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Clinical efficacy of the local use of Proteflazid® vaginal suppositories in the treatment of mild to moderate cervical intraepithelial neoplasia caused by human papillomavirus

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***The aim of the study*: to study the efficacy of the local use of Proteflazid® vaginal suppositories as a single agent treatment in CIN I–II, caused by human papillomavirus (HPV).**
***Materials and methods*. The study enrolled 50 women with cervical disease caused by various HPV strains. All of the female patients were assessed and managed in the Municipal Maternity Hospital No. 1, Vinnytsia. The liquid-based cytology PAP test, assessment of proliferation markers, genotyping of HPV with quantification, assessment of vaginal microbiome and bacterioscopy of vaginal discharge were performed by Synevo Laboratories.**
***Results*. First-hand clinical experience of using Proteflazid® vaginal suppositories as a single agent treatment for mild to moderate cervical intraepithelial neoplasia in a setting of papillomavirus infection and comprehensive assessment of clinical efficacy of the product (based on evaluation of patient complaints, liquid-based cytology PAP test, p16 and Ki-67 proliferation markers, viral burden, colposcopy and histological findings in the affected cervical areas has) have demonstrated a positive therapeutic effect of the suppositories; as a result, full reversal of the abnormal findings could be achieved in 96 % patients and 4 % of the women had conversion of CIN-II into CIN-I.**
***Conclusions*. A positive influence of Proteflazid® on the vaginal microbiome, its good tolerability and usability and the absence of adverse effects give grounds for its use in the healthcare system.**
Key words: *CIN I–II, papillomavirus infection, Proteflazid® suppositories.*

The research of cervical disease and its potential sequelae remains a current issue of modern gynecological practice and an important question of research and discussions by both academics and practicing physicians worldwide.

Multiple research studies have demonstrated that the presence of human papillomavirus (HPV) is a major cause of cervical disease, including cervical dysplasia and cervical cancer.

The target cells of HPV are mostly found in epithelial layers of the skin and of the mucous membranes. Viral effects in the epithelium may be either productive or transforming. Productive effects result in benign neoplastic lesions, such as papillomas and condylomas on the skin and on the mucous membranes. Transforming effects result in dysplasia of cervical epithelium, also referred to as cervical intraepithelial neoplasia (CIN), whose progression may lead to cervical cancer [3].

Contamination with HPV mostly occurs at the age of 16–25 years. However, in almost 70 % of cases, this infection is of a transient nature. Clinical manifestations of HPV infection tend to appear later in life due to the reduced capacity of immune defenses. Not infrequently, this is accompanied by the preneoplastic and neoplastic transformation of the affected epithelium. A characteristic feature of HPV is its ability to trigger an epithelial transformation in the skin and in the mucous membranes, including those in the genital tract. There is evidence for more than 130 types of papillomaviruses, which differ from one another by the structure of their DNA. There are approximately 630 million HPV-infected people worldwide. The following five highly carcinogenic HPV genotypes are detected most frequently: HPV16 (3.2 %), HPV18 (1.4 %), HPV52 (0.9 %), HPV31 (0.8 %) and HPV58 (0.7 %) [1]. However, these figures reflect only the incidence of clinically manifest HPV and not the actual numbers of infected people, since subclinical and latent forms of infection are frequently not reported/documented. The progress of papillomavirus infection may include several distinctive phases:

1) primary infectious contamination, when the virus is localized to a limited anatomical area;
2) persistence of viral genome in an episomal state, which is accompanied by the production of viral particles during differentiation of epithelial cells (repeated infection may occur at this phase);
3) oncogenic processes resulting from the interaction between viral oncogenes and cellular regulatory proteins after integration of viral DNA into their genome.

The principal HPV transmission route in women of childbearing age is the sexual route. Transmission of HPV occurs mainly at the time of sexual intercourse, including alternative sex practices (homosexual, oral and heterosexual anal contacts). In addition to that, the causative agent can be transmitted across the blood-placenta barrier and during labor and delivery; transmission through non-sexual contacts and sharp instruments (including medical and dental instruments) is also a possibility. However, the most significant risk factors for HPV infection include the following:

- early onset of sexual activity;
- multiple sexual partners;
- the presence of sexually transmitted disease;
- unhealthy lifestyles;
- physical illness with immunological deficits;
- multiparous women;
- long-term (for more than 5 years) use of hormonal contraceptives;
- hyperestrogenism-associated hormone-dependent processes;
- prolonged use of intrauterine contraceptive devices;
- dietary deficiencies of vitamins A, C and beta-carotene;
- women whose partners have been diagnosed with penile cancer;
- immune deficiency states (including AIDS);
- individual genetic predisposition to gynecological malignancy [2].

Many literature sources report that penetration of papillomavirus is occurring at the level of immature cells in the

epithelium of the skin and of the mucous membranes (i.e., the basal layer). This may result in cell proliferation, albeit without production of viral particles (since the proliferative epithelial cells are not capable of sustaining viral life cycles). Full-fledged HPV replication is possible only in the highly specialized cells of stratified squamous epithelium, including the cells of cervical mucosa.

As reported by a number of research papers, cytological testing of HPV-infected lesions has shown the cellular material to contain mostly anucleated cells or orthokeratotic cells.

When cervical epithelium is infiltrated by papillomavirus, the cells of the stratified squamous epithelium are altered, but the immune system does not recognize these affected cells. Therefore, further changes take place in the cellular structure of cervical epithelium.

This topic remains current, and, respectively, there is a large number of research studies and available methods of treatment for papillomavirus infection-associated cervical disease. There is the substantial experience of managing the cervical disease with locally-acting medicinal products (including interferon products) supplied as suppositories. There are many treatment regimens and numerous drugs exerting immunological effects. Interferons (IFNs) are host-dependent cytokines representing a group of biologically active proteins and glycoproteins, which are synthesized by the cells as a part of their immune response to various stimulants. Interferons are important immune factors, the first line of anti-inflammatory defense [4, 5]. The reason why interferons have their special place is that induction of interferon synthesis (primarily by natural killer [NK] cells, monocytic cells, and dendritic cells) prevents many specific immune responses. This is clearly seen in some viral infections. Similar to other cytokines, interferons exert their specific protective effects through signaling cascades.

At the first phase of infection, IFN-α and IFN-γ produce the following local effects (in sites of infection):

- intracellular inhibition of viral reproduction;
- elimination of the infected material with NK cells and cytotoxic lymphocytes;
- protecting other intact (not infected) cells from potential contamination.

The above effects, however, do not abort the infection process; besides, the use of interferon-based medicinal products is accompanied not only by many adverse effects but also by drug tolerance. This may necessitate increasing their doses, for example, due to emerging anti-drug antibodies against exogenous recombinant interferon (an especially frequent issue in long-term chronic disease, when using multiple-dose regimens and high strengths of interferon is required). Another limiting factor for the wider use of interferon-based products includes the high cost of treatment.

Within this framework, the issue of viral drug resistance is becoming increasingly more important than the issue of commercial availability of appropriate medicinal products. Viral drug resistance can be acquired only through a mutation: with a new genotype, a new viral strain appears, against which the immune system may be defenseless.

In this context, a promising strategy to solve the problem of virus-induced cervical disease (neoplasia of CIN-II and CIN-I) is using Proteflazid®, a domestically produced medicinal product supplied as vaginal suppositories, which has an important distinction from interferon-containing drug products. This drug exerts a direct antiviral action on the RNA and DNA of the viruses (without causing their mutations); therefore, the viruses are not capable of developing resistance to the active ingredient of this medicinal product. The active ingredient includes flavonoids obtained from a 1:1 mixture of two herbs, namely *Herba Deschampsia caespitosa L.* and *Herba Calamagrostis epigeios L.*; this makes the life cycle of the product virtually unlimited. The flavonoids inhibit DNA polymerase and thymidine kinase (specific viral enzymes) in virus-infected cells. Inhibition of these enzymes aborts replication of viral DNA, rendering reproduction of the virus impossible. In addition to that, Proteflazid® boosts non-specific immunity by increasing the levels of endogenous interferon and improves the resistance of the body not only to viruses but also to bacteria. Moreover, the drug has antioxidant properties, preventing accumulation of products of lipid peroxidation. Therefore, as Proteflazid® is used locally in the dosage form of suppositories, all of the above properties play a special role in the management of the papillomavirus-induced cervical disease.

The virus is essentially a living microscopic organism, acting as a parasite within host cells. If the virus is 'feeding' on the same things as human cells do, then, like the human cell, it will 'perceive' the components of the gramineous plants used in Proteflazid® (a herbal product), as phylogenetically native products. Gramineous plants (herbs) contain natural herbal components, which are more native to the human body than synthetic chemicals. Therefore, the first constituent of the general problem (that is, the mutability of the virus followed by resistance) may be considered solved (in this particular case, owing to an herbal antiviral drug, which is phylogenetically related to the human body).

Another important aspect of treatments used in the disease in question is their availability in pharmacies nationwide and their competitive pricing compared to other immunomodulating drugs. The usability of the product is also very important.

The aim of the study: to evaluate the efficacy of the local use of Proteflazid® vaginal suppositories as a single agent treatment in CIN I–II, caused by HPV.

MATERIALS AND METHODS

The study enrolled 50 women with cervical disease caused by various HPV strains. All of the female patients were assessed and managed in the Municipal Maternity Hospital No.1, Vinnytsia. The schedule of assessments used for patient screening and evaluation of treatment efficacy included the following assessments: review of complaints, liquid-based cytology PAP test (the BD SurePath technology); p16 and Ki-67 proliferation markers with immunocytochemistry; quantitative genotyping of HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 (the test system for HPV quantification had an analytical sensitivity of $1–5\times10^3$ copies/ml); colposcopy and histological testing of affected cervical areas. Study parameters were assessed before treatment and 8 weeks after treatment.

The women also had bacterioscopic assessment of vaginal discharge before and after each of the 14-day treatment periods (i.e., 4 times while in the study); this assessment was performed before treatment (assessment of microbial populations in vaginal discharge using the Floracenosis technique to rule out unconditionally pathogenic infection (such as *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Chlamydia trachomatis* and *Mycoplasma genitalium*) and to evaluate vaginal microbiome (bacterial vaginosis, *Mycoplasma* and *Ureaplasma* infection, vulvovaginal candidiasis and aerobic vaginitis) with PCR assessment for 17 pathogens. The liquid-based cytology PAP test, assessment of proliferation markers, genotyping of HPV with quantification, assessment of vaginal microbiome and bacterioscopy of vaginal discharge were performed by Synevo Laboratories.

Table 1

Patient complaints before and after treatment, n = 50

Complaints	Before treatment		After treatment	
	Absolute count	%	Absolute count	%
Vaginal discomfort	26	52	2	4
Vaginal discharge	20	40	2	4
Vaginal itching and burning	18	36	-	-
Contact bleeding	10	20	-	-
No complaints	10	20	46	92

***Note**:* The total count is different from 100 % because more than one complaint was reportable in a single patient.

Colposcopy assessment was done with a Scanner MK-300 colposcope (Ukraine) using vascular tests. A biopsy was performed under colposcopic visual guidance from sites with distinct adverse changes and using a conchotome.

The material for the PAP test and assessment of proliferation markers and HPV was obtained from the endocervix and the ectocervix using a Cervex-Brush Combi cervical brush. The PAP test was evaluated according to the Bethesda system (2014) correlated with the Papanicolaou, CIN and WHO grading. The investigators assessed the quality of the material, the presence of any specific infectious agents, non-neoplastic cellular processes (metaplasia, atrophy, etc.), the presence of endometrioid cells, reactive changes (inflammation) and changes of squamous epithelium: NILM Type I - cytogram within normal, NILM Type II - smear of an inflammatory type; ASC-US - atypical squamous cells of undetermined significance; ASC-H - atypical squamous cells, cannot exclude HSIL; LSIL - low-grade squamous intraepithelial lesions: Type III, mild dysplasia, CIN - I/Type III, signs of HPV infection, koilocytosis; HSIL - high-grade squamous intraepithelial lesions: Type III, moderate dysplasia, CIN-II/Type III, severe dysplasia, CIN-III/Type IV, suspected cancer/cancer in situ, CIS – invasive squamous cell carcinoma, as well as atypical glandular cells: AGC-US - atypical squamous cells of undetermined significance, AGS favor neoplastic - atypical squamous cells suspected for neoplasia, AIS - adenocarcinoma in situ, adenocarcinoma.

The reference values of proliferation markers included a negative or a positive response; the finding was assessed as positive if both p16 and Ki-67 were found simultaneously in the same cell, which informed the presence of malignant transformation in the cells of the cervical epithelium.

A sampling of vaginal discharge for bacterioscopic testing was performed with a gynecological pallet in the following three points: urethra, posterior vaginal vault and cervical canal; the material was then spread on a slide with subsequent Gram staining. During bacterioscopy, study personnel assessed leukocyte counts, squamous epithelium cells, mucus, Gram-positive bacilli, such as Döderlein's bacilli (*Lactobacilli*) and other Gram-positive and Gram-negative organisms as well as vaginal cleanliness (relative degree of microbial contamination).

Samples were taken at Day 10–20 of the menstrual cycle (provided there were no signs of bleeding) not before 24 hours after the gynecological exam, colposcopy, sexual intercourse or using various vaginal treatments and not earlier than 3 weeks after any prior cytology sampling.

The following inclusion criteria were used: the presence of Grade I–II cervical intraepithelial neoplasia (CIN) in a setting of infection by various strains of HPV; women who were able and willing to receive treatment.

Exclusion criteria: the presence of Grade III cervical intraepithelial neoplasia (CIN), vaginal infections and any vaginal dysbiosis, patients younger than 23 years (due to the possibility of congenital changes of the uterine cervix) and pregnancy.

The female study subjects received local single agent treatment with Proteflazid® vaginal suppositories according to the following regimen: 1 suppository b.i.d 14 days of each month for 3 consecutive months. The suppository had to be introduced deep into the vagina. No other vaginal procedures and/or drug therapies were used. For the entire duration of treatment and until follow-up assessment, the patients were advised to use the condom to prevent reinfection.

If only partial reversal was reported after completion of treatment, cryoablation was used in the affected cervical areas.

Treatment efficacy was evaluated based on changes in patient complaints profile, PAP test findings, proliferation markers, HPV viral burden, colposcopic presentation and histological findings. The investigators also assessed the influence on vaginal microbiota, tolerability of the product and adverse effects.

RESULTS AND DISCUSSION

Of 380 women who sought medical attention of a gynecologist for different reasons and who had a screening Papanicolaou cytological test, the investigators have selected 50 subjects, who were enrolled into the study according to the inclusion criteria.

Among study subjects, there were 30 (60.0 %) women 23–30 years of age and 20 (40.0 %) women 30–35 years of age. The average age of onset of sexual activity was 16.8 ± 1.9 years. The majority of female subjects (47–94 %) had two or more sexual partners. There were 26 (52.0 %) nulliparous women, but all of them had reproductive plans for the future. All of the patients refused to have the therapeutic destruction of their cervical disease.

The complaints reported by the women before and after treatment are summarized in Table 1.

Before treatment, the women mostly complained of vaginal discomfort (52 %), vaginal discharge (40 %), vaginal itching and burning (36 %) and contact bleeding (20 %). However, an alarming finding is that approximately one in five women (20 %) had no complaints and that their cervical changes were found during routine screening for gynecological cancer.

At the end of treatment, 92 % subjects reported improved well-being and no complaints; relief of discomfort was reported by 24 (92 %) of the 26 patients, and relief of vaginal discharge was reported by 18 (90 %) of the 20 patients who had respective complaints before treatment.

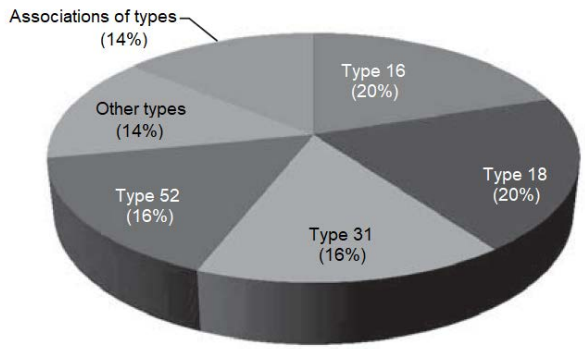

Fig. 1 – Genotypes of human papillomavirus in study subjects, n=50

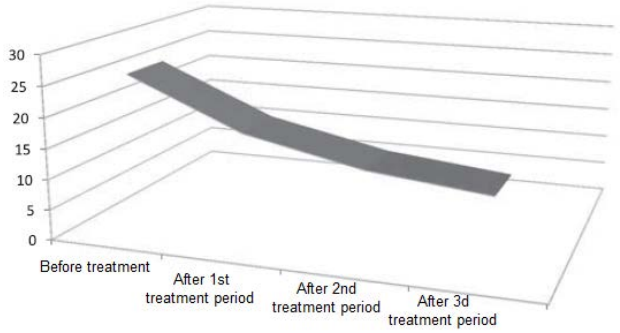

Fig. 2 – Leykocyte counts in vaginal discharge before, during and after treatment

Distribution of papillomaviruses by types identified with genotyping of cervical scraping material is shown in Fig. 1.

As can be seen from Fig. 1, the predominant types found in study subjects were Type 16 and Type 18 HPV diagnosed in 10 subjects (20 %) each, followed by Type 31 and Type 52 in 8 subjects (16 %) each; other types and type associations were found in a total of 7 (14 %) study subjects, respectively. Therefore, most women (36 [72 %]) were infected with a single virus of a high carcinogenic risk type.

The results of a bacterioscopic test of vaginal discharge before and after each of the 14-day treatment periods are summarized in Fig. 2 and Fig. 3.

As can be seen from Fig. 2, the leukocyte counts in vaginal discharge (per power field) had a trend to decrease from 26 ± 2.3 (at the onset of treatment) to 12 ± 1.8 (after the third 14-day period of treatment with Proteflazid® suppositories), which was an evidence of reduced inflammation of vaginal mucosa in a setting of study treatment.

The results of the study demonstrate that pre-treatment vaginal discharge in the women was dominated by cocci (in 25 or 50 % subjects), whereas bacilli (Döderlein's bacilli or *Lactobacilli*) were noted in only 8 (16 %) women. The number of women identified with *Lactobacilli* has been progressively increasing with time of treatment; after the third period of treatment with Proteflazid® suppositories, the number of such patients has reached 45 (90 %). This data suggests a positive effect of the study product on the vaginal microbiome, facilitating its recovery to a healthy condition.

Liquid-based cytology PAP test was performed before treatment and 8 weeks after the last administration of Proteflazid® suppositories. The resulting findings are presented in Table 2.

As seen from the results presented herein, the majority of women (40 [80 %)] had pre-treatment signs of mild cervical intraepithelial neoplasia, and 10 (20 %) subjects had atypical squamous cells of undetermined significance, the latter requiring

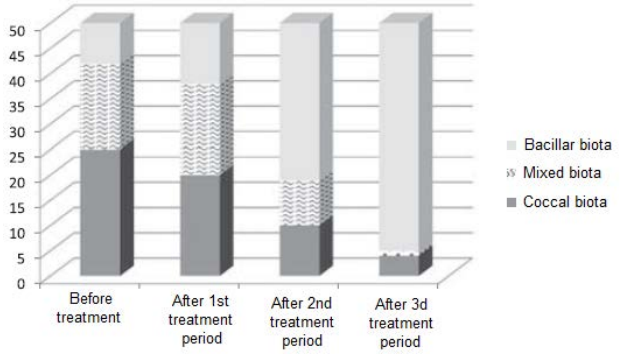

Fig. 3 – Vaginal microbiome profile before, during and after treatment

verification of the diagnosis. In 8 weeks after completion of 3 periods of treatment with Proteflazid® suppositories, 10 (20 %) patients were reported to have a completely normal cytological presentation and in 36 (72 %) patients the signs of intraepithelial neoplasia of the cervix were reported to have disappeared. Thus, a positive cytological effect was observed in 92 % of cases post-treatment.

During pre-treatment assessment of cervical material for p16 and Ki-67 proliferation markers, p16-positive status was found in 5 (10 %) patients and Ki-67-positive status in 4 (8 %) patients. Subjects with simultaneous positivity for both markers (p16 and Ki-67) were excluded from the study due to a high risk for malignant transformation. In 8 weeks after the last dose of treatment, all of the female subjects were negative to both markers.

The investigators have also assessed viral burden before treatment and 8 weeks after completion of the third period of treatment with Proteflazid® suppositories. The results are summarized in Table 3.

Table 2

The results of liquid-based cytology PAP test before and after treatment, n = 50

Assessment	Before treatment		After treatment	
	Absolute count	%	Absolute count	%
NILM, Type I	-	-	10	20
NILM, Type II	-	-	31	62
ASC-US	10	20	5	10
LSIL	40	80	4	8

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Table 3

HPV viral burden before and after treatment

Parameter	Viral burden (Lg HPV/10^5 cells)
Before treatment	5.1 ± 0.35
8 weeks post-treatment	2.8 ± 0.36
Effect of treatment	-2.3* ± 0.43

Note: *p<0.05

As seen from the data presented herein, the female patients had clinically significant pre-treatment HPV burdens (more than 5 Lg HPV/10^5 cells). After treatment, 40 (80 %) of study subjects were reported to have significantly (p<0.05) reduced measurements; there has been an almost two-fold reduction of viral burdens, that is, to clinically insignificant levels (less than 3 Lg HPV/10^5 cells). In 10 patients (20 %), the virus was completely undetectable post-treatment, which provides evidence of its complete elimination from the body with treatment and of a direct antiviral effect of Proteflazid® suppositories.

Changes of colposcopic presentation with time before and after treatment are summarized in Table 4.

The analysis of the resulting data has demonstrated that in 8 weeks after completion of the third period of treatment with Proteflazid® suppositories colposcopic presentation fully reversed to normal in 25 (50 %) women, 17 (34 %) patients were diagnosed with significant improvements and only in 8 (16 %) patients the colposcopic presentation has not improved. The respective reductions in detection rates were from 20 % to 4 % for leukoplakia/keratosis, from 24 % to 4 % for iodine-negative areas and from 30 % to 8 % for acetowhite epithelium. Mosaic patterns and punctation were reported pre-treatment in 20 % and 16 % patients, respectively; no women had these findings at the post-treatment colposcopic follow-up. Consequently, study treatment has produced positive cervical effects in 42 (84 %) of female subjects in the study (as reported by colposcopic findings).

In order to establish the final diagnosis and to evaluate treatment outcomes, the women had histological testing of affected cervical areas before treatment and 8 weeks after the last administration of Proteflazid® suppositories. The results are summarized in Table 4 and in Table 5.

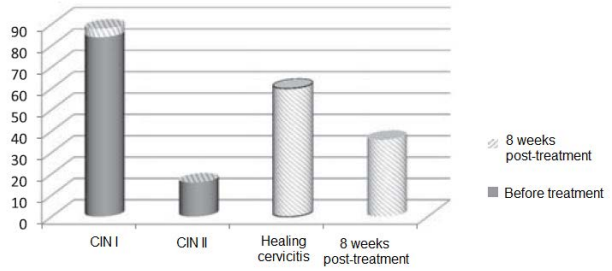

Fig. 4 – The results of histological assessment of cervical biopsy samples before and after treatment, n=50

According to these results, pre-treatment histological presentation was consistent with mild cervical intraepithelial neoplasia (CIN-I) in 42 women (84 %) and with moderate CIN (CIN-II) in 8 (16 %) women. After the last period of treatment with Proteflazid® suppositories, a total of 48 (96 %) patients had a full reversal of CIN (morphological evidence included healing cervicitis in 30 (60 %) patients or stationary cervicitis in 18 (36 %) patients), whereas 2 (4 %) patients were found to have conversion of CIN-II into CIN-I, that is, improvement of their histological presentation.

Therefore, a comprehensive efficacy assessment of a 3-period treatment with Proteflazid® suppositories (14 days each) has been performed in this study of mild to moderate cervical intraepithelial neoplasia in a setting of HPV. The assessment was based on clinical data, liquid-based cytology PAP tests, proliferation markers, viral burden and colposcopic and histological testing, which collectively improve the accuracy of reported results. The study product was found to produce a positive effect in 100 % of cases, with full reversal of abnormal findings in 96 % of cases and partial improvement of cervical status in 4 % of cases.

During assessments of tolerability and adverse effects of Proteflazid® suppositories, the product was found to be well-tolerated by all women. The administration was painless; only 5 (10.0 %) women communicated concerns over suppositories not dissolving well in the vagina. This, however, did not require any additional interventions. All women mentioned the ease of use associated with this product supplied as suppositories.

Table 4

Colposcopic signs in women before treatment and 8 weeks post-treatment, n = 50

Colposcopic sign	Before treatment		8 weeks post-treatment	
	Absolute count	%	Absolute count	%
Leukoplakia/hyperkeratosis	10	20	2	4
Iodine-negative areas	12	24	2	4
Acetowhite epithelium	15	30	4	8
Mosaic patterns	10	20	-	-
Punctation	8	16	-	-
Ectopy of cylindrical epithelium	10	20	17	34
Normal colposcopic presentation	-	-	25	50

Note*:* The total count exceeds 100 % because more than one sign was reportable in a single patient

Table 5

The results of the histological assessment of cervical biopsy samples before and after treatment, n = 50

Parameter	Before treatment		8 weeks post-treatment	
	Absolute count	%	Absolute count	%
CIN-I	42	84	2	4
CIN-II	8	16	0	0
Healing cervicitis	-	-	30	60
Stationary cervicitis	-	-	18	36

CONCLUSIONS

Clinical efficacy assessment of Proteflazid® vaginal suppositories used locally as 3 cycles (periods) of single-agent treatment (14 days in each of the 3 consecutive months) has provided evidence of positive cervical effects. This was supported by the following investigations: liquid-based cytology PAP test (reduction of LSIS detection from 80 % to 8 %, with reversal to normal in 82 % patients), colposcopy (normal post-treatment presentation in 82 % patients), disappearance of p16 and Ki-67 proliferation markers in all cases; a significant 1.8-fold reduction in viral burden and morphologically confirmed full reversal of cervical intraepithelial neoplasia in 96 % of cases and conversion of CIN-II to CIN-I in 4 % of cases. Also, the suppositories were noted to have a positive effect in the vaginal microbiome, manifested as a 2.16-fold reduction of leukocyte counts per power field and a 5.6-fold increase in *Lactobacilli*. Finally, this method of treatment was well-tolerated by the patients, it was easy to use, painless, used in an out-patient setting and had virtually no side effects.

Clinical efficacy of topical use of vaginal suppositories Proteflazid® in the treatment of cervical intraepithelial neoplasia of mild and moderate degree caused by the human papilloma virus

N.A. Godlevskaya, A.V. Starovir

The objective: to study the effectiveness of topical vaginal suppositories Proteflazid® in the form of monotherapy for CIN-the I-II, caused by the human papilloma virus (HPV).

Patients and methods. The study involved 50 women with cervical pathology caused by various strains of human papillomavirus (HPV). All the women were examined and treated in Vinnytsia city clinical hospital № 1. PAP test based on liquid-based cytology, determining proliferation markers HPV genotyping quantitative estimation, determination of the status of the vagina biocenosis bacterioscopy vaginal discharge performed in the laboratory Synevo.

Results. Own clinical experience vaginal suppositories Proteflazid® as monotherapy for the treatment of cervical intraepithelial neoplasia mild to moderate from HPV infection, the complex evaluation of clinical efficacy based on the study of patients complaints, PAP test based on liquid based cytology, proliferation markers p16 and Ki- 67, viral load, colposcopy and results of histological examination of altered cervical sites showed a positive therapeutic effect with suppositories, which resulted in 96% of women achieved complete regression of disease, and 4% marked shift in the CIN-II CIN-I.

Conclusion. The positive effect of the drug on the state of the vagina Proteflazid® microbiocenosis, good tolerability, ease of use and lack of side effects give reason for its use in the health care system.

Key words: *CIN-I-II, papillomavirus infection, suppositories Proteflazid®.*

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REFERENCES

1. V.V. Kaminsky, M.N. Shalko, L.I. Vorobieva, O.V. Romashchenko, A.I.Grinevich. Proteflazid®: specific activity in preclinical studies and efficacy and safety of use in clinical practice in the disease caused by human papillomavirus (systematic review). Woman's Health. 2015; 3 (99): p. 122–132.
2. N.A. Hodlevska, A.V. Starovir. The experience of using Proteflazid® in management of cervical disease associated with papillomavirus infection. Bulletin of State Medical University of Vinnytsia. 2012; Vol. 16(1): p. 91–96.
3. L.I. Vorobieva. Papillomavirus infection, a current issue of modern gynecology. Woman's Health. 2015; 3 (99); p. 21–24.
4. L.V. Suslikova, O.M. Borys, V.V. Sumenko, A.V. Kaminsky, A.V. Serbeniuk. The efficacy of use and tolerability of immunomodulating agents in women with papillomavirus infection associated with preneoplastic cervical disease and mixed urogenital infection. Woman's Health. 2009; 4 (40): p. 140–146.
5. S.M. Kartashov, O.A. Byeloded. Efficacy analysis of immunomodulators used in treatment of papillomavirus infection. Woman's Health. 2009; 4 (40): p. 40–41.