Antiviral effect of isoprinosine in HPV-associated diseases

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Objectives. To determine an antiviral efficiency of isopronosine in HPV-associated diseases, and adverse effects of Isoprinosine depending on different patients' age population.
Subjects and methods. Comparative analysis of results of 5650 patients with HPV-associated gynecological diseases, collected by 352 physicians from 33 cities of Russian Federation by standardized scoring system of main clinical and laboratory parameters (patient complaints, lesions and PCR DNA HPV testing) before and after isoprinosine treatment in mono and combined with routine methods depending on different patients' age population.
Results. There was a spontaneous elimination of HPV particles in 22.6% cases after 6 months follow up period in non-treated women, while HPV negative results were obtained in 35.5% cases after routine treatments, in 54.8% cases – after isoprinosine mono-treatment and in 84.2% - after Isoprinosine combined mode. There was significantly decreased degree of patient complains and remaining lesions after combined mode of isoprinosine than analogous parameters of both other treatment groups. Main adverse effects of isoprinosine were related with digestive system complains in young patients and skin (dryness and rash) in older women. The first time it was registered complains on a pain in joints in 2 patients above 46 years.
Conclusion. Regression of HPV-associated diseases with significantly decreased degree of patients complains and remaining lesions, as well as elimination of viral particles were demonstrated after treatment with combined mode of isoprinosine in comparison with both routine treatments and Isoprinosine mono-treatment options. Antiviral effects of isoprinosine can be related with activation of lymphocytes subsets, are responsible for the host antiviral defense, and synergistic action of different treatment modalities of HPV.

Keywords

Human papilloma virus **isoprinosine** **lymphocytes**

Under HPV-associated diseases understand the development of visible pathological formations on the skin or mucous membranes in the form of genital warts, papillomas and other diseases.
At the same time, pathognomonic signs for these conditions are cytohistological changes characteristic of cells transformed by the human papillomavirus (HPV).
Summarized literature data indicate the insufficiently high efficiency of traditional methods of treatment (TML) in the clinical manifestation of HPV infections [11, 19], since HPV affects the cells of the basal layer and during surgery, remove or it is not always possible to destroy all the affected cells, which leads to the persistence of HPV and the recurrence of the disease. Therefore, a search is underway for new agents for antiviral immunotherapy and therapeutic and prophylactic vaccination against HPV [10].

Based on the concept of choosing the optimal adjuvant immunotherapy [3], isoprinosine (IPD) was chosen as a suitable immunomodulator, which is a synthetic analogue of natural purine, has anti-inflammatory, anabolic, metabolic, antihypoxic, antiarrhythmic and immunomodulatory properties, takes part in the regulation of many physiological processes in body. In turn, IPD, thanks to the auxiliary component, acquires antiviral and immunomodulatory effects due to increased accessibility to lymphocytes. According to the literature, cases of serious side effects of PPI are not described, despite the almost 40-year period of its use.

Systematic reviews and meta-analysis [1, 2] served as a prerequisite for planning this study. It has been shown that despite the apparent superiority of the combined use of IPD with TML, there is a

high variability in the results presented. In addition, the mechanism of high efficiency of the combined HPV treatment remains unexplored.

Based on the foregoing, the aim of the study was to evaluate the antiviral efficacy of IPD in HPV-associated diseases, as well as to study the possibility of side effects after taking the drug, depending on the age of the patients.

Material and research methods

Project design
For this work, an individual registration card (IRC) was developed, according to the criteria of standard protocols for clinical trials. The CRF

recorded the name of the project, doctor's name and patient identification data (full name, outpatient card number), demographic data (age, gender, etc.), detailed description of the dose of IPD, concomitant course of TML, cases of side effects, conclusion about the state of health patients, the condition of the skin and external and internal genital organs before and after treatment. Full informing of patients about the upcoming treatment plan with the use of IPD, familiarization with the benefits and possible side effects of the drug. At the same time, IPD was prescribed at the rate of 50 mg/kg of body weight for 10 days in mono mode (IPZ-mono) or against the background of TML in combined mode (IPZ-combi).

Doctors participating in the project were instructed on the use of the drug, received detailed instructions on what to look for when studying the anamnesis of life and illness of patients in order to exclude the presence of contraindications to the use of the drug. According to the indications , it was planned to determine the concentration of uric acid and transaminases (ALT/AST) in the blood.

The inclusion criteria for the study were: clinical manifestation of HPV in the form of condylomas, papillomas and/or other pathological changes in the skin and mucous membranes associated with HPV in patients older than 16 years; the presence of complaints of rash and discomfort in the anogenital region and urethra; the presence of HPV-positive results , regardless of the absence of complaints; availability of a document on the informed consent of patients for the proposed treatment.

The exclusion criteria were: the presence of oncological and severe somatic diseases (including rheumatoid arthritis and gout); pregnancy and lactation; contraindications to IPZ; use by the patient during the last 6 months of any immunotropic agents (immunomodulators, immunostimulants, immunosuppressants, regardless of the method of application systemically or topically).

The exclusion criteria from the study were: individual intolerance identified during treatment; the development of side effects that threaten the life of the patient; self-cessation of treatment; non-attendance at the appointment with the doctor and the inaccessibility of the patient; ignoring the patient's doctor's instructions for the use of the drug.

Sampling was carried out according to the "principle of typical cases" in connection with HPV infection. When choosing a treatment method, physicians were advised to randomize patients with severe clinical manifestations of HPV, both with typical manifestations and in the form of cervical pathology (IPD-combi or TML), when there were indications for TML. At the same time, randomization was carried out as follows: the first patient was prescribed IPD-combi, and the second patient was assigned TML, or vice versa.

With the manifestations of HPV-associated ano/uro/genital diseases in the form of small dispersed condylomas, cervical pathology with mild cervical intraepithelial neoplasia and other similar conditions of the external genital organs , IPZ-mono was prescribed when patients insistently asked to prescribe this drug to them.
The exception was the cases of prescribing IPT-mono when HPV was manifested in a subclinical form with the presence of severe subjective symptoms. However, in the CRF (in the protocol), the treatment of subclinical HPV and latent HPV was not recommended.

The diagnosis of diseases of the external genitalia, urethra and perineum was established by a thorough visual examination, and, if necessary, using magnifying devices (colposcope or magnifying glass), as well as samples (acetoacetic test and Schiller test).
Further, the diagnosis was confirmed by cyto-histological examination of scrapings and biopsies from the affected areas.

A protocol for external examination and colposcopy was developed, according to the International Colposcopic Classification, updated by the International Association for Cervical Pathology and Colposcopy in 2003. At the same time, the diagnosis was consistent with the statistical classification of diseases and problems associated with reproductive health (ICD-X). Cytological classification was performed according to Bethesda and CIN, since the laboratories used in the results of cytological analyzes mainly the terminology "CIN" and "dysplasia".

From February to March 2010, 10,000 CRFs were distributed among 500 physicians in various regions of the Russian Federation (Fig. 1). In July 2011, after 1 year and 3 months, 6,000 CRFs were received from 352 doctors from 33 cities of the Russian Federation. Of these, 294 doctors were obstetrician-gynecologists, 56 doctors were dermatovenereologists, and 2 doctors were practicing immunologists. The practitioners involved in our project worked in the outpatient departments of both public and private institutions.

Figure 1. *Design of a multicenter project to study the effectiveness of the IPP* .

During the preparation of primary materials for statistical processing, 350 CRFs from 32 physicians were excluded from further analysis due to violations of the study protocol or in accordance with the "exclusion from the study" criterion. Consequently, the results of 5650 CRFs from 320 practitioners were subjected to statistical processing (Fig. 1).

Method of analysis
To evaluate the effectiveness of the method of treatment in the CRF were registered: complaints before and after treatment; careful description of visual data and recording of the results of laboratory studies (description and photographing of altered areas or warts) before and after treatment; PCR DNA HPV testing before and again after 6 months during follow-up; compliance with all points of the design of the study and the plan of therapeutic measures.

A scoring system for evaluating the effectiveness of treatment was also developed based on a comparative analysis of complaints and general well-being of patients, objective visual manifestations of the disease, as well as the results of HPV DNA testing before and after treatment with IPD (Table 1).

At the same time, the processing of the results of HPV DNA tests was carried out as follows: HPV-negative case as 0, and HPV-positive case as 1 point. It is generally accepted that a negative HPV DNA result on repeat testing after treatment is indicative of HPV clearance.

Table 1 . *A scoring system for assessing the effectiveness of treatment based on a comparative analysis* of disease parameters before and after treatment.

With regard to the reduction or disappearance of complaints as a result of treatment, a scoring system from 1 to 3 was used, respectively, the absence of complaints was assessed as 1 point, partial reduction - as 2 points, persistence of complaints - as 3 points. Papillomatous lesions of the vulva, anogenital region, and urethra were recorded at each examination and photographed whenever possible. During the analysis, photographs were compared or numerical data were calculated to determine the size of the residual lesions and the percentage reduction in the size of the lesion after treatment from the original area. On this basis, if the area did not change, the residual effects were considered as 100%, with a slight decrease - as 75%, with a decrease by half - as 50%, with a significant decrease - as 25%, and with no - as 0%.

Analysis materials
At the first stage, subjective and objective symptoms of HPV-associated pathological processes of the mucous membrane and skin of the urogenital and perianal areas were analyzed depending on the type of therapeutic effect and the age composition of the patients in the general population. Due to the vastness of the material, the assessment of the antiviral efficacy of the IPP was carried out in stages on representative samples for each analyzed parameter of the same type. At the same time, the effectiveness of treatment of HPV-associated diseases was compared in terms of the degree of elimination of complaints of itching and discomfort (TML, n=689; IPV-combi, n=1066; IPV-mono, n=818), by the area of regression of macroscopic changes (TML, n=224; IPZ-combi, n=240; IPZ-mono, n=200).

Further, the side effects were analyzed according to the results of treatment of patients who took IPD in both mono and combined regimens. The results were presented in absolute terms with an analysis of the frequency and nature of the manifestation of symptoms associated with the gastrointestinal tract (GIT) or changes in the skin, depending on age.

At the second stage, the antiviral efficacy of IPD in HPV-associated diseases of the cervix was analyzed in 120 patients according to the results of the HPV DNA test. To analyze the results of the PCR DNA HPV test, the sample size (number of patients for each group) was also preliminarily calculated. Then, 30 IRCs from each group were selected from the total mass by the method of "simple random sampling", patients who had positive results of HPV tests during the initial analysis and after 6 months were re-examined. At the same time, the selection of cards was carried out by an outside assistant who did not know the results of repeated PCR HPV DNA tests.

Statistical analysis Statistical analysis
was performed by blinding the meta-analysis expert (Dr. Ioannis Cosmas, Ioanina University, Greece) and his assistants. At the same time, the data of 3 groups according to subjective and objective parameters and 4 groups according to the PCR DNA HPV test were compared.

Statistical analysis was performed using one/two-way analysis of variance.
At the same time, "one way ANOVA and Tukey-Kramer test for Multiple Comparisons" was used to identify differences between the indicators of compared groups, and "two way ANOVA and Bonferroni post test for Multiple Comparisons" was used to identify differences between indicators of age subgroups. An analysis was made of the interaction of intragroup factors with each other. Differences were considered significant at $p<0.05$.

Research results and discussion

Patients by age groups were distributed as follows: the number of patients under 20 years old was 714; from 21 to 25 years old - 1410; from 26 to 30 years old - 1266; from 31 to 35 years old - 928; from 36 to 40 years old - 566; from 41 to 45 years - 396; from 46 to 50 years - 184; from 51 to 55 years - 93; from 56 to 60 years old - 68; from 61 to 65 years old - 19 and over 66 years old - 6 people.

The latent course of HPV infection was registered in 836 patients based on PCR HPV DNA tests and clinical studies. Various manifestations of HPV in the form of rashes (genital or flat condylomas) in the area of external ano/uro/genital organs, vagina and cervix were found in 2061 patients. Of these, 812 patients were found to have combined viral infections (HSV1/2, CMV) with HPV-associated diseases.

Gynecological examination revealed ectopia in 1621 patients, eroded ectropion with cervical deformity in 281 women, true erosion in 39 patients, cervicitis and endocervicitis in 516 women, cervical canal polyps in 53, vulvovaginitis in 88, and vulvovaginitis in 155. colpitis with the identification of various infectious agents: 80 - chlamydia and 13 - candidiasis. Bacterial vaginosis was found in 25 patients.

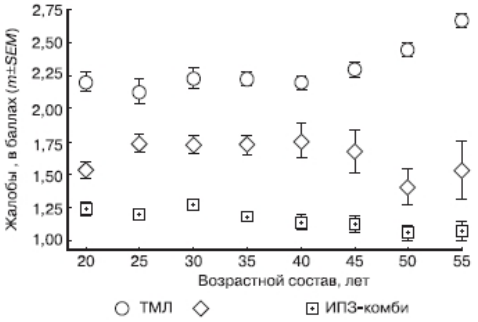
Based on cytological, colposcopic and pathomorphological studies, 506 patients were diagnosed with cervical intraepithelial neoplasia (CIN). It should also be noted that 390 women had leukoplakia and 232 patients had dysplasia of the stratified squamous epithelium of the cervix.

The following are the results of the analysis in relation to the regression of subjective and objective symptoms of the disease, as well as the incidence of side effects during the 6-month follow-up, depending on the age of the patients, supplemented by the analysis of HPV elimination in a limited cohort of patients.

I. Results of the analysis of subjective and objective symptoms and side effects
During the study, a disproportionate increase in the combined method of treatment was noted, which is explained by the desire of the majority of both practitioners and patients to achieve a better treatment result, which is also reflected in systematic reviews of domestic literature [1, 2, 4].

Statistical analysis of the interaction of intragroup factors showed the absence of both the influence of age on the effectiveness of the IPD, and their interaction in relation to both (subjective and objective) parameters within the groups.

Рис. 2. Динамика снижения жалоб на зуд или неприятные ощущения у пациенток с клинической манифестацией ВПЧ-ассоциированных заболеваний слизистых оболочек и кожи



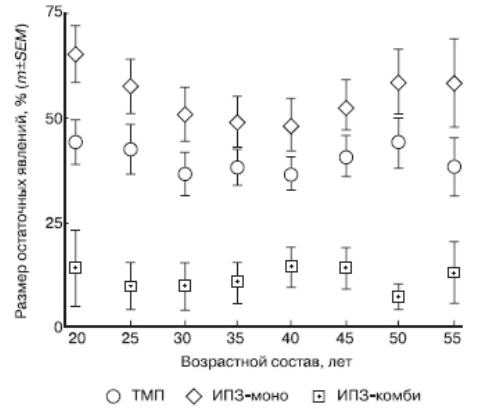
Примечание:
ТМЛ – традиционные методы лечения;
ИПЗ-моно – назначение ИПЗ в моно режиме;
ИПЗ-комби – назначение ИПЗ в комбинированном режиме

The results of the analysis indicate a significant decrease in itching and discomfort
from the initial basal level by the time of repeated examinations in all patients, regardless of their age in all groups (Fig. 2). At the same time, there was also a significant decrease in the frequency of complaints after the combined use of IPD (IPZ-combi) compared with similar indicators (Table 2) both with the use of TML and with the use of IPD in mono mode (IPZ-mono) in all age groups ($p < 0.05$). It should be noted that women in the older age groups (over 45 years) showed a difference between all methods of treatment ($p<0.05$).

Table 2. *Significance of difference (p) in the degree of elimination of complaints (LV) and regression of macroscopic changes (RMI) between the results of traditional methods of treatment (TML), the use of IPT-mono and IPT-combi regimens, depending on the age of patients.*

The results of a visual assessment of the decrease in the area of HPV-associated pathologically altered areas of the cervix, mucous membranes and skin of the urogenital, anal and perianal areas, as well as the perineum after their treatment by various methods with and without the use of IPD (Fig. 3) indicate that the most significant improvement has come after combined treatment (Table 2) compared with the use of IDA in mono mode ($p<0.001$). The results of using TML turned out to be more effective than those of IPD-mono ($p<0.001$) and lower than those of IPD-combi ($p<0.001$).

Рис. 3. Размер остаточных (визуальных макроскопических) явлений у пациенток с клинической манифестацией ВПЧ-ассоциированных заболеваний



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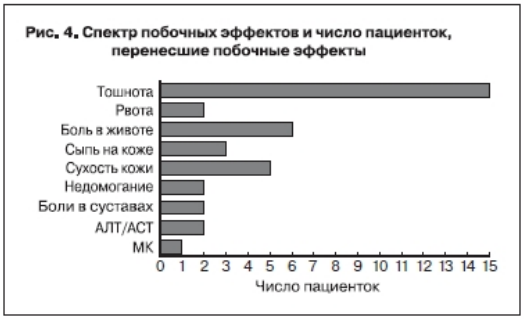
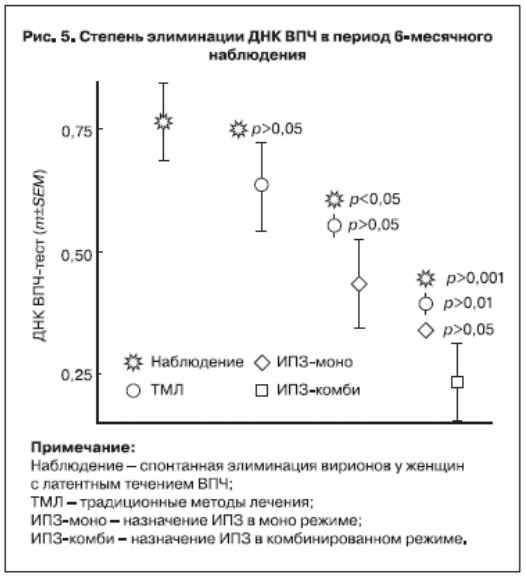
A comparative analysis of the frequency and nature of side effects was performed depending on the age of the patients. The data obtained indicate that side effects were recorded in 38 patients treated with IPD in both combined and mono modes (Fig. 4). However, they did not cause severe disorders in patients, and the patients continued treatment.



The analysis of side effects indicates that they were mainly associated with gastrointestinal symptoms or the presence of dryness and / or rash on the skin. At the same time, in women younger than 25 years, side effects were noted, mainly associated with symptoms of dysfunction of the gastrointestinal tract, rather than symptoms associated with the skin (14 vs 3), while in women older than 46 years, dryness of the skin prevailed (5 vs 0). In 2 women in the age groups over 46 years, pain in the joints was noted.

II. Results of the analysis of the results of PCR DNA HPV testing

The results of 120 observations distributed evenly in 4 groups were analyzed. The observation group included 30 HPV-positive women with a latent course of HPV infection, who after 6 months were re-analyzed for HPV DNA PCR, their results served to assess the spontaneous elimination of HPV. Then, 30 CRCs were selected from HPV-positive women with clinical signs of HPV-associated diseases of the cervix, who were treated with TML, IPD-mono and IPD-combi for pathologies of the cervix, who, 6 months after the end of the course of treatment, also underwent re-evaluation of the PCR DNA HPV test (Fig. 5).



After 6 months, in women with latent HPV, the results of repeated HPV DNA PCR analysis were positive in an average of 77.4 ± 0.08% of cases with a 95% CI from 61.8 to 93.0%, in women after TML - 64, 5 ± 0.09% of observations with 95% CI from 46.7 to 82.4%, in patients after IPD-mono - 45.2 ± 0.09% with 95% CI from 26.6 to 63.7%, in women after IPD combi - 25.8±0.08% with 95% CI from 9.5 to 42.1%.

Analysis of the results shows that the use of both IPV-mono and IPD-combi contributes to a significant elimination of HPV ($p<0.05$ and $p<0.001$, respectively) compared with the same indicator of spontaneous elimination of HPV in the observation group. At the same time, the use of IPV-combi contributes to a significant decrease in DNA HPV-positive results compared to the same indicator for TML ($p<0.01$).

It should be noted that our results are consistent with the data of Tay [18], who showed a regression of subjective and objective symptoms after the use of inosine pranobex compared with placebo control in the subclinical course of HPV-associated vulvar infections. Subsequently, similar results were presented in numerous studies by domestic and foreign authors [1–4, 8]. However, the mechanism of HPV elimination and CIN regression remains unclear.

It is known that initially IPP was developed as an antiviral agent. For example, Ohnishi et al. [13] demonstrated that PPI, having penetrated into infected lymphocytes, inhibits the synthesis of viral mRNA, while in normal lymphocytes, on the contrary, it accelerates the expression of both RNA and mRNA. It follows from this that IPD, on the one hand, blocks the reproduction of virions by inhibiting viral mRNA in infected cells, and, on the other hand, supports the function of lymphocytes by activating RNA synthesis and the translational ability of lymphocytes. This phenomenon may provide an interpretation of the clinical observations of Coleman et al. [6] in relation to regressing condylomas, which showed that such formations contain more cytotoxic subpopulations of lymphocytes (CD8+T cells), helper subpopulations (CD4+T cells) and macrophages compared to non-regressing condylomas. At the same time, CD4+ T cells infiltrated the stroma and the epithelial layer of cells with a violation of the ratio of CD4+ and CD8+ T cells and high activity of lymphocytes due to increased expression of markers of predominantly "antigen binding" phenotypes. Further, Scott et al. [16], demonstrating in 7 patients the expression of cytokines by lymphocytes (CD4+ cells) of the Th1 type, when interferon gamma (IFN-γ) is predominantly expressed even in the absence of interleukin-4 (IL-4) secretion, we concluded that such a cytokine secretion profile is a precursor to HPV elimination - infections. In addition, Song et al. [17] based on observations of regression of HPV lesions in IFN-γ-

positive patients for 12 months concluded that the presence of IFN-γ inside the affected areas can be a predictor of high-risk CIN elimination. that such a profile of cytokine secretion is a precursor to the elimination of HPV infection. In addition, Song et al. [17] based on observations of regression of HPV lesions in IFN-γ-positive patients for 12 months concluded that the presence of IFN-γ inside the affected areas can be a predictor of high-risk CIN elimination. that such a profile of cytokine secretion is a precursor to the elimination of HPV infection. In addition, Song et al. [17] based on observations of regression of HPV lesions in IFN-γ-positive patients for 12 months concluded that the presence of IFN-γ inside the affected areas can be a predictor of high-risk CIN elimination.

Literature data indicate that the cytotoxic subpopulation of lymphocytes (CD8+T cells) is an important mediator of protective immunity against HPV infection, and another subpopulation - helpers (CD4+T cells) is the key one in relation to HPV-associated CIN. Thus, CD4+ T cells accumulate during spontaneous elimination of skin warts and genital warts. These assumptions have been confirmed in observations with the development of flowering warts, papillomas and condylomas, as well as the progression of HPV-associated diseases in patients with acute CD4 + T cell deficiency in immunosuppression and immune reconstruction syndrome, as well as with the development of severe HIV infections [5, 7, 9, 12, 14, 15].

Summarized literature data suggest that CD4+ and CD8+ T cells are key players in the control of HPV-associated mucosal and skin lesions. In general, patients with severe CIN usually show a decrease in the concentration of circulating CD4+ T cells in the peripheral blood, and an increase in the number of these cells after antiviral therapy correlates with spontaneous regression of HPV-induced CIN in patients with HIV.

In the future, the mechanism of action of PPIs in relation to local HPV-associated lesions is apparently associated with the ability of these subpopulations of lymphocytes (CD4+ and CD8+) to migrate from the bloodstream to the epithelium through antigen stimulation, and the development of severe CIN and cervical cancer was associated with insufficiency in the formation of stable specific helper (CD4+) and cytotoxic (CD8+) antigenic responses against Th1 HPV type.

Surgical intervention appears to be the key factor stimulating the migration of lymphocytes and peripheral blood mononuclear cells into the lesion. This can interpret the well-known phenomenon of "synergism" of various methods in the treatment of HPV-associated diseases. Therefore, the mechanism of high efficiency of the IPV combi is explained by the "preliminary preparation" of immunocompetent cells that rush into a fresh surgical wound and eliminate the remaining infected HPV cells.

Thus, the results of this multicenter study allow us to conclude that IPD has an antiviral effect, which is reflected in a critical decrease in the manifestation of HPV-associated diseases (subjective and objective symptoms), a decrease in the frequency of HPV-positive tests after a course of treatment with this drug compared with similar TML parameters. This may be due to the synergism of the surgical method of treatment with adjuvant immunotherapy for IPD. The mechanism of the antiviral effect of IPD may be associated with the activation of a subpopulation of lymphocytes responsible for the antiviral defense of the body.

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