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Proteflazid®: specific activity in preclinical studies, efficiency and safety of administration in clinical practice in diseases caused by human papillomavirus (systematic review)

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Systematic review is devoted to the analysis of specific activity, safety and efficacy of Proteflazid® (drops) in preclinical study and at the stage of clinical observation, in case of diseases caused by human papilloma virus (HPV). Independent clinical data (more than 1500 patients) is substantiated and reflected in 20 scientific literary sources which are commensurate by aims and results of conducted treatment, and confirm antiviral influence of medicinal agent regarding human papilloma virus.
Key words: *Proteflazid®, human papilloma virus, specific activity, safety, efficacy.*

In practice of obstetricians, gynecologists, urologists, dermatologists and sexologists genital organs' diseases caused by human papillomavirus (HPV), are one of the major problems, as the clinical manifestations, diagnosis and tactics of patients with various forms of human papillomavirus infection (PVI) are inconsistent and not standardized, especially due to absence lack of medicines with active substances, which have a direct mechanism of antiviral action of HPV. The current trend in recent years is unreasonable and sometimes violent treatment of women infected with HPV, often leads to long-term complications, disease recurrence, especially during pregnancy [13, 20, 27].

Viral diseases occupy a prominent place in the structure of urogenital infections. PVI can be a cause of clinical and subclinical diseases of the genital organs. Clinical forms include various types of genital warts that affect the penis, vulva, vagina, cervix and anus. PVI often (in 60% of cases) combined with inter epithelial neoplasia, and some (cancer-causing) HPV types, penetrating into the cervical area, lead to the development of cervical carcinoma [4, 20]. This is especially noticeable in pregnant women, due to the emergence of a large number of cells, which are divided with impaired differentiation and hyperplasia. This causes activation of PVI and carcinogenesis processes.

The mucous membrane of the cervical canal hypertrophies due to an increase in the size of columnar epithelial cells and strengthen them in the processes of mucus. And also, there is a degradation of collagen fibers, creation of new blood vessels and new cells, which are similar in morphology to decidual in the cervical stroma [13, 20, 26, and 27].

Genital PVI is quite common throughout the world. More than 70 species of AAH are human pathogens. Globally, about 630 million people are infected with PVI. Most frequently detected five highly oncogenic HPV genotypes: PVI_16 (3.2%), PVI_18 (1.4%), PVI_52 (0.9%), PVI_31 (0.8%) and PVI_58 (0.7%) [11, 14, 21].

In most patients, the infection is caused by infection during sexual contact with patients.

The incubation period varies from 3 weeks to 9 months, sometimes greatest, and an average of 2 to 3 months. Virus transmission to sexual partners occurs in the 46-67% cases. Natural reservoir of HPV is considered to be the population of men with Bowenoid papulosis with symptomatic form of the disease, as well as men with subclinical PVI patients and penile cancer. The lesions on the skin and head of the penis, in the urethra, bladder, ureters, cervix, perianal region define a wide range of different types of HPV. Since 1996, WHO has decided to consider HPV types 16 and 18 are carcinogenic to humans, HPV types 31 and 33 may be carcinogenic, and a number of other types of conditional carcinogens [5, 14, 15, 20, 21, 27].

There is evidence that about one in three sexually active women has various forms of clinical manifestations of AAH. 95% of cases, HPV is localized in the area of the junction of stratified squamous and columnar epithelium, where there is epithelial dysplasia of the cervix. During conducting multicenter studies on the prevalence of HPV in adolescents, the persistence of viruses in a year provided only 30% of cases, after 2 years - 9%. In this clinical regression took place in 80% of patients. Regression of cervical squamous intraepithelial lesions of low degree was observed in 90% of teenagers, while in adult women in 50-80% of cases. These figures confirm the picture of the sexual transmission of the virus. Thus, the risk of cervical disease in women at first sexual intercourse before the age of 18 years, five times the risk of women who had sex after 22 years [6, 11, 15,20, 27].

Risk factors for developing cervical cancer (CC) include cervical disease which exist for a long time (benign and precancerous), and, if left untreated, lead to cancer.

In carcinogenesis other than HPV, involved a number of other cancer-causing agents of various natures. These include: the early onset of sexual activity (15 years), frequent change of partners (more than 5), smoking (more than 10 cigarettes a day), the lack of sexual health of both partners, a history of an ovulatory menstrual cycles before pregnancy, hyperestrogenia, primary infertility, the effect of radiation before and during pregnancy, birth trauma and cervical abortion, sexually transmitted infections

(STIs) [13, 15, 20, 27]. According to the literature, 5-year survival rate of patients with cervical cancer in combination with pregnancy in the early stages (I-II stage) - is 68, 2-77% of cases, in advanced (III-IV stage) - 44-55% [20, 26].

Now it is proved that the viral infection can remain latent for several years, and its presence increases the risk of cervical cancer, on average, 300 times [5, 14] .Infection men is also an important factor as a result of their disease and how carriers of these viruses. HPV can cause in men a significant number of cancers, including cancer of the anus, penis, and oropharyngeal cancer. The frequency of anal and oral forms of cancer associated with HPV, increases in the general population, and even faster in immune-compromised patients, such as HIV-infected. Penile HPV is very common among both heterosexual and among homosexuals, regardless of the age range. Other diseases associated with HPV, which is clinically significant, are genital warts and recurrent respiratory warts [7, 14] Referring least 40 HPV strains belonging to the genus papillomavirus may infect the skin of the head and shaft of the penis. The warts cells that begin to degenerate, more often are highly oncogene strains, such as PVI-16 and PVI-18 and low oncogene PVI-6 and PVI-11 [7, 15].

One of the most important risk factors for PVI is immune disorders. PVI is often found in patients with dysfunction of cellular immunity, and more frequently in HIV infected and those who have been treated with immunosuppressive therapy. Clinical observations and experimental studies indicate the leading role of the immune system in controlling the occurrence, course and outcome of PVI [5, 7, 20, and 26].

PVI can take place in several steps:

1) primary infection, when there is a localization of the virus in a limited anatomic region;
2) the persistence of the viral genome in episomal form which is accompanied by production of viral particles during the differentiation of epithelial cells (An opportunity for this step, secondary infection);
3) oncogene processes as a result of the interaction of viral proteins with regulatory oncogene - cells after integration of viral DNA into their differentiation genom. Without differentiation of cells the virus cannot be replicated. The period between infection and cell basal release of virus from 3 weeks to 3 months [5, 7, 11,16, 21].

Widespread replication and dissemination of the virus during primary infection counteract various factors of a natural antiviral resistance of the organism, including the ability of cells of stratified squamous epithelium of the mucous membrane of urogenitals to permanent desquamation and regeneration, production of interferons (IFN) that can limit the dissemination of viruses process within the affected area, and also the action of natural killers (NK cells) and macrophages [4, 14].

Since the virus is a non-lytic, inflammatory response to HPV is much less pronounced than in other infections, for example, C.trachomatis. In the early stages of infection with HPV is the body, so to speak, an immunologically not aware of the virus, since the virus are released only in the outer epithelial layer, away from the submucosa, that is, the primary place of the immune defense. At the same time, the primary runs PVI innate immune response through activation of Toll-like receptors (TPR) that recognize pathogen-associated membrane proteins, or through activation of natural killer cells. It is believed that the innate immune response is responsible for the rapid clearance of the organism from antigens - for a few weeks [4] .Chronic PVI also causes activation of the adaptive immune response associated with the presentation of viral antigens of antigen presenting cells (APCs), such as Langerhans cells and dendritic cells. To successfully acquired immune response is necessary from several months to several years, especially oncogene HPV types, especially PVI-16 can suppress both the innate and acquired immune responses through different mechanisms. Since the MOC is localized mainly in the epithelium, it is believed that the immune responses in this case are mucosal. All of these immune parameters you need to consider when choosing an immune modulatory and antiviral therapy in patients with HPV [4, 15].

Diagnosis of typical manifestations of AAH is not difficult, however, is difficult to define them in the early stages. The main method of diagnosis of atypical varieties PVI is a cytological and histological studies (with the identification coilocytic cells in the biopsy), and polymerase chain reaction (PCR) with the definition of the type of virus. [4]

In the literature more than 30 years there is a constant debate about the most appropriate treatment of severe dysplasia, in epithelial cancers (SIN_III) and early forms of cervical cancer in young women. The encouraging results of treatment of early forms of tumors with a gradual decrease in the volume of surgical interventions became an occasion for the development of a new direction in gynecological oncology - organo-preserving treatment (EG Novikova, 1998). Given that a malignant tumor in the pre-invasive and invasive micro stages is local removal of the primary tumor and may lead to a cure, is increasingly used sparing surgical treatment [8, 26, 27].

A common treatment of PVI in the presence of clinical manifestations is a surgical method, including using electrocautery, cryoablation, and others. For therapeutic purposes when HPV is also used drugs that cause chemically induced necrosis exophytic manifestations PVI (Solkoderm, Ferezol, Collomak et al.). To prevent recurrence of the disease is currently used recombinant forms of IFN inducer of endogenous IFN, ointments with antiviral drugs. However, it is possible to achieve stable clinical effect, not all patients [4, 15, 27] .To suppress replication of HPV is necessary to use antiviral agents. Representatives of the group of direct antivirals is a drug Proteflazid® (drops) (SMC «Ecopharm», Kyiv, Ukraine) exhibiting pronounced antiviral activity against DNK viruses, which include viruses genus Papillomavirus (family Papovaviridae).

Proteflazid® **(drops) - a liquid alcohol extract obtained from wild cereals pickerel Soddy (**Deschampsiacaespitosa L.) and Veinik Ground (Calamagrostisepigeios L.). The active ingredients of the drug are flavonoids. Flavonoids are a group of biologically active compounds - benzapyrene derivatives, which are based phenylpropane skeleton composed of units C6-C3-C6-carbonaceous with oxygen atom in the heterocyclic ring. Depending on the degree of oxidation and hydroxylation of propane skeleton and position of the phenyl radical flavonoids are divided into several groups: flavones, isoflavones, flavonols, flavonones and flavononoly. Flavonoids are natural phenolic compounds. The specific properties of the drug are determined by the fact that in terms of pharmacological more than one flavonoid is valid under the conditions of the body, and there is the effect of the system of biochemical transformations the presence of highly active radical intermediates [3, 4, 15, 20, and 22].

Objective: To analyze the specific activity of Proteflazid® (drops) at the stage of preclinical study; evaluate the effectiveness and safety in clinical practice with genital diseases caused by HPV.

MATERIALS AND METHODS

We used scientific publications, reports on preclinical and clinical study, systematic analysis.

RESULTS AND DISCUSSION

Studies have exposed systematic analysis, carried out at the stages of preclinical and clinical study of the drug Proteflazid® **(drops) on the bases NIINANU far and the Ministry of Health of Ukraine (SE «Institute of Urology**

NAMS of Ukraine «Kharkiv regional nephrotoxicity urological center named after VI Shapoval, National Medical Academy of Postgraduate Education named after PL Shupyk, Chernivtsi, Vinnytsia, Dnipropetrovsk, Zaporizhia, Ivano-Frankivsk, Kyiv, Luhansk, Ternopil, Kharkiv medical universities, etc.) as well as Scientific and Re-

Table 1

The scheme of Proteflazid® medicine (drops)

Stages of treatment	dose (drops) and the number of intakes per day
1st week	7 drops 2 times per day
2nd and 3rd weeks	15 drops 2 times per day
4th week	12 drops 2 times per day

search Institute of Obstetrics and Gynecology, Ministry of Health of the Republic of Uzbekistan, the Ministry of Health of Kazakhstan, the Ministry of Health of Russia.

The study of the specific activity of the drug Proteflazid® **(drop) in the preclinical studies.** The specific activity of the active ingredient of the drug in Proteflazid® **infection caused by HPV, the preclinical study stage is set using HPV culture model (SV** Rybalko, 2010). HPV-producing cell culture was obtained by transfection of DNA isolated from human patients infected cells, suspension cultures MT_4 cells (suspension culture of human lymphoblastoid cells) and transplanted cells BHK (hamster kidney cells). HPV testing was performed by PCR on the cytopathic effect of the virus and cytological characterization - mitotic index and abnormal mitosis. HPV isolates tested primers for HPV 16, 18, 31, 33, 35, 39, 45, 52, 58, and 67 of 59_go genotypes. It was found that when cultured Proteflazid® **transplantable HPV cell culture has a** cytopathic effect, a characteristic feature of which was the formation of foci of transformation. The invitro experiment installed capacity Proteflazid® **drug to inhibit the reproduction of HPV in cell culture by 2** lg ID50 [1].

Cytological study confirmed that the level of abnormal Proteflazid® **under the action of the drug mitoses HPV infected cells was the same as that of the uninfected cells.** Proteflazid® **significantly reduces the level of mitotic activity and abnormal forms of mitosis, the cells infected with HPV. These results indicate a relatively high proliferative inhibition of HPV and destructive action on the cells to assume the clinical efficacy of the specific effect of the drug on** Proteflazid® **oncogenic HPV (**Rybalko SL, et al., 2011). Proteflazid® **also inhibits the synthesis of virus specific enzymes, thymidine kinase, DNA and RNA polymerases and reverse transcriptase in the virus-infected cells, which is particularly important when a viral infection mix [2].**

The inhibition of cell transformation involves three mechanisms: inhibition of cell proliferation, induction of cell differentiation, induction of apoptosis. Stimulates apoptosis Proteflazid® **therefore can inhibit reproduction of HPV and cell proliferation.** Proteflazid® **in infected cells is able to destroy the DNA polymerase mRNA of viruses. This mechanism is detected while testing the drug** Proteflazid® **in model systems: transcription (DNA dependent RNA polymerase bacteriophage T7) and replication (**taq DNA polymerase) [1].

Analyzing mentioned above preclinical studies, we can state that Proteflazid® **has specific antiviral activity against DNA-containing HPV.**

Proteflazid® **induces the synthesis of endogenous IFN-a and IFN-y and that is one of the mechanisms of antiviral action and is confirmed by detected levels of IFN-**a expression, RCC, an RNA L. The drug induces the synthesis of IFN to the physiological level; it increases not specific resistance to viral and bacterial infections. In addition, the drug stimulates tissue macrophages (increasing exciting, absorbing and digesting ability of macrophages), which is an important link in no particular protecting the body from infectious agents, the drug can affect both the early and the late immune response when PVI by restoring performance levels local immunity [1].

The study of efficacy and safety of Proteflazid® **(drops) in the clinic in diseases caused by PVI.**

In clinical practice, drug Proteflazid® **(drops) is used since 2001. A systematic review carried out on the basis of the available post marketing comparative clinical studies and observations in the course of treatment various diseases of the sexual sphere, due to HPV up to and including 2015.**

A significant part of the literary publications devoted to clinical experience with the drug Proteflazid® **(drops) for opportunistic infections, the development of which takes place in conditions of immune deficiency. The median prominence belongs to** herpes, cytomegalo viral infection and chlamydia, which today infect, according to the domestic and foreign literature, more than 90% of the female population, both in our country and abroad. However, in recent years, more and more studies are carried out aimed at preventing the development of cancer pathology, due to its rejuvenation, to provide organic preservation in the reproductive part of humanity.

That is to say, adequately chosen etiotropic antiviral treatment is quite effective and can reduce the proliferative activity of the tumors, which allows for conserving therapy [8]. In the treatment of PVI Proteflazid® (drops) is administered orally within 3 months, in accordance with the scheme that is shown in table 1.

Proteflazid® (drops) can also be used for 15-12 drops 2 times a day, starting from the first day of application. At the same time carry out a local therapy with Proteflazid® (drops) used vaginal swabs with a solution of the drug. To prepare the solution needed 3.0 ml (75-72 drops) to dissolve the drug in 20 ml of physiological sodium chloride solution. Time tampons exposure - 40-30 minutes. Local therapy applied twice a day for 2 weeks [10 ,6, and 23].

Given that one of the main etiological factors in the development of cancer of the genital organs is HPV, of particular importance is the availability of antiviral drugs with specific antiviral mechanism against HPV. Thus, the results of study of V.G. Radionova et al in 2002, on monitoring of patients with various manifestations of HPV in the background of Proteflazid® (drops) administration, with the active examination of patients within 6 months showed the relapse of condylomatous manifestations in the next 3 months after therapy in 4 out of 15 patients from control group (26.7%) and 3 out of 24 patients from main group (8.3%). The positive effect of the drug on the natural resistance of the organism has been confirmed by the analysis of leukogram [4].

Thus, 599 patients who were divided into three groups, based on the prevalence of the etiological factors of cervical pathology, GA Vakulenko, EV Kohanevich and AV Godu marketplace in 2003 [8] The drug treatment was administered Proteflazid® (drops) as a topically (in the form of vaginal tampons diluted 4 :1 with normal saline) and peros scheme: 1 week - 5 drops 3 times a day, 2 -3 weeks 10 drops three times a day, week 4 -by 8 drops 3 times a day for 1.5-2 months.

The reduction of subjective and objective changes was registered in patients as a result of etiotropic treatment. The area of inflammation focus has decreased, signs of inflammation decreased or disappeared in the colpocervicoscopic picture in 96% of patients. In 3 patients, in whom there has been the spread of vaginal vaults, after local administration of Proteflazid® (drops), the process remained only in the I and II zones of exocervix. In one case, colposcopic signs of dysplasia characterized by fields without the polymorphism; while cytology material cervical cervical canal surface evidence of a moderate dysplasia [8].

Repeated bacterioscopic inspection revealed the absence of pathogenic microorganisms in 93.7% of patients. The frequency of HPV DNA detection by PCR decreased s69, 2% (before treatment) to 5.4% (after treatment). The immunological imbalance declined in 74% of patients in this group, but the normalization of all investigated immunological parameters was not achieved [8]. According to the study V.V. Makagonova, N.G. Korniets, N.A. Udovik (2003) with the participation of 48 women with benign cervical pathology in age from 20 to 45, who were hospitalized in the gynecological department of the 2nd maternity hospital of Luhansk, show that in 21 women (43.8% of the total surveyed) according to PCR was diagnosed with PVI and / or herpes infection (GUI). Of the 48 tested, 41 women (85.4%) as a treatment for cervical CO_2 - laser milling has been performed. At the stage of preparation before the operating conducted anti-inflammatory immune modulating therapy. Laser vaporization was performed on 6-7 day of the menstrual cycle [9].

The best results were obtained in the study group patients with HPV and / or GUI, part of which included therapy with Proteflazid® (drops) already on day 21 of treatment in %88.88 of the cases reported disappearance of these viruses replicate in the cells of stratified epithelium. In comparison to the group 21_y day of treatment effect was registered only in %58.34 of patients. SO2_lazerovaporizatsiya pathological sections in all cases lead to complete epithelialization of the cervix, which is confirmed by the results of colposcopy. Repair processes in all cases 5_y ended at week after surgery. When viewed from the control study group patients, the disease relapses were observed [9]

Analyzing the experience of L.M.Malanchuk, T.V.Zaykova, V.M. Flehnera and NI Bagno obtained in 2003 as a result of examination and treatment of 22 women with diagnostically confirmed cervical dysplasia mild, we conclude that the use of antiviral drugs, IFN-a and IFN-y inductors, in particular, the modern Proteflazid® (drops), is effective in complex therapy of cervical dysplasia. Simultaneous oral and vaginal inside the drug improves the effectiveness of therapy by %30 than when only orally, which makes it possible to provide effective prevention of secondary cervical cancer [12].

The study of 27 women with PVI on a background of atrophic vaginitis with postvarioectomic syndrome, conducted in 2003 by C.A. Galnykina on the basis of medical diagnostic center (Ternopil), was aimed at studying the effect of Collomak in topical administration, in combination with Proteflazid® (drops) by oral and topical use in combination with hormone replacement therapy on the clinical course of PVI in women postvarioectomic syndrome, a condition of the system of lipid peroxidation and cellular and humoral immunity, given the important role of these disorders in the pathological process. [18] It was found that before treatment in the body of examined women there were constant changes in the immune regulatory interaction of relations system of cellular and humoral immunity, which cannot be considered adequate. So, there was a lack of cell-mediated immunity, as evidenced by the reduction in the number T-lymphocytes at the cost of T-helpers. The number of T-suppressors/ killers (T s/k) was significantly higher of control markers respectively, immunoregulatory index was decreased. Assigned therapy with Proteflazid® (drops) eliminated the identified immuno suppression. That is, by 30th day from the start of treatment, the deficiency of general population of T-lymphocytes was partly eliminated (CD3); there was a clear trend of reduction of T s/k-CD8, the number of which reached the normalization by 10th day; physiological stabilization of the number of T lymphocytes (CD3) and the normalization of the regulatory index, followed by the restoration of an adequate response of humoral immunity – B- lymphocytes (CD19) [18].

Therefore, in women with PVI on a background of atrophic colitis due to postvarioectomic syndrome who have been treated with Proteflazid® (drops) and Collomak (drug for cytodestructive effects on pointed warts of vulva and vagina), decreased antigen excess tension and immune deficiency states, improved processes antioxidant system, decreased lipid peroxidation, which contributed to the normalization of the pathogenetic mechanisms of disturbed PVI, which indicates a high clinical efficacy of prescribed therapy [18].

In studies by I.T. Kishakevich (2003) 60 women with cervical background diseases (from including 28 women who had a viral infection (HSV - 1,2go types, HPV types 6-11_go, 16-35_go types 18-59_go types), 16 women had mixed infection (a combination of a viral infection with chlamydia, mycoplasmosis or ureaplasmosis) were examined; in accordance with genital infections detected, the women were divided into 2 groups: 1st group - women with a viral infection, 2nd group - viral infection in combination with other genital infections. 1st group of women received in the treatment of the antiviral drug - Proteflazid® (drops), 2nd group of women - acrid one acetic acid [19].

In analyzing the data obtained during use prescription drugs showed increased levels of lysozyme in the serum and in cervical content, as compared with the level of lysozyme before treatment which were substantially close to normal levels. It should be noted that lysozyme activity in cervical contents when using Proteflazid® (drops) in women of 1st group was slightly higher than 0.24 ± 12.85 mcg / ml, than in administration of acrid one acetic acid in 2nd group of women 12,54 ± 0 , 18 ug / ml, and content analysis of serum lysozyme showed efficacy greater Proteflazid® drug (drops), which was used in women 1_y group 8.87 ± 0.35 pg / ml, compared with locusts acetic acid, which was used in women 2_y group 8.64 ± 0.12 ug / ml [19]. Lysozyme levels of serum and cervical content can be one of the criteria for diagnosis of background cervical diseases associated with viral infections, which in immune modulating treatment experienced complete recovery of its activity [19].

According to I.T. Kishakevich (2004) in a survey of 120 women, HPV was detected in 45 women (37.5%). In most cases of HPV was diagnosed in bacterial viral associations, which significantly affect the state of the vagina microbiocenosis and contribute to the progression of the background cervical pathology manifesting by pathological changes of cervical epithelium, colposcopic and cytological signs of a viral infection in 30.7% of subjects. It is found that the therapeutic effect Proteflazid® (drops) with pseudo-erosions of the cervix on the background of PVI and GUIs due to clinical and laboratory effects and provides: acceleration of epithelialization of cervical mucosa with normoplasia of flat multilayered epithelium; restoration of vaginal micro-biocenosis, due to the formation of humoral antibodies against pathogenic microorganisms; balance the local immunity, due to induction of IFN; It eliminates viruses, which is confirmed by PCR studies; reduces pathological focus area and suppresses the inflammatory process; improves the reproductive function, reduces the recurrence rate [11, 24].

Drug treatment of domestic pharmaceutical product Proteflazid® (drops) promoted normalization colposcopic pattern in 62.4% of patients. It should be noted that the highest efficiency was low in patients with cervical lesion of uterus, moderately expressed relief and in patients who did not have extra genital diseases [11].

After 8-10 weeks after completion of antiviral treatment of the repeated diagnosis of PVI by PCR in 85.8% of patients were negative survey data [11].

Thus, the simultaneous use of Proteflazid® (drops) into and locally reduces the affected area, and the degree of severity of the process that allow to treat this pathology conservatively in %62.4 of patients [11].

Analyzing the experience of a comprehensive survey of 11 women aged 22-39 years diagnosed with cervical cancer (8 - John situ conservation, 3 - stage Ia1), which were held organ-preserving surgery (amputation and electro cauterizing conization of cervix uteri followed by laser destruction) in the study of cervical pathology Cherkassy Re-

gional Oncology Center by A.V. Paliychuk in 2004, after the combined treatment with antiviral, antimicrobial and immune correcting preparations using the drug Proteflazid® (drop), it is proved that the use of a comprehensive anti-viral and immune therapy, in patients with early forms of cervical cancer with the presence of infection with herpes simplex virus (HSV) and HPV, provides an opportunity to organ-preserving surgery. Treatment of deregulatory disorders of immune system functions and dysfunction secondary cellular immunity arising in the postoperative period may treat immunocorrective immunomodulating drugs, including the inclusion in national drug regimens Proteflazid® (drops) [6].

Study of A.A. Mamon (2004), conducted in patients with skin PVI, disease duration of which exceeds one year, with one or multiple focal poly clinical forms, proves that the method of complex treatment of the individualized using Proteflazid® drug (drops) as compared with the conventional therapy, improves the quality of treatment to prevent and reduce complications in patients receive results that They were resistant to therapy, and significantly reduces the number of recurrences [25].

D.D. Kurbanov and colleagues in 2004 showed that adequately matched etiotropic treatment with Proteflazid® (drops) in combination with an antimicrobial, anti-inflammatory therapy and substances that normalize vaginal biocenosis is very effective is to reduce the proliferative activity of the tumors, which allows for conserving therapy. They have also proven not only beneficial effect of the drug on the infectious component in pregnant women, but also its complex effect on the course of the pregnancy itself. That is, the use of Proteflazid® (drops) to reduce the frequency of threatened abortion from %73.3 to %36.7, placental insufficiency from %46.7 to %23.3, pre-eclampsia varying severity from 23.3 to 10% , 0%, premature birth from 16.7% to 6.7%, premature rupture of the membranes from 46.7% to 20.0% and anomalies of labor activity from 26.7% to 10.0%. In addition to the positive aspects of the intake of this drug also provides a reduction of newborn asphyxia of varying degrees of severity - from 43.3% to 23.3%, intra amnionic manifestations of infection - from 23.3% to 10.0% [26].

Building on the work of the Kharkiv scientists OV Grishchenko VV. Bobritskaya, SA Pak (2005), it can be argued that Proteflazid® (drops) is the drug of choice for etiopathogenic therapy in pregnant women, due to lack of teratogenic effects of the drug, and its ability to inhibit the replication of viral DNA. Due to the use of the drug Proteflazid ® (drops) in patients of the main group was obtained regression of genital warts in 5-7 days after the start of treatment, complete disappearance of the warts was observed in 76.2% of patients, the remaining 23.8% of women expressed regression of warts in reducing the size of formations on the skin and mucous membranes. Relapse or progression of the process was not observed in the study group patients, the effectiveness of the drug Proteflazid® (drops) was %100. Patients in the control group who received topical treatment drug Collomak without a systemic immune modulation therapy, 41.7% patients had recurrences of external manifestations of the disease in the form of re-education warts or the appearance of new lesions as small warts. [10]

This therapy was used in 21 patients in gestation from 30 to 41 weeks, who received systemic antiviral treatment with Proteflazid® (drops) according to scheme recommended by the manufacturer for 5 drops 3 times a day for two days, 8 drops 3 times a day for two days, then 10 drops three times a day in months techenie3-2 during repeated cycles of pregnancy and after childbirth (minimum rate - 1.5 months). The duration of dosing up to 3 months was due to the prevention of recurrence of the disease and the achievement of sustainable clinical effect. Condylomata were treated with Collomak and Proteflazid® solution in the form of applications (lotions) [10].

Clinical study of V.V. Bodyan (2005), which involved 45 women with cervical warts of vagina and vulva, infected with HPV treated by Proteflazid® (drops) per os and locally confirms that this therapy provides a significant reduction in the area of lesions on the vulva, vagina and cervix [22].

Analysis of the clinical trial by V.M. Lesovoy and A.V. Yakovleva (2006), Kharkiv regional nephrotoxicity urology center, in 34 patients (8 women i26 men) with PVI highly oncogenic strains, 20 of which received Proteflazid® (drops) in combination with specific therapy, suggests that this therapy significantly affects the elimination of pathogens from the body, and the positive effect is more stable in nature [5].

Based on the results of PCR analysis, it can be argued that in patients receiving Proteflazid® (drops), significantly reduced the risk of transmitting an infectious agent sexual partner, as well as the risk of the virus-induced neoplastic processes (by 5] (%50-47].

According to clinical studies conducted by employees of Zaporozhye MAPS (NN Voloshin et al., 2007) on the basis of the Zaporozhye Regional Clinical Oncology Center at 136 pregnant women with cervical pathology associated with PVI, which in the II trimester were treated with Proteflazid® (drops) orally and topically, there was no progression of precancerous lesions to invasive cancer, which was the basis for deferred treatment after completion of the pregnancy [13].

In identifying clinical, and subclinical form of PVI and II CINI abortion is not shown, but it is necessary to conduct dynamic monitoring and antiviral therapy [13].

In 2007 T.V. Gerasimova, A.N. Gopchuk have conducted study involving 50 women with menstrual irregularities (NMC) and HPV who have been treated with Proteflazid® (drop) per os and locally on the background of symptomatic therapy, showed that the clinical efficacy of the proposed method was 82.8% (normalization of the menstrual cycle). The absence of the pathogen in PCR was observed in 32 (64.0%) women. Lymphocytic link systemic immunity is informative with respect to the forecast of possible systemic disorders. The results of studying the effect of the proposed method on the humoral immunity (the dynamics of changes in the content of the main classes of immunoglobulins (A, F, G) in the serum, as well as normalization of IFN-a, and IFN-y) showed an improvement immunogenesis processes. The results confirm immunity changes the clinical effectiveness of the proposed method and explain the highlights of changes in the state microbiocenosis genital tract and the immune status of patients with the NMC on the background of a viral infection. The complex of medical preventive measures among women of reproductive age in the background of viral infection, can reduce the frequency of the NMC in 5,3 times, including hypomenstrual syndrome - in 2,2 times, hypoestrogenism - 3.5 times, and restores hormonal balance, immune status microbiocenosis and genital tract. Using antiviral drug immuno correcting Proteflazid® (drop) in the combined treatment with symptomatic therapy reduced the number of relapses of HPV- 2-1.5 times, in the case of herpes infection - B3-2 times [17].

N.N. Voloshin in 2007 released data that Proteflazid® (drops) in infection with HPV should be used within 6 months against a background of morphological and cytomorphologic and PCR studies, as well as the fact that the drug is not cause complications, is well tolerated, has a strong antioxidant effect [27].

Analyzing the study conducted in 2010 by I.I. Gorpinchenko and O.V. Romashchenko on the basis of sexual pathology and andrology department of SI «Institute of Urology of NAMS of Ukraine», in the study of 32 women with chronic inflammatory diseases of the pelvic organs with PVI (latent) and disease duration from 2 to 5 years, followed by the appointment of systemic and local treatment of Proteflazid® (drops) showed improvement of general well-being and decrease secretions (intensity) and hyperemia of the genital tract in %59,4 of patients after a week of scheduled therapy and further were combined with the normalization of titles IFN production of tumor necrosis factor (TNF), functional activity of phagocytic cells , cellular and humoral immunity after treatment. The effectiveness of such

treatment according to genetic studies using PCR was 81.3%. There has been persistent therapeutic effect colposcopic pattern in 24.9% of women in the form of complete epithelialization of the cervix and the eroded surface of the mosaic epithelialization in 32.2% of patients [15].

E.I. Liliantsy, N.R. Safronnikova, L.A. Redko, V.M. Merabishvilli in 2010 at the City Clinical Oncology Center in St. Petersburg conducted a study involving 625 patients with virus types associated pathology. All patients were divided into two groups: the first group of patients have been treated with Panavir - intravenously and topically, the second - Proteflazid® (drops) per os and locally. The study was a negative result of PCR in 70% of patients receiving the drug Panavir and in 89% of patients who took Proteflazid® (drops) [16].

In 2011, to assess the impact of the drug Proteflazid® (drops) for HPV in males' sexual pathology and andrology department of SI «Institute of Urology of NAMS of Ukraine,» the study was conducted, which was attended by 187 men infected with HPV. M.G. Romanyuk, A.M. Kornienko and P.V. Aksenov demonstrated that exchange the drug reduces the frequency carriers are highly oncogenic HPV strains and improves the results of surgical treatment of penile warts in men, reducing the frequency of relapses in 1.5 times, and the degree of dysplasia tissue in recurrent warts. Perspective is a combination of oral course of Proteflazid® (drops) and the topical application of its solution, which can lead to regression of warts without surgery and reduces the incidence of recurrence compared with only oral administration [7].

On the basis of the Vinnitsa hospital antenatal clinic number 1, since 2012, the employees of the Vinnitsa National Medical University(N.I. Pirogov – N.A. Godlewski and A.V. Starover) were examined 32 women with cervical pathology associated with HPV and treated drug Proteflazid® (drop) as monotherapy with systemic and local his appointment. Due to such treatment the decrease in viral load is set on PCR results for PVL 3,6lg / 105 cells, the normalization of the cervix uteri of women in 68.8% and 31.2% in a significant improvement, i.e. Therapeutic efficacy was 100%, which allowed the researchers to avoid or reduce the degradation of the area of the cervix of the affected area, which is especially important for women planning to give birth [14].

In the years 2010-2013.on the basis of Odessa Regional Hospital, V.N. Zaporozhan, V.G. Maricheredoy, L.I. Dimcheva have conducted the study to evaluate the clinical efficacy of flavonoid glycosides derivatives in the treatment of benign and precancerous cervical conditions. The study involved 80 women of reproductive age with verified epithelial dysplasia of the cervix uteri mild to moderate (main group) and 30 healthy women who were examined in the order of the clinical examination. The main group was randomly divided into two subgroups depending on the clinical treatments. In the subgroup of I (n = 40) used the standard medical therapy, and in the II subgroup (n = 40) used the direct antiviral drug with immune modulating action Proteflazid® (drops) orally (8-4 weeks) and topical (vaginal swabs) on 14 days, 2 times with an interval of 10 days [28].

The results of the study suggest that the standard drug therapy is inferior to virostatic and antirecurrent effect of treatment with Proteflazid® (drops). In the usual way the treated patients' viral load is practically constant, whereas in group II had reached a significant reduction of HPV 3,0lg D50. At the same time, under the action of the drug Proteflazid® (drop) increases the number of antigen-presenting cells. The results indicate the appropriateness of Proteflazid® (drop) in the complex therapy in all patients with PVI [28].

To evaluate the efficacy and safety of Proteflazid® (drops) in patients with dysplasia of cervical epithelium caused by PVI, in 2015-2014 a study was conducted of Obstetrics, Gynecology and Reproduction of the National Medical Academy of Postgraduate Education named after PL Shupyk on the basis of the Kyiv City Center for Reproductive and Perinatal Medicine under the direction of a member of. corr. NAMS of Ukraine, Doctor of Medical Science, Professor V. Kaminsky. The study involved 76 women with verified diagnosis of dysplasia of cervical epithelium caused by PVI. Patients using the method of simple randomization were assigned to the main (n = 38) and control (n = 38) group. Patients in the control group was administered Proteflazid® (drops) of production of SMC «Ecopharm» in the form of vaginal swab with a solution of the drug (in 3.0 ml of the drug in 20 ml of physiological sodium chloride solution) na30-40 minutes, 2 times a day [29].

According to the results of the study after 14 days course with the use of tampons solution Proteflazid® **(drops) and at the end of the observation period of 8 week there was normalization of the cytological picture or change of cervical intraepithelial** neoplasia grade CIN_II (moderate dysplasia) to CIN_I (weak degree of dysplasia), reduces the severity of signs of dysplasia of cervical epithelium, there was significant compared with baseline, the decrease in viral load of HPV DNA. This change was especially pronounced after 8_nedelnogo observation period (from 2.37 to 0.71 points), suggesting a delayed antiviral effect of the drug. Use of the drug eliminates disbiotic state of vaginal micro flora and restores normal biotope of genital tracts [29].

Table 2

The results of clinical studies on Proteflazid® (drops) efficacy and safety in PVI from 2002 to 2015

№	Authors, year, source	Number of patients		The results of using of Proteflazid® (drops) in general clinical practice
		General	Took per orally/ local applications	
1	V.G.Radionov et al., 2002 [4]	39	24 / 0	Observation for 6 months showed that relapse condylomatous manifestations in the next 3 months of taking the drug after drug therapy Proteflazid® came at %8.3, against %26.7 in the control patients group. The positive effect of the drug on the natural resistance of the organism is confirmed by the analysis carried out leukogram.
2	G.A .Vakulenko et al., 2003 [8]	599	533 / 533	Proteflazid® in combination with etiotropic treatment (with antimicrobial, anti-inflammatory therapy and means of normalization of vaginal biocenosis) is very effective and reduces the proliferative activity of cervical tumors that allows you to apply conserving therapy. The detection rate PCR of HPV DNA in cervical cancer patients decreased from 69.2% (before treatment) to 5.4% (after treatment).
3	V.V. Makagonova et al., 2003 [9]	48	9/9	Patients with HPV and / or HSV, in the therapy which included Proteflazid®, already at 21? Day treatment in %88.88 of cases reported the disappearance of replication of these viruses in the cells of stratified epithelium. In comparison group - only %58.34 of the patients. CO-2laser vaporization of pathological areas led to a complete epithelialization of the cervix, which is confirmed by the results of colposcopy. Repair processes in all cases were ended on 5th week after surgery intervention. On examination, the disease relapses were observed.
4	L.M. Malanchuk et al., 2003 [12]	22	22 / 12	In patients who have been treated with Proteflazid® per orally, dysplasia regression occurred in %60 of cases, in a group where, in addition to oral administration, and still used vaginal swabs with drug - in %83.3 of cases, respectively. Therefore, simultaneous oral and vaginal taking the drug increases the effectiveness of treatment by %30.
5	I.T. Kishakevich, 2003 [19]	44	28 / 28	Antiviral therapy with the drug in the treatment of background Proteflazid® cervical disease provides full recovery of lysozyme activity (Factor specific and nonspecific immune responses) in the blood serum and the content in cervical.
6	I.T. Kishakevich, 2004 [11]	120	45/45	Proteflazid® contributes to the normalization of clinical, laboratory parameters and elimination of HPV in %85.8 of patients, which was confirmed by PCR.
7	O.V. Paliychuk, 2004 [6]	11	11 / 0	In patients with early forms of cervical cancer with the presence of the virus HSV infection and HPV use of combination therapy with antiviral, antimicrobial and immune correcting preparations using Proteflazid® preparation allows for organ-preserving surgery. also recommended the inclusion of the drug in the complex troubleshooting of dysregulation disorders of immune system function and dysfunction of secondary cellular immunity arising during the postoperative period.

8	O.S. Galnykina, 2004 [18]	53	27 / 27	Proteflazid® reduces excess tension and antigenic immunodeficiency, improves processes of anti-oxide system reduces lipid peroxidation, which contributes to the normalization of the pathogenetic mechanisms of disturbed PVI that It is an important pathogenetic treatment. The product allows you to eliminate the failure of the immune system. It is noted that in the 30 hours from the start of treatment was partly overcome shortages of the general population of T lymphocytes (CD3) - 58,3 ± 2,9%, there was a clear trend towards a decrease in T / s CD8 - 23,1 ± 1,7 %, whose number reaches normalization 10 hours. The physiological stabilization of the number of T lymphocytes (CD3) and the normalization of the regulatory index accompanied by the restoration of an adequate reaction of humoral immune B lymphocytes (CD19) -? 9, 5 ± 1, 0%.
9	O.V. Gerashchenko, 2005 [10]	33	21 / 21	The regression of genital warts in the group where Proteflazid® was administrated was observed after 5.7 days after the start of treatment. Complete relief was observed in 16 of 21 patients, in 5 pregnant regression of warts is expressed in reducing the size of formations on the skin and mucous membranes. Relapses or progression of the process was not observed. Patients in the control group in 5 cases out of 12 observed marked recurrence of external manifestations of the disease in the form of re-education warts or the appearance of new lesions.
10	V.V. Bodean 2005 [22]	45	45 / 45	After 8, 10 weeks after treatment in 48% of patients with HPV in samples not determined. The tendency to decrease in the area papillomatous lesions genitals.
11	V.N. Lesovoy,E.V. Yakovlev,2006 [5]	34	20 / 0	The preparation increases the effectiveness of therapy by 15, 17%. Besides, positive effect is more persistent. The risk transmission to sexual partner, as well as the risk of virus-induced neoplastic processes at 47, 50%.
12	N.N. Voloshin et al., 2007[13]	136	136 /136	In pregnant women with HPV infection who took Proteflazid®, the progression of precancerous disease to invasive cancer was not observed which gives reason to stitch for treatment, after completion of the pregnancy.
13	T.V. Gerasimova, O.M. Gopchuk 2007 [17]	150	50 / 0	Proteflazid® in treatment of viral etiology NMC reduces the number of relapses in the case of HPV Infections - 1.5, two times. Proteflazid positive effect on regeneration and function of the reproductive system immunogenesis.
14	I.I.Gorpinchenko, O.V. Romashchenko, 2010 [15]	32	32 / 32	Proteflazid® in %32.2 of women leads to a mosaic-epithelialization of eroded surface, in %24.9 - to complete epithelialization. PCR proven therapeutic effect in 81.3% of cases. Improving health in patients receiving the drug combined with restoration to normal serum IFN, functional titles activity of phagocytic cells, cellular and humoral immunity after treatment.
15	E.I. Liliantsi et al., 2010 [16]	625	307 / 48	Proteflazid® has high efficiency of treatment of vulvovaginal virus associated pathologies (89% vs. 70% of those taking a comparison drug - Panavir).
16	M.G. Romanyuk et al. 2011 [7]	187	108 / 30	In exchange Proteflazid® reception leads to a reduction in the frequency carrier high risk HPV strains as well as improves the results of surgical treatment of penile condylomata in men, reducing the frequency of relapses in 1.5 times (52.8% compared with 35.5% (p = 0.025) in the group not treated with drug) and decreases the degree of dysplasia, recurrent condylomata tissues. A promising course is a combination of oral ingestion and topical application of its solution, which can lead to regression of warts without surgery.

17	O.N. Godlevskaya, A.V. Starover 2012 [14]	32	32 / 32	The combination of systemic and topical drug Proteflazid® as monotherapy cervical disease associated with HPV, helped to reduce viral load to clinically insignificant levels, normalization of the cervix uteri in 68.8% of cases, 31.2% of women had partial regression of the disease. It helps to avoid the destructive treatment or reduce the area of destruction of pathologically altered cervical area, which is especially important in nulliparous woman.
18	V.M.Zaporozhan and et al., 2014 [28]	80	40 / 40	Proteflazid® reduces the viral load in HPV infections to 3,0lg D50, promotes the growth of the number of antigen-presenting cells. Marked strong virostatic and an anti-effect of the drug.
19	R.B. Abdiraimova et al., 2013 [21]	12	12 / 0	It is shown that immediately after the end of treatment in 91.7% (11) cases there was a full clinical recovery. At 3 months after treatment in all patients no relapses were negative PCR results in 83.3% (10) in the absence of clinical signs. Proteflazid® contributes to the elimination of leucopenia and neutropenia and thrombocytopenia, which was confirmed in the picture peripheral blood. Undesirable side effects and allergic reactions to the drug were absent.
20	V.V.Kaminsky, 2015 [29]	76	38 / 38	After a 14-day course of the use of tampons with a solution of Proteflazid® and after 8 weeks of the observation period, there was normalization of the cytological picture or transition of cervical intraepithelial neoplasia of CIN-II (moderate dysplasia) to CIN- I (weak dysplasia), reduces the severity of symptoms of cervical dysplasia of the epithelium, there was significant compared with baseline, the decrease in viral load of HPV DNA. Marked delayed antiviral effect of the drug. The drug eliminates disbiotic state of vaginal micro flora According to immunoassay results there was an increase in the level of local immunity (secretory of IgA - from 1553 to 2234 ug / L; lysozyme - from 26.73 to 45.33 mg / L; the C3 component of complement - to 15.41 to 40.29 mcg / g protein)

According to the immunoassay by the end of the course of treatment Proteflazid® (drops) showed an increase in the level of local immunity (secretory of IgA - from 1553 to 2234 ug / L; lysozyme - from 26.73 to 45.33 mg / L; the C3 component of complement - from 15.41 to 40.29 mcg / g protein) [29].

The main results of clinical observations are shown in Table. 2.

CONCLUSIONS

A systematic analysis of the available literature devoted to the results of preclinical study, indicates the presence of the active ingredient of the drug Proteflazid® **(drops) direct antiviral action against DNA containing HPV. Along with this,** Proteflazid® **(drops) has the ability to enhance the synthesis of interferon, which plays an important role in the indirect antiviral effect of the drug. A systematic analysis of the available literature, devoted to the results of clinical application of the drug** Proteflazid® **(drops), confirmed the antiviral activity of the drug against HPV, confirming the results of preclinical phase of study proves the effectiveness of the drug for diseases caused by HPV in women (including in pregnancy) and male reproductive age. High clinical effect obtained by using drug therapy** Proteflazid® **(drops) in more than 1,500 patients. Safety confirmed by the absence of side effects. Information is based on the results of 20 independent clinical observations coincidence orientation results of the treatment.**

Results from clinical studies indicate that Proteflazid® **(drops) poly drug has** polypharmacological action, namely antiviral, immunocorrective, antioxidant and apoptose modulating that contributes to the achievement of lasting therapeutic effect of HPV eradication, elimination dysbiotic status vaginal microflora, restoration of normal biotope of the genital tract, reduce the frequency of relapses and HPV infection, as well as normalization of cervical status, reduction of proliferative activity of tumors that allows for conserving therapy in the reproductive part of the population as a guarantee of future parenthood.

The Proteflazid® **(drops) in the local,** intravaginal therapy normalizes the cytological picture and promotes the transformation of cervical intraepithelial neoplasia from CIN-II (moderate dysplasia) to CIN-I (low dysplasia), reducing the severity of symptoms of cervical dysplasia epithelium, contributing significant at compared with baseline, a decrease in viral load of HPV DNA.

Proteflazid® **(drops) in the treatment of diseases associated with the PVI contributes to the normalization of clinical and laboratory indices and the elimination of HPV more than 3,6lg in %80 of patients, which was confirmed by PCR.**

The efficacy of Proteflazid® **(drops) at the stage of preconception preparation of infected women to pregnancy and reducing the incidence of perinatal complications gestational period. For a long time the drug was not pregnant adverse reactions were registered.**

Given the high efficacy and safety of drug Proteflazid® **(drop) in the treatment of PVI, its use is justified and implemented in a number of guidelines and newsletters in Ukraine and abroad [-23 34 ,30 ,29 ,26].**

Proteflazid®: efficacy and safety in clinical practice for diseases caused by human papillomavirus (systematic review) ***V.V. Kaminskyy, M.N. Shalko, L.I. Vorobyova ,O.V. Romaschenko, O.I. Grynevych***

Systematic review is devoted to the analysis of specific activity, safety and efficacy of the medicinal agent Proteflazid® (drops) in conditions of preclinical investigation and at the stage of clinical observation, in case of diseases caused by human papilloma virus. Independent clinical data (more than 1500 patients participated) is substantiated and reflected in 20 scientific literary sources that could be compared by goals to results of conducted treatment, and confirm antiviral influence of medicinal agent regarding human papilloma virus.

Key words: *Proteflazid®, human papilloma virus, specific activity, safety, efficacy.*

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