriers of HPV and underwent systemic therapy by a human leukocyte ultrafiltrate in a dosage of 5 IE, 6 times in the first 2 weeks, and additionally as a single dose at weeks 4, 6, 8 and 10.

Results: The leukocyte ultrafiltrate was administered to 97 HPV-positive women. In follow-up 88.7% were HPV negative at week 6; the remaining 11 women were tested negative after completion of a second course of therapy.

Conclusions: These preliminary data on the successful treatment of HPV infection by a leukocyte ultrafiltrate are very promising but have to be supported by additional research. *Infect. Dis. Obstet. Gynecol.* 8:120–123, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS

cervical HPV infection; immunomodulating therapy; antiviral therapy

Prevalence of HPV in our population is estimated to be as high as 10% in women in the reproductive age, but significantly higher in symptomatic patients. In the past decade convincing data on the relationship of human papilloma virus (HPV) infection to cervical neoplasia have been published.

About 30 of more than 100 serotypes appear to be relevant in this respect. HPV detection seems to be associated with at least a 10 times greater risk of cervical neoplasia.^{1,2} Lorincz et al.³ defined the following categories for the associated risk of common anogenital types:

1. low risk (HPV 6/11, 42, 43, 44)
2. intermediate risk (HPV 31, 33, 35, 51, 52, 58)

3. high risk/HPV 16
4. high risk/HPV 18.

The presence of oncogenic HPV conferred relative risks in the range of 65.1–235.7 for the occurrence of a high-grade lesion and 31.1–296.1 for an invasive cancer. However, an intermediate or high amount of HPV 16 DNA predicted the presence of high-grade CIN in a subsequent biopsy in almost 90% of patients, irrespective of the cytological grade of the referral smear.⁴ According to De Villiers et al.⁵ the progression of HPV-positive women from normal cytology to CIN, or cancer, occurred at an annual frequency of 0.082%. With an assumed infected life span of 45 years, the lifetime risk is 3.7%. On the other hand, in another study by

*Correspondence to: Heinz Spitzbart, Department of Obstetrics and Gynecology, Frauenklinik Erfurt Gorkistrasse 6, D-99084 Erfurt, Germany. E-mail: uhoyme@klinikum-erfurt.de

Nuovo et al.,⁶ most women showed no evidence of squamous intraepithelial lesions on follow-up if the concurrent Pap smear was normal, even when HPV-DNA was detected. This suggests that HPV detection per se does not necessarily correlate with subsequent squamous intraepithelial lesion. In addition, coexistent active cervical infections (e.g., chlamydial infection) seem to have no influence on the clinical course of HPV lesions, as reported by Yliskoski et al.,⁷ but suppression of local immunity may be important.

Topical podophyllin and surgery have been used for years in the routine treatment of condylomata acuminata and HPV infection, respectively, but podophyllotoxin, interferon, and imiquimod are alternatives under serious consideration. Von Krogh and Hellberg⁸ reported a complete and permanent cure with 0.5% podophyllotoxin cream in 77% of their study group (34 out of 44 patients). Stellato⁹ achieved a complete response of 33% (8 of 24 women) in their study group and a partial regression one year after treatment of 58% (14 of 24 women) with recombinant 2*b* interferon administered by intra-/perilesional injection. Edwards et al.¹⁰ reported a 72% success rate in women with condylomata acuminata following treatment with 5% imiquimod cream, however, most reports about these latter regimen lack data concerning cervical HPV infection.

Considering the high prevalence of HPV infection, its infectious and oncogenic potential, as well as the poor treatment results, a great deal of interest is directed towards the evaluation of alternative therapies. In this preliminary investigation the outcome of women following systemic treatment of cervical HPV with a leukocyte ultrafiltrate is reported.

MATERIALS AND METHODS

Cervical brush specimen of 819 women with low-grade CIN-1 were evaluated by means of in situ hybridization (Biohit, Helsinki, Finland) and polymerase chain reaction (PCR) (biotin marked primer, provided by A. Stelzner, University of Jena, Germany) for HPV infection at the Department of Obstetrics and Gynaecology, Klinikum Erfurt. HPV-positive patients were treated either by cone biopsy because of suspicious colposcopy (e.g., punctated acetic white lesions) or by antibiotics for clinical symptoms of bacterial cervicitis. The re-

TABLE I. Prevalence of selected HPV types in 273 patients

HPV type	Percent (%)
6	58.6
11	65.2
16	84.3
18	81.0
31	31.5
32	16.9

maining women were considered as asymptomatic carriers of HPV and underwent systemic therapy by a commercially available human leukocyte ultrafiltrate (LeukoNorm Cyto-Chemia®, Ihringen, Germany) of patented, but not stated composition in a nonrandomized prospective fashion.

The inclusion criteria were as follows:

- nonbacterial chronic cervicitis, HPV 16/18 positive,
- low-grade CIN-1 (koilocytosis facultative), HPV 16/18 positive,
- colposcopic signs of HPV-infection, HPV 16/18 positive, and
- age \geq 18 years, informed consent.

Women with histological proven carcinoma, CIN-2 or CIN-3, other untreated infections, or pregnancy were excluded from the treatment trial. The leukocyte ultrafiltrate was suspended in a 5-ml isotonic NaCl solution and administered intramuscularly (*M. gluteus maximus*) in a dosage of 5 IE (I.E. = Internationale Einheit, International Unit), six times in the first two weeks and additionally as a single dose at weeks 4 and 6 and if indicated because of HPV persistence at weeks 8 and 10.

All women were evaluated by PCR for HPV at week 6 and if still positive at week 10. In women testing positive at week 10, a second course of therapy was administered (10 doses of 5 IE 2 weeks apart). Complete long-term follow-up was not possible for technical reasons.

RESULTS

A total of 33.3% of all women investigated (273/819) were found to be HPV positive. A total of 921 different strains of HPV were found, at least two in each of the patients (Table 1).

Therapy of the HPV-positive patients was as follows: 49 (17.9%) underwent cone biopsy and 127

(46.5%) were treated for cervicitis by antibiotics. The leukocyte ultrafiltrate was administered to 97 (35.5%) HPV-positive women (mean age 27.0 years).

In follow-up 86 of the 97 patients who received leukocyte ultrafiltrate (88.7%) were HPV negative at week 6; the remaining 11 women tested negative after completion of therapy at week 30. All women were asymptomatic following treatment. Adverse reactions possibly due to the leukocyte preparation were not observed.

DISCUSSION

Convincing data in the literature support the hypothesis that cervical lesions referred to as CIN comprise two distinct and histologically separable entities: low-grade CIN-1 with HPV types 16, 18, or 33, in less than 30% of cases, and high-grade CIN-2 and CIN-3 associated with these types in almost 90% of cases. The high oncogenic risk types 16, 18, or 33 were detected in 29% of 100 cases with CIN-1 and in 88% of 176 cases with CIN-2 or CIN-3.¹¹ To put the reported findings into practice it appears efficient, at present, to re-evaluate patients with oncogenic HPV types in association with low-grade cytology, as well as women with high-grade cytology or suspicious colposcopy at frequent intervals.

The management of women with low-grade or borderline cytology is still unsettled. An efficient therapy for HPV infection would be promising, since it is likely that it would be able to reduce the risk of subsequent carcinoma. However, other contributing risk factors such as smoking, drugs, promiscuity, immunosuppression or incompetence, and chronic diseases also have to be taken into account.

In our study we used a leukocyte ultrafiltrate that is supposed to induce an immunological response by means of ribonucleopeptides of still unknown structure. The mechanism is thought to be enhanced by immunological stimulation of proliferation and maturation of T-lymphocytes as well as by stimulation of lymphokines.¹² The same mode of action has been applied successfully in treatment of chronic infections in general medicine.

These preliminary data on the successful treatment of HPV infection by a leukocyte ultrafiltrate have to be supported by additional research focusing on two topics: (1) What is the mode of action of

this immunomodulating (ribonucleopeptide) substance and (2) is the surprisingly high cure rate reproducible and long lasting in a randomized, double-blinded prospective study?

Until now the leukocyte ultrafiltrate is registered in Germany for primary and secondary immunodeficiencies and for immunocompromised hosts suffering from viral infections. Treatment of HPV infection by leukocyte ultrafiltrate, however, is still experimental and rather expensive (pharmacy costs about \$3500/case, so the indication for therapy is limited and to be defined with caution. From our experience with patients suffering from persistent HPV infections, we can recommend immunotherapy as trial for the following cases:

- young fertile women with a desire for children, reliable in cytological control, and no indication for cone biopsy
- persistent HPV infection with type 16/18, especially with remaining koilocytosis after cone biopsy or laser treatment, or
- chronic HPV infection with recurrent suspicious cytology (also in pregnancy?).

However, in the current stage of research, the use of the leukocyte ultrafiltrate investigated has to be limited to proven low-grade CIN-1 in order not to postpone adequate therapy of possible carcinoma.

REFERENCES

1. Sherman ME, Schiffman MH, Lorincz AT, et al. Toward objective quality assurance in cervical cytopathology. *Am J Clin Pathol* 1994;102:182-187.
2. Kataja V, Syrjänen S, Mäntyjärvi R, et al. Prognostic factors in cervical human papillomavirus infections. *Sex Trans Dis* 1992;19:154-160.
3. Lorincz A, Reid R, Jenson AB, et al. Human papillomavirus infection of the cervix: relative risk associations of 15 common anogenital types. *Obstet Gynecol* 1992;79:328-337.
4. Cuzik J, Terry G, Ho L, Hollingworth T, Anderson M. Human papilloma-virus type 16 DANN in cervical smears as predictor of high-grade cervical cancer. *Lancet* 1992;339:959-960.
5. De Villiers EM, Wagner D, Schneider A, et al. Human papillomavirus DNA in women without and with cytological abnormalities: results of a 5-year follow-up study. *Gynecol Oncol* 1992;44:33-39.
6. Nuovo GJ, Maritz J, Walsh LL, Mac Connell P, Koulos J. Predictive value of human papillomavirus DNA de-

- tection by filter hybridization and polymerase chain reaction in women with negative results of colposcopic examination. *Am J Clin Pathol* 1992;98:489-492.
7. Yliskoski M, Tervahauta A, Saarikowski S, Mäutyjärvi R, Syrjänen K. Clinical course of cervical human papillomavirus lesions in relation to coexistent cervical infections. *Sex Transm Dis* 1992;19:137-139.
 8. Von Krogh G, Hellberg D. Self-treatment using a 0.5% podophyllotoxin cream of external genital condylomata acuminata in women. *Sex Transm Dis* 1992;19:170-174.
 9. Stellato G. Intralesional recombinant alpha 2b interferon in the treatment of human papillomavirus-associated cervical intraepithelial neoplasia. *Sex Transm Dis* 1992;19:124-126.
 10. Edwards L, Ferency A, Baker D, et al. Self-administered topical 5% imiquimod cream for external genital warts. *Arch Dermatol* 1998;134:25-30.
 11. Lungu O, Sun XW, Felix J, Richart RM, Silverstein S, Wright TC. Relationship of human papillomavirus type to grade of cervical intra-epithelial neoplasia. *JAMA* 1992;267:2493-2496.
 12. Evans CH, Flugelman AA, Dipaolo JA. Cytokine modulation of immune defenses in cervical cancer. *Oncology* 1993;50:245-251.



Hindawi

Submit your manuscripts at
<http://www.hindawi.com>

