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EFFICACY OF GENERIC DRUG WARTOCID® (IMIQUIMOD 5% CREAM FOR EXTERNAL USE) IN ANOGENITAL WARTS TREATMENT

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Abstract. *Aim.* To evaluate the efficacy and safety of the generic drug Wartocid® (Imiquimod cream 5% for external use) in patients with external anogenital (venereal) warts (AGW). *Materials and methods.* The single-blind comparative, randomized, placebo-controlled clinical trial included 50 women aged 18 to 60 with an established clinical diagnosis of AGW in the vulva and perianal region. Patients in group 1 received placebo cream for external use, while patients in group 2 received therapy with Wartocid in a daily dose of 10 mg cream/cm^2 of skin area. The drug was applied every other day until the complete disappearance of AGW, but in any case, not more than 16 weeks. A follow-up was carried out for 4 more weeks. The study evaluated the dynamics of subjective and objective symptoms, the presence and the frequency of relapses, and the percentage of full treatment of AGW. *Main results.* Treatment with Wartocid resulted in a complete cure of AGW in 16% of patients, and a reduction in the focus area of AGW in 36% of patients. Against the background of the placebo no dynamics of the disease were reached. Neither serious adverse events nor clinically significant changes in blood tests, urine or serum biochemical parameters in any of the patients who received treatment with Wartocid were observed. *Conclusion.* The generic drug Wartocid has been proved to be effective and safe for AGW treatment and its effectiveness is similar to the original drug Aldara® (Imiquimod cream 5% for external use).

Key words: *Imiquimod, Wartocid, clinical trial, efficacy, safety, external anogenital (venereal) warts.*

ЭФФЕКТИВНОСТЬ ВОСПРОИЗВЕДЕННОГО ПРЕПАРАТА ВАРТОЦИД® (ИМИХИМОД 5% КРЕМ ДЛЯ ВНЕШНЕГО ИСПОЛЬЗОВАНИЯ) В ЛЕЧЕНИИ АНОГЕНИТАЛЬНЫХ БОРОДАВОК

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Резюме. *Цель.* Оценка эффективности и безопасности воспроизведенного препарата Вартоцид® (Имихимод крем 5% для наружного применения) у пациентов с наружными аногенитальными (венерическими) бородавками (АГБ). *Материалы и методы.* Простое слепое сравнительное рандомизированное плацебо-контролируемое клиническое исследование включало 50 женщин в возрасте от 18 до 60 лет с установленным клиническим диагнозом АГБ в вульве и перианальном регионе. Пациенты в группе 1 получали плацебо-крем для наружного применения, тогда как пациенты в группе 2 получали терапию Вартоцидом в суточной дозе 10 мг крема/см^2 области кожи. Препарат применялся через день до полного исчезновения АГБ, но в любом

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случае не более 16 недель. Последующее наблюдение проводилось еще 4 недели. В исследовании оценивалась динамика субъективных и объективных симптомов, наличие и частота рецидивов, а также процентное соотношение полного лечения от АГБ. *Основные результаты.* Лечение Вартоцидом привело к полному излечению от АГБ у 16% пациентов и снижению площади локализации АГБ у 36% пациентов. На фоне плацебо не было достигнуто никакой динамики болезни. Не наблюдалось ни серьезных побочных эффектов, ни клинически значимых изменений в анализах крови, мочи или сывороточных биохимических показателей у любого из пациентов, получавших лечение Вартоцидом. *Вывод.* Было доказано, что воспроизведенный препарат Вартоцид эффективен и безопасен для лечения АГБ, и его эффективность аналогична оригинальному препарату Aldara® (Имихимод крем 5% для наружного применения).

Ключевые слова: *Имиквимод, Вартоцид, клинические испытания, эффективность, безопасность, наружные аногенитальные (венерические) бородавки.*

The prevalence of papillomavirus infections, including anogenital warts (AGW), has still persist at a high rate, accounting in 2012 for more than 26.0 cases per 100 000 in the population of the Russian Federation [14]. In other countries the prevalence of such infections is significantly higher and accounts for 196 cases per 100 000 of the population [6, 21].

The clinical implications of genital infections caused by human papillomavirus (HPV) are quite variable. There are two types of AGW: exophytic and endophytic forms. Both forms can co-exist and are usually evoked by different genotypes of HPV. Namely, benign AGW are more often evoked by low-risk HPV types 6 and 11, whereas HPV types 16 and 18 produce higher risk lesions [4, 16]. The vast majority of patients with AGW primarily carries HPV types 6 and 11. In most cases AGW are not a serious danger from a prognostic perspective, though they definitely cause some psychosocial problems for the patient [21]. However, in some cases, AGW can transform into anogenital malignancies, especially in immune-compromised patients, for example following organ transplantation and the associated immunosuppressive therapy, or when infected with HIV [17]. Depending on the anatomical location of the AGW, HPV infected patients can develop both frequent and sometimes unpleasant forms of pointed anogenital condylomas or recidivating respiratory papillomatosis, which can cause dysfunction of the upper respiratory tracts [15]. It is believed that these more serious pathologies associated with AGW are triggered by a complex of local immunosuppressive reactions manifesting in abnormal cellular responses, changes in Langerhans cell maturation, alteration in the polarization of adaptive immune responses, and the suppression of natural killer cell function [15, 18]. Pathologies can also be influenced by the expression of certain major histocompatibility complex class II alleles [8]. The capacity to produce such alterations in immune responses suggests a rationale for the use of immunocorrective drugs in HPV treatments.

A common approach for AGW treatment has been recently limited by mechanical or chemical destruction. AGW can be surgically removed, treated with cryotherapy, or treated with electrocoagulation or chemicals (podophyllin, podophyllotoxin, fluorouracil, trichloracetic acid etc.). However, these methods of AGW treatment are not always sufficiently effective since frequent relapses can occur because of reinfection, reactivation of viral replication, viral genome segregation, and the associated transit into an active state. One of the most significant risk factors for HPV relapse is reduction of immune defense. Hence, there is a need for identifying new therapeutic agents for AGW treatment [2].

The use of immune-modifying agents represents a new approach for AGW therapy. The most widely used drug is an imidazole derivative called imiquimod (1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine), which is structurally similar to nucleosides. This drug is widely used to treat human herpesvirus infections, and reports of its use accounts for more than 2,500 references in PubMed as of May 2016 (http://www.ncbi.nlm.nih.gov/pubmed). Imiquimod has been approved by the US Food and Drug Administration as a pharmaceutical product against AGW and other symptoms of HPV infection. It is produced in the United Kingdom under the trade name Aldara® [27]. In November 2007 patent protection expired and several countries launched the manufacture of generic analogues [11]. The generic drug Wartocid® (Imiquimod cream 5% for external use), an analogue of the brand product Aldara, was produced and registered in the Russian Federation. Pre-clinical studies in guinea pigs showed full bioequivalence of the brand and reproduced product.

The purpose of the current study was to evaluate the efficacy and safety of Wartocid in a phase III single-blind comparative, randomized, placebo-controlled clinical trial in patients with AGW.

Materials and methods

Participants. The clinical trial included 50 women aged 18 to 60 (average age: 20.8) with AGW located in the vulva and perianal area. Gender uniformity during recruitment of the patients was due to pronounced prevalence of such pathology in females.

To exclude any sexually transmitted co-infections (STIs), all patients were examined for syphilis,

HIV, *Neisseria gonorrhea*, chlamydial genitourinary infections, trichomoniasis, *Mycoplasma genitalium*, and genital herpes. All patients underwent a PAP test and HPV status identification by means of PCR.

A complete blood count (CBC) and blood chemistry were done prior to and following Wartocid treatment. Evaluation of blood chemistry parameters included levels of transaminase, total bilirubin, creatinine, and glucose levels.

Inclusion criteria. Patients matching the following criteria were included in this study:

– age between 18 and 70;
– presence of AGW in the form of a small fusing papillomatous rash (≥ 1 cm^2) or papules/isolated warts (2 or more elements);
– negative pregnancy test (for women of childbearing age only) and acceptance of using reliable contraception during the study and 1 month upon its completion;
– informed consent for clinical trials;
– willingness to strictly follow the doctor's recommendation regarding prescribed therapy.

Exclusion criteria. Patients were excluded if they had:

– intolerance to any components of Wartocid;
– prior therapy with drugs containing Imiquimod for 3 months before the clinical trial began;
– PAP test with a Class III, IV and V diagnosis;
– AGW with a colonic, vaginal, cervical mucosa or intraurethral localization;
– impaired liver, kidney and/or other inner organ functions associated with their decompensation, central nervous system disorders;
– STIs — syphilis, HIV, *Neisseria gonorrhea*, chlamydial genitourinary infections, urogenital trichomoniasis, urogenital diseases, caused by *Mycoplasma genitalium*, genital herpes with signs of infectious processes;
– pregnancy, lactation;
– participation in any other clinical trials 30 days before Visit 1;
– suspicion of malignant neoplasms in the vulva;
– any serious or uncontrolled physical or mental illnesses considered by the investigator as risky for the patients in connection with their participation in the trial, illnesses which could affect the results of the trials or impede the performance by the patients of all study requirements;
– clinically significant deviations of the CBC/blood chemistry or study data, with the exception of AGW-related conditions;
– consumption of any pharmaceutical products for co-therapy, not allowed by the current protocol for clinical trials or conditions when the required period after consumption of such products had not yet been completed;
– indication in personal history of any drug dependence or alcohol abuse, which could negatively impact patient compliance;
– affiliation with research center personnel, sponsor company as well as their family members (according to GCP);
– lack of willingness to cooperate.

Study design. All participants were randomly divided into 2 groups of 25 persons. The patients in Group 1 received placebo-cream for external use, whereas the patients in Group 2 were treated with Wartocid. Maximum duration of the therapy was 16 weeks (the earlier disappearance of AGW occurred in patients allowed to complete the trial ahead-of-schedule). Upon completion of the therapeutic course all patients were observed for 4 more weeks.

The drug was applied for 6–10 hours (mainly at night) on a washed (using soap with neutral pH) and dried area of lesional skin by means of gentle application using a tube tip as an applicator. After a period of 6–10 hours, the treated skin was washed under running water (using soap with neutral pH).

A single dose of the drug was approximately 10 mg/cm^2 of skin surface (a treated area of 2 mm in width and 5 mm in length).

Estimation of therapeutic efficacy was performed on day 21±2 (visit 3), 35±2 (visit 4), 63±7 (visit 5), 91±7 (visit 6), 119±7 (visit 7) and 147±7 (visit 8) according to the following criteria:

– presence/absence of subjective symptoms of disease (patient complaints);
– presence/absence of objective symptoms of disease;
– frequency of AGW relapses;
– percentage of patients who stopped their participation in the clinical trial ahead-of-schedule due to inefficiency;
– estimation of therapeutic efficacy by a doctor (clinical outcome);
– estimation of therapeutic efficacy by the patient.

The following parameters were also evaluated:

– percentage of patients who were completely cured during therapy;
– percentage of patients in which the AGW amount or area were decreased during therapy;
– presence and intensity of subjective clinical symptoms of disease.

Intensity of each parameter was assessed according to a scale of 0 to 3: 0 — absence, 1 — weak, 2 — moderate, 3 — strong.

The patient self-assessed the total therapeutic efficacy according to a scale of 1 to 4: 1 — significant improvement, 2 — slight improvement, 3 — unchanged, 4 — deterioration.

For the doctor's assessment of therapeutic efficacy, symptoms were assessed according to a scale of 1 to 5: 1 — clinical convalescence, 2 — significant improving, 3 — improving, 4 — unchanged, 5 — deterioration.

Statistical analyses. All statistical analyses were performed with GraphPad Prism 5.04 software

(GraphPad Software Inc., La Jolla, CA, USA). All data were expressed as mean (M)±standard error (SEM). Statistical significance is reported at $p < 0.05$. All the data underwent testing for normal distribution (D'Agostino&Pearson omnibus normality test). Rash intensity, itching, pain, rash area and efficacy by patient/doctor were analyzed using a repeated one-way ANOVA followed by Bonferroni post-hoc test (within group comparison of normally distributed data) and a Friedman rank sum test followed by a Dunns post-hoc test (within group comparison of non-normally distributed data). The intergroup comparison was assessed at one point (final visit 8) using an unpaired t-test (for normally distributed data) or Mann–Whitney U-test (when data failed the normality test).

All the blood and urine parameters were analyzed using a paired t-test (for normally distributed data within one group), an unpaired t-test (for normally distributed data for intergroup comparison), a Wilcoxon matched pairs test (for non-normally distributed data within group) and a Mann–Whintey test (for non-normally distributed data for intergroup comparison).

Results and discussion

In the current study the dynamics of subjective and objective indicators were assessed in all patients. Among patients from Group 1 (placebo) no significant changes were found in rash intensity, pain, rash area (Table 1).

Patients treated with Wartocid cream showed a reduced number of AGW ($F(6.25) = 16.5$; $p = 0.011$) though this effect was not statistically significant when compared to placebo group ($U = 270.5$; $p = 0.36$). A more apparent response was observed when rash surface area was measured. Namely, on Visit 1, mean rash areas were statistically identical in Group 1 and 2 (2.30 vs. 2.28 cm^2 respectively) (Table 1). Placebo decreased AGW area by 0.06 cm^2 at a maximum, i.e. by 2.6% ($F(6.24) = 1.301$; $p = 0.26$), whereas Wartocid, especially near the end of the treatment period (visit 8), decreased lesion sizes by 0.68 sm2 or 28% ($F(6,24) = 8.364$; $p < 0.0001$) and this effect was statistically significant when compared to placebo ($t = 2.2$; $p = 0.032$). The surface area analysis of each patient revealed that 3 people from Group 1 (12%) exhibited a reduction of the lesional area and in 1 person (4%) such an area expanded. In Group 2, already by Visit 3, a reduction of the lesional area was noted in 6 patients (24%), and by the end of the treatment period it reached 52% (13 patients), 4 patients of which (16%) showed full convalescence while the rest of the 9 patients (36%) exhibited significant AGW reduction.

Imiquimod is considered to be an effective non-invasive immune-modifying remedy against STIs and in particular against pointed anogenital condylomas [5, 10], since it affects both innate and adaptive immune systems. By binding with the toll-like receptors 7 on the plasmocyte-like dendrites, imiquimod causes proinflammatory cytokine secretion [3, 23] with subsequent activation of Th1 and inhibition of Th2 immune responses leading to Langerhance cells migration to local lymph nodes and elevation of antigen presentation by naïve T-cells. In other words, the mechanism of antiviral action of imiquimod is indirect and its effects are mediated mostly via secretion of IFNα/β, thus modulating course and outcome of infectious process [23, 26]. The regress of AGW observed in our study was most likely due to cell-dependent immune response caused by local induction of cytokines and cellular infiltration [7].

As for clinical manifestations, for example, itch intensity and pain syndrome in the AGW area, patients in Group 2 displayed a higher itch intensity level than patients in Group 1, whereas pain syndrome was higher in patients in Group 1. It seems likely that the decrease of pain syndrome in patients receiving

Table 1. Main parameters of AGW therapy efficacy (mean±SEM)

Parameter	Patient group	Visit number						
		1	3	4	5	6	7	8
Rash intensity as evaluated by patient, scores	1	0.88±0.19	0.88±0.18	0.84±0.17	0.84±0.18	0.84±0.18	0.84±0.18	0.84±0.18
	2	0.72±0.19	0.60±0.18	0.52±0.17	0.60±0.18	0.60±0.18	0.60±0.18	0.60±0.18*
Itching and burning intensity in the vulva, scores	1	0.28±0.13	0.28±0.15	0.08±0.11	0.12±0.10	0.12±0.10	0.08±0.09	0.08±0.09*
	2	0.36±0.13	0.44±0.15	0.28±0.11	0.20±0.10	0.20±0.10	0.20±0.09	0.16±0.09
Decreasing of pain syndrome intensity, scores	1	0.08±0.10	0.08±0.09	0.08±0.06	0.08±0.06	0.08±0.06	0.08±0.06	0.16±0.08
	2	0.20±0.10	0.16±0.09	0.04±0.06	0.04±0.06	0.04±0.06	0.04±0.06	0.04±0.08*
Therapeutic efficacy evaluation (by patient), scores	1	–	3.00±0.12	2.84±0.13	2.84±0.12	2.84±0.15	2.84±0.18	2.84±0.18*
	2	–	2.84±0.12	2.64±0.13	2.72±0.12	2.64±0.15	2.40±0.18	2.40±0.18
Therapeutic efficacy evaluation (by doctor), scores	1	–	4.00±0.07	3.92±0.13	3.92±0.17	3.92±0.20	3.92±0.22	3.92±0.22
	2	–	3.68±0.07	3.28±0.13	3.24±0.17	3.12±0.20	3.00±0.22	3.00±0.22*
Rash area in the vulva, cm^2	1	2.30±0.16	2.30±0.16	2.24±0.18	2.24±0.20	2.24±0.20	2.24±0.20	2.25±0.20
	2	2.29±0.17	2.04±0.17	1.82±0.19	1.66±0.20	1.64±0.20	1.62±0.20	1.60±0.20*

Notes: there was no efficacy assessment on visit 2 (this visit was for randomization only); *statistically significant differences before (visit 1) and after (visit 8) treatment ($p < 0.05$). The data is expressed as M±SEM. Group 1 is for placebo, group 2 is for Wartocid.

Table 2. Complete Blood Count (CBC) and blood chemistry

Parameter	Groups			
	1 (placebo)		2 (imiquimod)	
	Before treatment	After treatment	Before treatment	After treatment
CBC parameters				
Hb, mg/L	13.07±0.11	13.42±0.12	13.07±0.12	13.36±0.11
Erythrocytes, 10^{12}/L	4.29±0.06	4.57±0.09	4.28±0.06	4.53±0.08
Leukocytes, 10^9/L	6.08±0.18	6.75±0.15	6.39±0.21	6.17±0.15
Platelets 10^9/L	267.40±8.67	309.40±9.09	260.80±8.34	297.80±10.54
ESR, mm/h	5.04±0.32	4.40±0.31	3.32±0.28	3.96±0.25
Blood chemistry				
ALT, u/L	14.07±0.86	13.12±0.96	13.34±0.97	12.51±0.90
AST, u/L	12.52±0.73	11.11±0.77	12.91±0.70	10.95±0.77
Total bilirubin, μmol/L	9.04±0.45	9.44±0.61	9.49±0.58	8.74±0.43
Creatinin, μmol/L	70.56±2.29	69.68±2.69	71.32±1.76	68.00±2.33
Glucose, mmol/L	4.95±0.10	5.15±0.08	4.71±0.10	5.0±0.08

Notes: ALT — alanine aminotransferase; AST — aspartate aminotransferase. The data is expressed as M±SEM.

Wartocid was due to reduction of AGW area, whereas the itch intensity remained at an elevated level due to the specific nature of the mechanism of activity of imiquimod causing a local pro-inflammatory reaction [1, 8, 21].

Since efficacious treatment of skin lesions of viral etiology reduces positive tests for viral DNA, particularly for HPV, all patients underwent qualitative evaluation for the presence of viral DNA using PCR upon completion of the trial. It was shown that placebo treated patients retained HPV DNA by PCR, as all samples taken from Group 1 remained positive. In contrast, 12% of Wartocid treated patients produced a negative reaction for HPV DNA, while the remaining test samples from Group 2 were positive (viral load was not determined). This is consistent with the literature data that treatment with imiquimod reduced the number of positive HPV DNA tests by 7–15% [8, 20].

The integral treatment efficacy assessment was significantly elevated for Wartocid. Namely, according to patients' assessment, a reduction in the size of rash areas after Wartocid therapy occurred 3.7 times more often than in patients receiving placebo. According to «improvement» estimation scale, the positive assessment of therapy efficacy in patients receiving Wartocid was observed 3 times more often than in the placebo group (36% and 12% respectively). The positive estimation of therapeutic efficacy assessed by a doctor was observed in 52% of patients receiving Wartocid and only in 4% of patients receiving placebo. These results are in line with the results obtained when the brand product Aldara was used [9, 12, 19, 20, 22, 25].

One of the main tasks of the study was to evaluate the safety of Wartocid. For this purpose all patients from Groups 1 and 2 underwent CBC and blood chemistry testing before and right after treatment with either placebo or Wartocid (Table 2). As we found out, neither Wartocid nor placebo caused any significant deviation in blood parameters beyond the standards rate suggesting a similar safety profile of Wartocid compared to Aldara [8, 13].

In addition to this, the investigated drug was well-tolerated in patients. Adverse effects were rare and insignificant. Specifically, there were no adverse events and/or other unintended side effects with the exception of a slight increase in itch intensity in patients receiving Wartocid.

In summary, our study demonstrated comparable efficacy and safety profiles of Wartocid to the brand product Aldara in AGW treatment, since a clinical therapeutic effect was achieved in 52% of patients with AGW, of which 16% showed complete convalescence and 36% showed a reduction of the AGW area.

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