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Abstract
The study aims at evaluating the efficacy of combined administration of imiquimod 5% crème and human papillomavirus (HPV) quadrivalent recombinant vaccine in order to achieve a long-term clinical remission in patients with chronic HPV infection manifested in condyloma accuminata (CA) of the anogenital area. The study enrolled 36 subjects aged 26.4 (4.1) years (including 22 men) with one to five condyloma accuminata of the anogenital area. Study participants were vaccinated with human papillomavirus quadrivalent recombinant vaccine using a 0–2–6-month regimen with concomitant administration of imiquimod 5% crème applied three times per week for not more than 16 weeks. Patients were monitored over 2 years. Complete disappearance of condyloma accuminata was observed in 34 out of 36 subjects (94.4%) after 1 year from the start of treatment. Two patients still having condyloma accuminata of the anogenital area after 1 year of combination treatment underwent a successful course of treatment with Solcoderm (one patient for 1 year 3 months and the other for 1 year 4 months), which resulted in complete disappearance of condyloma accuminata. Within 2-year period, no recurrence of condyloma accuminata of the anogenital area has been observed.

Keywords: HPV infection, condyloma accuminata, vaccination, human papillomavirus quadrivalent recombinant vaccine, imiquimod, combined administration
1. Introduction

It is well known that 15–20% of all human neoplasms have a viral cause, that is, they are developed due to so-called oncogenic viruses. The experts of the International Agency for Research on Cancer (IARC) consider the following viruses as human oncogenic viruses:

1. RNA viruses:
   - Hepatitis B and C viruses (HBV/HCV) causing hepatocellular carcinoma;
   - Human T-cell leukemia virus (HTLV-1) which is the etiological agent of adult T-cell leukemia, as well as of tropical spastic paraparesis and several other non-oncologic diseases;
   - Human immunodeficiency virus (HIV) which contains no transforming genes yet provides the requisite conditions (immunodeficiency) for the development of cancer.

2. DNA viruses:
   - Epstein-Barr virus (EBV) participating in the development of a whole host of malignant tumors, such as Burkitt lymphoma, nasopharyngeal carcinoma, and Hodgkin’s lymphoma;
   - Human herpesvirus type 8 (HHV-8) playing an important role in the occurrence of Kaposi’s sarcoma, primary effusion lymphoma, Castleman disease, and some other pathological conditions;
   - Human papillomaviruses (HPV) which are an etiological agent of cervical cancer and several other anogenital tumors.

Considering the severity of and unfavorable prognosis in these diseases, as well as their proven viral etiology, the development of prophylactic methods for such viral infections is becoming a topical issue. Currently, vaccines against hepatitis B virus and HPV are already available.

The problem of HPV infection is one of the most topical health issues in the modern world. According to the World Health Organization (WHO), about half a million new cases of cervical cancer are reported annually worldwide, and 240 thousand women are dying from this disease.

In Russia, symptoms of papillomavirus infection are found in 15.0–34.4% of women aged 19 years or older, and among women attending the gynecology clinic for suspected sexually transmitted diseases, the fraction of HPV-infected subjects is reaching 44.9%. The risk for acquiring HPV infection begins from the moment of a sexual debut and continues throughout an individual’s life [1].

HPVs are the oncogenic viruses, that is, they can induce tumors, from harmless to fatal forms. The oncogenic effect is due to their ability to impair differentiation and induce proliferation of the skin and mucosal epitheliocytes which manifest in the form of papillomas (warts) of different types and various localization, as well as epithelial dysplasias which can be transformed into invasive (cancerous) tumors.
Skin warts more often occur in children and usually persist for several years causing only cosmetic inconveniences. The genital (or anogenital) warts are a much more serious condition. They are called condyloma acuminate and form a warty growth that in its typical form resembles the cauliflower. Genital warts more often occur on the outer genitals, although they may affect vagina, cervix, or penis. This is one of the most common sexually transmitted infections [2].

Papillomavirus infection affects both women and men; however, owing to hormonal differences, the likelihood of tumor development in men is much lower than in women. Nonetheless, men can be the HPV carriers for a long time and able to transmit the virus to women. Papillomaviruses are small (55–60 nm in diameter) non-coated viruses. They are represented by cubical capsids containing two proteins—L1 and L2. The L1 is the major capsid protein comprising more than 80% of capsid material to form the blocks (capsomers) from which the capsid is built.

The anti-L1 antibodies possess the virus-neutralizing activity which underscores the significance of L1 in the initiation of infection. L2 is a minor protein that is not a part of the capsid structure but is involved in capsid stabilization and its coupling with viral genome [3].

Anogenital warts are manifestations of mostly sexually transmitted HPV infection caused by low-oncogenic risk HPV types, such as HPV types 6 and 11. The HPV infections tend to self-resolve on their own but more often they are characterized by recurrent course due to virus persistence. Among the general population, the overall prevalence of HPV infection reaches 80%.

On exceptionally rare occasions, anogenital warts can become cancerous. Anogenital warts may negatively impact patients' quality of life owing to the development of depression and occurrence of psychological and sexual problems [4].

There are numerous approaches for the treatment of anogenital warts (liquid nitrogen cryotherapy, surgical removal, laser therapy, electrocoagulation, use of podophyllotoxin, interferons, imiquimod, and other immune preparations). However, none of the above proved to be ideal. Current therapy for anogenital warts is essentially symptomatic and is aimed at reducing the intensity of symptoms. According to numerous data, the risk of wart recurrence following any type of treatment reaches 30% [4].

One of the new frontiers for solving this problem is the use of an immune preparation imiquimod in combination with HPV quadrivalent recombinant vaccine aiming at eliciting immunity to HPV types 6, 11, 16, and 18. The likely mechanism of combined action of imiquimod and HPV quadrivalent recombinant vaccine is as follows: imiquimod plays an important role in HPV elimination from the infected tissue, while the vaccination using quadrivalent recombinant vaccine promotes specific immune response to prevent re-infection. However, this hypothesis needs to be elaborated and confirmed in further studies using laboratory investigations capable of detecting HPV.

Currently, the following HPV vaccine dosing schedules are being used:

1. A classic three-dose vaccination schedule: 0–2–6 months (i/m in deltoid muscle of arm).
2. An alternative two-dose vaccination schedule: two doses 6 months apart.

3. Three-dose extended schedule: three doses of which the first two are administered within 6 months followed by a booster (third) dose given 5 years later.

Along with the bivalent (Cervarix®) and quadrivalent (Gardasil®) HPV vaccines, currently a 9-valent HPV vaccine (Gardasil-9) has been registered worldwide, which evokes immune response against the following HPV types: 6, 11, 16, 18, 31, 33, 45, 52, and 58. To date, Gardasil-9 is not registered in Russian Federation [5].

The aim of this study is to evaluate the effectiveness of combined use of 5% imiquimod crème and human HPV quadrivalent recombinant vaccine to achieve a durable clinical remission of chronic HPV infection manifesting in anogenital warts.

2. Material and methods

2.1. Clinical characteristics of patients

A single-center, non-randomized, open-label, prospective, pilot study was conducted on 36 patients of whom 22 were men aged 26.4 (4.1) years having from one to five anogenital warts. Among study participants, there were six HIV-infected female patients who received a highly active antiretroviral therapy (four patients received lamivudine 300 mg + abacavir 600 mg + atazanavir 300 mg/ritonavir 100 mg once daily and two patients received lamivudine 300 mg + efavirenz 600 mg once daily plus zidovudine 300 mg twice daily). All six HIV-infected female patients had an undetectable viral load (<50 HIV RNA copies) and CD4+ count >500 cells per 1 μL of blood. The HIV-infected patients represented a population for which the likelihood of immune response to vaccine antigens is ambiguous owing to the presence of possible immune deficiency. We included these patients in the study as at the time of enrollment they had no obvious immune deficiency against a background of highly active antiretroviral therapy. All patients signed the informed consent form.

2.2. Diagnosis of genital warts

The diagnosis of anogenital warts was based on medical history of disease (patients admitted to having unprotected sexual contacts, physician diagnosed the presence of anogenital warts in patient’s permanent sex partner) and clinical examination data. Patients with an unequivocal diagnosis, pearly penile papules, or vestibular (labial) papillomatosis were excluded from the study.

Inclusion criteria for the study were as follows:

- Men and women above 18 years of age.
- Presence of one to five anogenital warts.
- Patients with no prior vaccination with human HPV quadrivalent recombinant vaccine.
• Availability of signed and dated informed consent for participation in a pilot study.
• Ability to adhere to study protocol requirements.
• For women of childbearing age—negative pregnancy test before vaccination (the human chorionic gonadotropin test).

Exclusion criteria for the study were as follows:
• Persons under 18 years of age.
• Presence of more than five anogenital warts.
• History of vaccination with human HPV quadrivalent recombinant vaccine.
• Administration of immunoglobulin preparations or blood transfusion within the last 3 months before study commencement.
• Long-term (more than 14 days) use of immunosuppressive drugs within 6 months before study commencement.
• Any confirmed or suspected immunosuppressive or immunodeficiency disorder.
• Respiratory or cardiovascular insufficiency, hepatic, or renal impairment revealed during physical examination during visit 1.
• Marked congenital disorders or exacerbations of serious chronic diseases including any clinically significant exacerbations of chronic pulmonary, liver, kidney, cardiovascular, nervous system, psychiatric diseases, or metabolic disorders confirmed by medical history data or objective examination data.
• History of severe allergic reactions and autoimmune diseases.
• Acute infectious and/or non-infectious diseases within 1 month prior to study commencement.
• Chronic alcohol abuse and/or history of substance abuse.
• Breastfeeding.
• Pregnancy.
• Participation in the other clinical study within the last 3 months.
• Evidence of past or present oncohematologic and other oncologic diseases.

2.3. Intervention

Study participants were prescribed 5% imiquimod crème (Aldara, “MEDA,” Sweden) to apply to the warts three times per week before going to sleep followed by washing the cream off with water and soap in the morning. Treatment should last until visible disappearance of anogenital warts but not longer than 16 weeks, and accompanied by concomitant three-dose injection of HPV quadrivalent recombinant vaccine intramuscularly in the deltoid muscle of arm or in the upper outer triceps area using a three-dose series (0–2–6-month schedule). The vaccine is intended for
prevention of diseases caused by HPV types 6, 11, 16, and 18, and contains the L1 proteins of the above HPV types. Control visits were made in 1 and 2 years after vaccination. When necessary, patients had an opportunity to contact physician-investigator at any time. According to recent data, vaccination with HPV quadrivalent recombinant vaccine can be done using the “eased” two-shot 0–6-month schedule; however in our study, we used standard 0–2–6-month schedule.

2.4. Safety evaluation

In order to evaluate treatment safety, we collected information about treatment-related adverse events. Safety of vaccination was assessed in the following way: after injection of each dose for 7 days, all patients filled in a specially designed questionnaire which included both local and general adverse events. The recorded local adverse events included pain at the injection site (yes/no) and size of a hyperemic focus (in cm). Within a week following vaccination, we also evaluated general (systemic) symptoms, such as body temperature, headache, general malaise, and joint or muscle pain.

Safety of topical application of 5% imiquimod creme was evaluated by the presence of tenderness at the site of crème application and occurrence of ulceration. The information was collected at 6 months after treatment commencement at the time of injection of the third vaccine dose.

2.5. Statistical analysis

Statistical analysis was carried out using the applied software package StatPlus 2009 Professional 5.8.4. The choice of measures of central tendency and measures of dispersion was made based on the type of distribution of variables. The description of quantitative variables corresponding to normal distribution was performed using the mean values (standard deviation) and variables that differ from normally distributed variables as the median values (interquartile range). The qualitative variables were expressed as proportions (%) of the absolute numbers. Also, the 95% confidence intervals were calculated.

3. Results and discussion

3.1. Assessment of safety

3.1.1. First dose

Table 1 shows adverse events for the first 7 days after administration of the first dose of the human papillomavirus quadrivalent recombinant vaccine.

3.1.2. Second dose

Table 2 shows adverse events for the first 7 days after administration of the second dose of the human papillomavirus quadrivalent recombinant vaccine.
3.1.3. Third dose

Table 3 shows adverse events for the first 7 days after administration of the third dose of the human papillomavirus quadrivalent recombinant vaccine.

All vaccination-related adverse events were self-resolved on their own within the first 7 days post-vaccination and required no medication therapy.
3.2. Assessment of topical administration of 5% imiquimod crème

At 6 months after treatment commencement, all patients reported tenderness at the site of crème application and occurrence of ulcerations which self-resolved on their own in 100% of cases within 14 days after discontinuation of treatment.

All patients completed the study in accordance with study protocol. Patient compliance with treatment was 100%.

3.3. Clinical assessment

At 12 months from study commencement, a complete disappearance of anogenital warts was observed in 34 (94.4%) out of 36 study participants including HIV-infected patients (Table 4).

In two patients without HIV infection, the number of anogenital warts decreased from five at baseline to one after 1 year. Two patients with anogenital warts after 1 year, at 1 year 3 months,

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>1 day</th>
<th>2 day</th>
<th>3 day</th>
<th>4 day</th>
<th>5 day</th>
<th>6 day</th>
<th>7 day</th>
<th>8 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at the site of injection</td>
<td>13.9 (5/36)</td>
<td>33.3 (12/36)</td>
<td>13.9 (5/36)</td>
<td>2.8 (1/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
</tr>
<tr>
<td>Hyperemia at the site of injection of up to 5 cm in size</td>
<td>0 (0/36)</td>
<td>11.1 (4/36)</td>
<td>13.9 (5/36)</td>
<td>5.6 (2/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
</tr>
<tr>
<td>Temperature up to 37.5°C</td>
<td>2.8 (1/36)</td>
<td>11.1 (4/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
</tr>
<tr>
<td>General malaise</td>
<td>22.2 (8/36)</td>
<td>36.1 (13/36)</td>
<td>19.4 (7/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
<td>2.8 (1/36)</td>
</tr>
<tr>
<td>Headache</td>
<td>13.9 (5/36)</td>
<td>27.8 (10/36)</td>
<td>25 (9/36)</td>
<td>8.3 (3/36)</td>
<td>0 (0/36)</td>
<td>2.7 (1/36)</td>
<td>11.1 (4/36)</td>
<td>0 (0/36)</td>
</tr>
<tr>
<td>Joint pain or muscle pain</td>
<td>5.6 (2/36)</td>
<td>27.8 (10/36)</td>
<td>33.3 (12/36)</td>
<td>19.4 (7/36)</td>
<td>11.1 (4/36)</td>
<td>5.6 (2/36)</td>
<td>0 (0/36)</td>
<td>0 (0/36)</td>
</tr>
</tbody>
</table>

Table 3. Adverse events for the first 7 days after administration the third dose of the human papillomavirus quadrivalent recombinant vaccine.

3.2. Assessment of topical administration of 5% imiquimod crème

At 6 months after treatment commencement, all patients reported tenderness at the site of crème application and occurrence of ulcerations which self-resolved on their own in 100% of cases within 14 days after discontinuation of treatment.

All patients completed the study in accordance with study protocol. Patient compliance with treatment was 100%.

3.3. Clinical assessment

At 12 months from study commencement, a complete disappearance of anogenital warts was observed in 34 (94.4%) out of 36 study participants including HIV-infected patients (Table 4).

In two patients without HIV infection, the number of anogenital warts decreased from five at baseline to one after 1 year. Two patients with anogenital warts after 1 year, at 1 year 3 months,

<table>
<thead>
<tr>
<th>Anogenital wart number</th>
<th>At baseline</th>
<th>In 6 months</th>
<th>In 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abs.</td>
<td>%</td>
<td>Abs.</td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>11.1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>22.2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>16.7</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>11.1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>38.9</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>100</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 4. Distribution of study participants and observation dynamics in relation to the anogenital wart number.
and 1 year 4 months successfully underwent the treatment course with “Solcoderm,” which resulted in complete disappearance of warts. Over the study period, no recurrence of anogenital warts has been found.

Using a given treatment regimen, no clinically significant local or general reactions have been observed.

We have conducted the calculation of several statistical parameters, the results of which are presented in Table 5.

The problem to be discussed is not new. However, in author’s opinion, a new concept in the treatment of anogenital warts presented in this study deserves attention.

Many authors have been involved in the development of methods of treatment of anogenital warts. Thus, for example, Gomberg and Solovyov [6] reported the use of destructive methods of treatment of anogenital warts, such as electrosurgery, cryosurgery, laser treatment, surgical excision, and laser photothermolysis. It was found that the recurrence rate of anogenital warts does not depend on the selected method of destructive treatment at that. The advantage of these methods is that warts are destroyed quickly and often in a single step. The drawbacks of these methods include the pain caused by the procedure, wart recurrences, requirements in special facility, expensive equipment, and trained medical staff qualified to perform this type of medical activity [6].

Kuznetsova [7] studied the results of treatment of anogenital warts using the application of “Solcoderm” via the capillary tubing with its subsequent mechanical rubbing using a spatula to ensure deeper penetration of the solution. The effectiveness of this method was 80.1%, with the wart recurrence rate of 6–10% within a year. The benefits of this method include treatment

<table>
<thead>
<tr>
<th>Parameter (formula)</th>
<th>At baseline</th>
<th>In 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with AGW</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Chance of AGW presence (n of patients with AGW/n of patients without AGW)</td>
<td>–</td>
<td>2/36 = 0.06</td>
</tr>
<tr>
<td>AR (n of patients with AGW/n of patients with AGW risk)</td>
<td>36/36 = 1 = 100%</td>
<td>2/36 = 0.06 = 6%</td>
</tr>
<tr>
<td>RR (AR with intervention/AR without intervention), 95% CI</td>
<td>0.06/1 = 0.06 = 6%(0.06; 0.07)*</td>
<td></td>
</tr>
<tr>
<td>ARR (AR with intervention – AR without intervention), 95% CI</td>
<td>0.06 – 1 = –0.94 = –94%(-1.02, –0.86)*</td>
<td></td>
</tr>
<tr>
<td>RRR (difference AR/AR without intervention)</td>
<td>(100% – 6%)/100% = 0.94 = 94%</td>
<td></td>
</tr>
<tr>
<td>NTT (1/ARI)</td>
<td>1/0.94 = 1.06</td>
<td></td>
</tr>
</tbody>
</table>

AGW, anogenital warts; AR, absolute risk; RR, relative risk; ARR, absolute risk reduction; RRR, relative risk reduction; NTT, number of patients needed to be treated to prevent one unfavorable outcome.

* P < 0.05.

Table 5. Statistical parameters (chance, AR, RR, ARR, RRR, and NNT) for study participants over 1 year.
in the outpatient setting, no need for using expensive equipment and anesthesia, absence of scars after treatment, and affordability of treatment. The drawbacks of this method are the recurrence of anogenital warts and the requirement to perform the procedure by a physician.

Apolikhina and Salekh [8] studied the use of podophyllotoxin applied twice daily for 3 days with a subsequent 4-day intermission (duration of treatment did not exceed 5 weeks). The effectiveness of treatment was 87% in men and 77% in women, with the wart recurrence rate of 6–100% within a year. The benefits of podophyllotoxin therapy for anogenital warts included treatment in the outpatient setting, plus the possibility to perform the procedure by a patient without assistance. The drawbacks of this method are wart recurrence, high cost of podophyllotoxin, and long duration of treatment against its not very high effectiveness [8].

Nejmark et al. [9] studied the results of treatment of anogenital warts using isoprinosine which was administered at 3 g/day (two tablets 3 times a day) as an adjunct to topical therapy or surgery for 14–28 days or 5 days a week sequentially for 1–2 weeks per month for 3 months. The effectiveness of combination therapy with isoprinosine was 41–87.5%, and the wart recurrence rate was 7–28%.

The major shortcoming of the above approaches to treatment of anogenital warts is a high wart recurrence rate. In our study, we offer a new approach to solving this problem. The combined use of HPV quadrivalent recombinant vaccine and 5% imiquimod cream aims, on the one hand, at clinical cure (i.e., disappearance of anogenital warts) with possible elimination of the virus, and on the other, at preventing the re-infection with HPV types causing warts with a subsequent long-term remission.

Imiquimod has no direct anti-viral action. Its effect is due to activation of non-specific defense mechanisms and stimulation of TLR7 receptors, induction of synthesis of interferon-alpha and other cytokines which attract to the site of imiquimod application the immunocompetent cells with cytotoxic activity to mediate the anti-viral effect and destroy the virus-infected cells [10–13].

This is a crucial point setting this treatment apart from other therapeutic approaches. Use of imiquimod results not only in visible disappearance of anogenital warts but, perhaps, in the destruction of virus-infected cells that never occurs when other known therapeutic approaches are used. However, this hypothesis needs further exploration as we did not perform laboratory tests for HPV detection.

Imiquimod therapy may lead to clinical remission owing to virus elimination. However, following the imiquimod monotherapy, we observed recurrence of anogenital warts. Perhaps, this is due to incomplete destruction of virus-infected cells, for instance, in immunodeficient patients (e.g., absolute deficit of cytotoxic cells or their functional incompetence), low adherence to imiquimod therapy, or re-infection with HPV type 6 or 11. Overall, the efficacy of annual imiquimod monotherapy varies between 35 and 68%, and the wart recurrence rate between 6 and 26% [14–16].

This pilot study has a number of limitations such as small sampling size, absence of control group, and absence of randomization and placebo control. The well-designed, randomized, placebo-controlled, double-blind, multicenter, prospective studies are needed to elaborate on and confirm our
revealed therapeutic effect of combined use of HPV quadrivalent recombinant vaccine and 5% imiquimod crème in the treatment of anogenital warts to achieve a long-term clinical remission. The issue of virologic cure using this therapeutic approach also awaits clarification.

Our developed approach to the treatment of anogenital warts using the HPV quadrivalent recombinant vaccine and 5% imiquimod crème demonstrated high clinical effectiveness. However, in designing future clinical studies on this subject, a special attention should be paid to laboratory investigation of HPV DNA carrier state in studied patient population to verify our hypothesis on the virologic cure. Nonetheless, our data are important as they provide a new insight into the possibility of complete HPV elimination in a given patient cohort [11, 12].

4. Conclusions

Vaccination with HPV quadrivalent recombinant vaccine using a three-dose vaccination schedule (0–2–6 months) and a concurrent 5% imiquimod crème application three times daily for not more than 16 weeks ensures the achievement of a long-term clinical remission of chronic HPV infection which is manifested in anogenital warts in at least 94.4% of cases over a 2-year follow-up. This treatment method proved to be safe. The adverse events observed during combined vaccination and 5% imiquimod crème administration were, as a rule, mild and self-resolved on their own (within 7 days following vaccination and within 14 days after discontinuation of 5% imiquimod crème). Clinical significance of these results awaits confirmation in future studies supported by methods of laboratory diagnosis.

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