Use of Proteflazid for the treatment of human papillomavirus infections in men

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The purpose of the study was to investigate the effect of the immune modulator Proteflazid on human papillomavirus (HPV) infection in men, manifested predominantly in the form of genital warts or HPV carriage. The following results were obtained on the basis of an examination of 187 men, 97 of which had genital warts. Course administration of the product leads to a decrease in the incidence of HPV strains as well as improves the results of surgical treatment of genital warts in men, reducing the frequency of relapses by 1.5 (52.8%, compared with 35.5% p = 0.0251), and also reduces the degree of tissue dysplasia in recurrent warts. A promising combination consists of oral course of Proteflazid and topical applications of its solution, which can lead to warts regression without surgical intervention.

Key words: Proteflazid, immune modulator, human papillomavirus, condyloma.

Genital human papillomavirus infection is one of the most frequently diagnosed sexually transmitted infections in the world. The most common cause of death, associated with human papillomavirus (HPV), is cervical cancer. But, infection in men is also an important factor, both because of their morbidity and as carriers of these viruses. HPV can also provoke in men a large number of cancers, including anal, penile and oropharyngeal cancer. The frequency of anal cancer and oral cancer associated with HPV is increasing in the general population, and even more rapidly in immunocompromised patients, for example, HIV-infected. Penile HPV is very common both among heterosexuals and among homosexuals, regardless of the age range. Other HPV-related diseases that are clinically important are pointed condylomas and recurrent respiratory condylomatosis [1].

Minimum 40 strains of HPV belonging to the genus Alpha Papillomavirus can infect the skin of the balanus and stem of the penis. Condyloma cells that begin to regenerate contain most often highly oncogenic strains such as HPV16 and HPV 18 [9] and low oncogenic strains, such as HPV 6 and HPV 11.

Knowing the cycle of viral replication is important in understanding the clinical effect of HPV DNA and in diagnosing the disease in adults. Target cells for HPV infection are epithelial basal cells. The life cycle of a virus depends on the ability of these cells to divide, differentiate and advance to the epithelial surface [2]. In the basal layer, the so-called early proteins E6 and E7 promote the replication and maintenance of the viral genome, as well as cause cellular proliferation. When cells mature, different HPV proteins are expressed by the cell, which continues to support viral replication. Expression of the late proteins, which form the actual outer capsid of the virus, occurs in the upper layer of the epithelium. This is followed by immersion of DNA in the capsid and release of infectious virions from the normal desquamating epithelial cell.

The virus cannot replicate without differentiation of cells. The period between basal cell infection and release of the virus is from 3 weeks to 3 months.

Viral replication and associated expression of proteins induce low-grade squamous intraepithelial lesion (LSIL), which is characterized by moderate basal cell proliferation and increase in nuclei. An increase in the degree of intraepithelial dysplasia is accompanied with an increase in expression of products participating in cell transformation such as E6 and E7, usually resulting in chromosomal aberrations and aneuploidy in squamous epithelial cells (HSIL = higher-grade squamous intraepithelial lesion).

Since the virus is non-lytic, the inflammatory response to HPV is significantly less pronounced than to other infections, for example, C. trachomatis. In the early stages of HPV infection, the body remains, figuratively speaking, immunologically unaware of the virus, since virions are released only in the outer epithelial layer, far from submucosal, the primary site of immune defence. At the same time, primary HPV infection triggers an innate immune response [3] through the activation of Toll-like receptors (TLR) that recognize pathogen-associated membrane proteins or through the activation of natural killers [4]. It is believed that the innate immune response is responsible for rapid purification of the body of antigens – for several weeks.

Chronic HPV infections also trigger activation of the acquired immune response [5, 6] associated with the presentation of viral antigens to antigen-presenting cells (APCs), such as Langerhans cells and dendritic cells [7]. Successful acquired immune response requires several months to several years, moreover oncogenic HPV types, especially HPV 16, can inhibit both congenital and acquired immune responses through various mechanisms [3]. Since HPV infections are localized primarily in the epithelium, it is believed that immune responses are mucosal in this case. All these immune parameters must be remembered when choosing immunomodulatory and antiviral therapy in patients with HPV.

To suppress replication of the virus, a wide range of antiviral agents is used. One of them is Proteflazid produced by Ecopharm. Proteflazid has a pronounced antiviral activity due to inhibition of the DNA polymerase enzyme of virus-induced cells, as well as by induction of endogenous beta and gamma-interferons. In addition, it stimulates tissue macrophages, which are a link in the nonspecific defence of the body from infectious agents. Thus, the product can affect both early and late immune response in case of papillomavirus infection.

MATERIALS AND METHODS

A study of 187 men was conducted in the Department of Sexopathology and Andrology of the State Establishment Institute of Urology of the National Academy of Medical Sciences of Ukraine to evaluate the effect of Proteflazid on HPV.

97 patients had clinical manifestations of papillomavirus infection in the form of genital warts and foreskin. These patients were randomized into 3 groups: in group 1 (n = 36), patients underwent electrovaporization of condylomas without any antiviral therapy; in group 2 (n = 31) a week before vaporization patients received Proteflazid according to the scheme: 5 drops 3 times a day for 7 days, then vaporization, after which the dose was up-titrated to 10 drops 3 times a day for 3 months; in group 3 (n = 30), in addition to the oral administration of Proteflazid, the patients received applications of the product for 60-90 minutes per condyloma area twice a day. To prepare applications, Proteflazid solution (1.5 ml of the product + 10 ml of physiological solution) was used. All patients underwent an examination of the site of condylomatosis before treatment, before vaporization, 1, 3 and 12 months after vaporization. Upon vaporization, the tissue of condylomas was subjected to the histological analysis. A repeated histological examination was performed 12 months after relapse. Each patient underwent tests (scraping from the urethra) for the presence of highly oncogenic HPV strains (16, 18, 31, 33, 35, 39, 45, 52, 56, 58, 59, 66) before the vaporization, as well as 3 and 12 months after.

The second part of the patients (n = 90) had no clinical signs of papillomavirus infection either on the genitals or in the anal region, but were carriers of one or several highly oncogenic HPV strains. They were divided into 2 groups. Patients of group A (n = 47) received Proteflazid according to the scheme for oral use (5 drops 3 times a day for 7 days, then 10 drops 3 times a day up to 3 months). Group B (n = 43) was control and did not receive specific therapy. All patients in groups A and B were examined for presence of HPV with high-oncogenic properties in the urethral smear before the study, at the end of taking Proteflazid (3 months) and 9 months after the end of the therapy (in group B – only at the beginning of the study and 12 months after). To test for the presence of highly oncogenic HPV, urethral scrapings were performed at least 4-5 hours after the last urination. The presence of viruses was determined by polymerase chain reactions (PCR).

RESULTS OF THE STUDY AND THEIR DISCUSSION

All patients included in the study were evaluated with respect to the presence of HPV. Of these, Group 1 and Group B patients (79 in total) did not receive Proteflazid, the remaining 108 men received an immunomodulator according to the scheme. A control study in 12 months detected highly oncogenic HPV in 27/108 patients (25%) among patients treated with Proteflazid, compared with 64/79 (81%) among patients without specific therapy ($p < 0.03$). The most frequent strains of viruses before therapy were HPV 16 (105/187, 56.1%), HPV 33, HPV 35 and HPV 58 (47/187; 25.1%). About 81% (152/187 patients) had more than one type of highly oncogenic HPV (from 1 to 9 types, on average: 3.4 types). There was no significant difference in the number of HPV strains at the end of therapy (after 3 months) and at the end of the follow-up period (12 months) ($p = 0.8$); nevertheless, the number of HPV strains was significantly lower at the end of the whole observation than before the initiation of the therapy ($p = 0.026$). These data indicate that the use of Proteflazid in the recommended regimen for 3 months significantly inhibits HPV activity, reduces the detection of highly oncogenic HPV strains, and this effect is stable, considering the control tests 9 months after the end of therapy. The lack of specific therapy leads to HPV persistence in 81% of patients, which may pose a risk for developing genital warts, penile cancer, and also as a carrier of the virus to a sexual partner.

Interesting data were obtained in the analysis among patients with positive HPV and condylomas. As a result of vaporization of condylomas without accompanying therapy with Proteflazid among 36 patients of Group 1, relapses of condylomatosis at the places of vaporization were detected in in 4 patients (11.1%) in a month after vaporization, after 3 months already 11/36 (30.6%) had a relapse and after 12 months relapse was observed already in 19/36 (52.8%) patients. In group 2, when taking Proteflazid orally after 1 month, relapses of condylomatosis in 1/31 (3.2%, $p < 0.04$, compared to group 1) was observed after the end of the course of the immunomodulator in 7/31 (22.6%, $p < 0.05$, compared with group 1) and in 11/31 (35.5%, $p = 0.0251$, compared with group 1) 1 year after initiation of treatment. In group 3, two patients refused from vaporization, as they experienced regression of condylomas following topical applications of Proteflazid. On re-examination, one of the patients had a relapse of condyloma after 3 months, the second had no recurrence even after 1 year. Among the remaining 28 patients, 1 month after vaporization, following an oral course of Proteflazid, no patient showed any genital warts, in 3 months – in 4/28 (14.3%, $p = 0.62$, compared with group 2) and in 12 months – in 8/28 (28.6%, $p = 0.56$, compared with group 2). In this analysis, we see that the vaporization of genital warts without specific antiviral and immunomodulatory therapy leads to a high incidence of recurrence after 3, and especially 12 months following the operation. However, the addition of the immunomodulatory Proteflazid to the surgical treatment significantly reduces these indices. However, even better data are obtained by combining the oral administration of Proteflazid for 3 months and applications of the solution of the immunomodulatory to the sites of genital warts before they are removed. In some cases, this may even help to avoid surgery due to regression of the condyloma. The difference between the incidence of recurrence after vaporization + oral administration of Proteflazid and the same scheme with topical application of the immunomodulator is not reliable according to our study, but the indices are still lower in the group with topical applications of the product. This indicates that the main mechanism of Proteflazid action is systemic, namely, inducing production of interferons that reduce viral DNA replication, as well as blocking production of specific early virus proteins in the basal layer of the epithelium, to the level of which the product does not reach upon topical administration. It can be assumed that topical administration of Proteflazid with any tissue conductors (e.g., dimethylsulfoxide or ultrasound) can increase the efficacy of HPV combined treatment regimen (oral + topical) with the immunomodulator.

We also conducted an analysis of the histological data of genital warts upon vaporization and recurrence. Among all 97 patients, 4 patients (4.1%) had intraepithelial neoplasia (IEN), which is a precancerous condition, higher-grade squamous intraepithelial lesion (HSIL) was observed in 54/97 (55.7%) and the rest (40, 2%) had low-grade squamous intraepithelial lesion (LSIL). In the analysis of all patients who experienced a recurrence of genital

warts (n = 19), 1 patient (5.3%) in group 1 of IEN was previously diagnosed with HSIL, HSIL was observed in 10 patients (52.6%) and LSIL – in 8 patients (42.1%). These data are comparable with the results before vaporization. No patient with a relapse of condyloma was observed in groups 2 and 3 following administration of Proteflazid.

It should be noted that no patient experienced serious side effects associated with administration of Proteflazid. Six patients noted non-compliance, but they were insignificant, so they can be neglected.

CONCLUSIONS

Proteflazid produced by Ecopharm is an effective and safe immunomodulator that can be successfully used in the therapy of human papillomavirus infection. The therapeutic courses of the product leads to a decrease in the frequency of carriage of highly oncogenic HPV strains, as well as improves the results of surgical treatment of genital warts in men, reducing the frequency of relapses by 1.5, and also reducing the degree of tissue dysplasia in relapse condylomas. The combination of oral course of Proteflazid with topical application of its solution is a promising combination, which can even lead to regression of warts without surgery as well as reduces the incidence of recurrence compared with only oral administration.

Use of Proteflazidum for the treatment of human papillomavirus infections in men

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The aim of our study was to examine the effect of the immunomodulator Proteflazidum on HPV in men, which manifests itself mainly as genital warts or HPV carrier. Based on a survey of 187 men, 97 of which had penile warts below are the results that were obtained. Course the immunomodulator reduces the frequency of a carriage of high cancerogenic HPV strains, but also improves the results of surgical treatment of penile warts in men, reducing the recurrence rate for 1,5 times (52,8%vs 35.5%, p=0,0251), and also reduces the degree of tissue dysplasia in recurrent warts. The combination of oral course of Proteflazidum with topical application of its solution is a promising combination, which can even lead to regression of warts without surgery.

Key words: *Proteflazidum, immunomodulator, human papilloma virus, warts.*

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