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Comparative efficacy and safety of Proteflazid® suppositories and drops in patients with cervical dysplasia caused by HPV infection

Data of phase II clinical study of comparative efficacy and tolerability of Proteflazid® suppositories (Pharmex Group LLC) and Proteflazid® drops (Fitofarm PJSC) in patients with cervical dysplasia caused by HPV infection have been presented. High therapeutic efficacy of Proteflazid® suppositories comparable to that of Proteflazid® drops have been demonstrated. Proteflazid® suppositories can be recommended as an effective and safe agent for the treatment of this group of patients.

Key words: *Proteflazid®, suppositories, drops, human papillomavirus (HPV) infection, dysplasia of cervical epithelium.*

Introduction

In obstetric-gynaecological and urological practice, diseases caused by human papillomavirus (HPV) are one of the most important problems. The clinical manifestations, diagnosis of various forms of papillomavirus (HPV) infection, and tactics of managing such patients are contradictory and non-standardized, primarily due to the lack of agents that have direct antiviral effects on HPV. The tendency of unreasonable, sometimes aggressive treatment of women infected with HPV in recent years often leads to long-term complications, relapses of the disease, especially during pregnancy (Voloshyna N.N., 2006; 2007; Voloshyna N.N. et al., 2007).

A common treatment in the presence of PVI clinical manifestations is the surgical method, including electrocoagulation, cryodestruction, etc. For therapeutic purposes, agents causing chemically induced necrosis of (HPV) infection exophytic manifestations are also used for HPV. To prevent recurrence of the disease, recombinant forms of interferons, inducers of endogenous interferon, ointments with antiviral agents are currently used. Nevertheless, a stable clinical effect cannot be achieved in all patients (Radionov V.G. et al., 2002; Voloshyna N.N., 2007).

In order to suppress HPV replication, antiviral agents must be used, one of which is Proteflazid® in the form of suppositories (Pharmex Group LLC) – an active antiviral agent with immunotropic properties, whose active substance (flavonoids) inhibits the synthesis of viral DNA and RNA in infected cells due to inhibition of activity of virus-specific RNA and DNA polymerases, thymidine kinase and reverse transcriptase. The product promotes the synthesis of endogenous alpha- and gamma-interferons to a physiologically active level (without refractivity), which increases local non-specific resistance to viral and bacterial infections. Clinical studies have shown that the use of Proteflazid suppositories promotes the restoration of the protective function of the vaginal and cervical mucosa due to the normalization of local immunity factors (secretory IgA – sIgA, lysozyme and C3-complement component). The active substance of the product has been shown to have specific antiviral activity and inhibit HPV reproduction in experimental models of oncogenic HPV *in vitro*. Cytological studies demonstrated inhibition of HPV proliferative and destructive effect on cells under the influence of the product.

With genital herpes, the use of suppositories Proteflazid® prevents emergence of new rash elements, reduces the likelihood of dissemination and visceral complications, accelerates healing of damaged areas; with vaginosis, vaginitis and inflammatory diseases of the cervix – it promotes restoration of local immunity and faster and more effective elimination of the pathogen. Proteflazid® in the form of suppositories possesses antioxidant activity, inhibits the course of free radical processes, thereby preventing accumulation of products of lipid peroxidation, enhancing the antioxidant status of cells. The product is a modulator of apoptosis, enhancing the effect of apoptosis inducing factors, namely, activating caspase-9, contributes to faster elimination of virus-infected cells and primary prevention of the onset of chronic diseases against latent viral infections.

During the clinical study Phase I of Proteflazid® in the form of suppositories, the staff of the Reproductive Function Rehabilitation Department of the Institute of Paediatrics, Obstetrics and Gynaecology of the National Academy of Medical Sciences of Ukraine assessed the efficacy and tolerability of the product in 30 patients with genital herpes in remission phase. Following treatment there was a decrease in IgG level of the virus, sag, an increase in the levels of lysozyme and C3-complement in the cervical mucus of patients, which indicated an increase in both general and (at the local level) immunological resistance of the body. There was a good tolerance of the product, without any serious side effects and negative changes in laboratory parameters and objective examination findings.

The purpose of this study is to compare the efficacy and tolerability of Proteflazid® in the form of suppositories (Pharmex Group LLC) [hereinafter referred to as the investigational product – IP] and Proteflazid® in the form of drops (Fitofarm PJSC) [hereinafter referred to as the reference product – RP] in patients with cervical dysplasia (CD) caused by HPV infection.

Object and methods of the study

A clinical, randomized, open, controlled, parallel-group phase II study involved 76 patients aged 18-50 years with CD caused by PVI, who were hospitalized in the department of reproductive and endocrine gynaecology of the Kyiv Municipal Centre for Reproductive and Perinatal Medicine.

The participants underwent:

- clinical examination;
- complete blood count;
- urinalysis;
- blood biochemistry;
- bacteriological and bacterioscopic examination of material from the

cervical canal (CxC), urethra and vagina;
- detection and typing of HPV DNA in smears-scrapes from CxC/cervix uteri (CU) by polymerase chain reaction;
- Pap cytological examination of smears from CxC/CU with determination of coilocytosis;
- evaluation of local immunity parameters at the end of the course of treatment (sIgA, lysozyme, C3-complement component);
- colpocervicoscopy with determination of colpocervicoscopic signs of cervical dysplasia.

The cytological picture of the smear of patients corresponded to class I-II of CIN (cervical intraepithelial neoplasia), or mild/moderate CD. All participants had DNA of high-risk HPV in smears-scrapings from CxC/CU epithelium by polymerase chain reaction, coilocytosis. In women of reproductive age, the negative result of the pregnancy test was received. The subjects had to avoid sexual contact during the study period. An informed written consent of each patient to participate in the study was obtained.

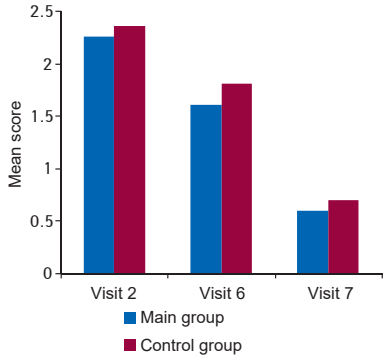
The subjects were divided into two statistically homogeneous groups (n = 38 in each group), comparable in age, gynaecological history, cytological examination of the CU smear and cervical smear, local immunity parameters and colposervicoscopy findings. The groups were statistically compared in terms of hemodynamic parameters and body temperature.

After normalizing the vaginal biotope (if necessary), the patients of the 1st (main) group were administered IP by inserting deep into the vagina after performing hygienic procedures 2 times a day; it was recommended to start treatment immediately after menstruation. The subjects of the 2nd (control) group used RP in the form of vaginal tampons with the product solution (for the preparation of 3.0 ml (72-75 drops) solution of the product diluted in 20.0 ml of physiological solution, exposure time 30-40 min 2 times a day).

The course of treatment was 14 days, the follow-up period, during which the subjects should report possible adverse reactions, as well as cases of relapse of the disease, was 8 weeks.

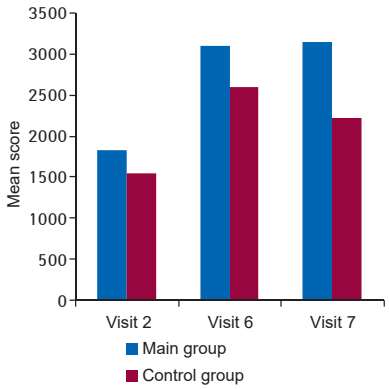
The state of CxC and CU epithelium was the main variable of treatment efficacy evaluation, according to the cytological study by the end of the course of treatment; secondary variables – CxC and CU epithelium, according to the cytological study by the end of the follow up period, the level of HPV viral load at the end of the course of treatment and follow up period; severity of colposcopic/colpocervicoscopic HPV signs by the end of the course of treatment and the follow up period, level of local immunity parameters by the end of the course of treatment (sIgA, lysozyme, C3-complement component).

Fig. 1



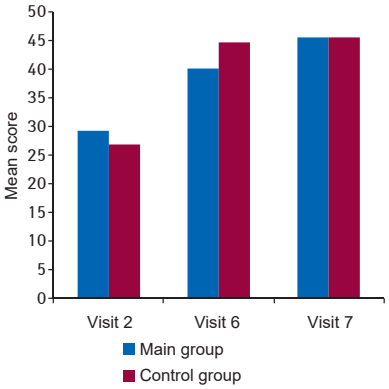
Dynamics of the level of HPV DNA viral load in the groups

Fig. 2



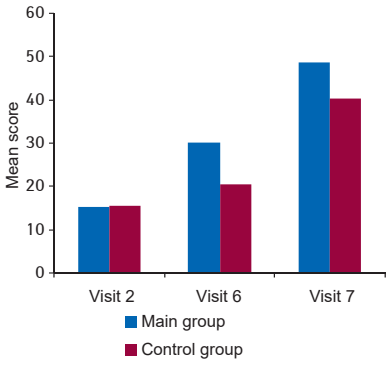
Dynamics of sIgA level in the groups

Fig. 3



Dynamics of lysozyme in the groups

Fig. 4



Dynamics of C3-complement component in the groups

Results and their discussion

All subjects underwent a full course of treatment for 14 days.

Dynamics of the level of HPV DNA viral load in groups is shown in Fig. 1, local immunity parameters – in Fig. 2-4. Based on the analysis, a conclusion was made about a significant reduction in the level of HPV DNA viral load and a significant improvement in local immunity parameters in both groups.

In both the main and control groups, there was a significant improvement in colposervicoscopy in most cases.

Treatment was found to be effective in 38 (100.0%) patients in the main group and 35 (92.11%) patients in the control group. Based on the data of Table 1 it was concluded that the groups did not significantly differ in the efficacy of treatment.

The conclusion about non-inferiority of the IP compared to the RP in this category of patients is made on the basis of confidence intervals (CI) (Table 2). Given the fact that the lower limit of 95% CI (- 9.18%) is greater than the lower limit of the zone of non-inferiority (-20%), it is concluded that the IP is not inferior to the RP.

Significant differences in the assessment points for the dynamics of HPV DNA viral load levels and local immunity parameters between the groups were absent throughout the study period.

The hemodynamic parameters and body temperature of the participants in both groups did not change significantly during the study.

According to the statistical analysis results, it was concluded that in both groups, in most cases, there were no statistically significant differences in the majority of the test parameters of complete blood count and blood biochemistry, as well as urinalysis before and after the course of treatment.

Serious adverse reactions and cases of early termination of participation in the study due to adverse events were not reported.

Table 1 Distribution of patients by efficacy categories

Efficacy of the product	Group			
	Main (n = 38)		Control (n = 38)	
	Frequency	%	Frequency	%
Effective	38	100.0	35	92.11
Lack of efficacy	–	–	3	7.89

Table 2 Limits of 95% CI for the difference in the proportion of positive results

Statistical parameters	Value
Type I error probability, α	0.025
Percentage point of standard normal distribution for α	1.96
Zone of non-inferiority (δ), %	–20
Proportion of positive outcomes for the main group, %	100.0
Size of the main group	38
Proportion of positive outcomes for the control group, %	92.11
Size of the control group	38
Difference of proportion, %,	7.89
Lower limit of 95% CI	–9.18
Upper limit of 95% CI	9.18

Conclusions

1. The IP is highly effective and not inferior to the RP when used in patients with cervical dysplasia caused by HPV infection.

2. By the end of the course of treatment with the IP, normalization of the cytological picture or transition of cervical intraepithelial neoplasia from CIN-II (moderate cervical dysplasia) to CIN-I (mild cervical dysplasia).

3. After treatment with the product, an 8-week follow up period showed:

- a decrease in the severity of cervical dysplasia signs (leucoplakia, punctuation, acetowhite epithelium, mosaic, atypical transformation zone);
- improvement of the cytological picture (decrease of leukocytosis, coilocytosis, dyskeratocytes);
- significant as compared with the baseline, increase in the level of local immunity parameters (no significant differences between the groups for all local immunity parameters in all evaluated points);
- significant reduction in HPV DNA viral load, as compared with the baseline, especially after the 8-week follow up period, which indicates the delayed antiviral effect of the products (no significant differences between the groups in terms of the level of HPV DNA viral load in all evaluated points).

4. Both drugs showed good tolerability, but the IP suggested a more convenient dosing regimen, unlike the RP, which, with the same frequency, required time to prepare the desired dilution and a tampon.

Thus, Proteflazid^{E} in the form of suppositories (Pharmex Group LLC) can be recommended as an effective and safe antiviral agent for treatment of gynaecological diseases caused by HPV infection.

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Summary. *Data of phase II clinical study of comparative efficacy and tolerability of suppositories and drops Proteflazid® in patients with cervical dysplasia caused by HPV infection has been presented. It was shown the high therapeutic effectiveness of suppositories Proteflazid® comparable to that of drops Proteflazid®. Suppositories Proteflazid® can be recommended as an effective and safe agent for the treatment of this group of patients.*

Key words: *Proteflazid®, suppositories, drops, human papillomavirus infection, dysplasia of cervical epithelium.*

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