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Human papillomavirus persistence or clearance after infection in reproductive age. What is the status? Review of the literature and new data of a vaginal gel containing silicate dioxide, citric acid, and selenite

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Abstract

Cervical cancer, the third most common cancer in women, is caused in nearly all cases by a persistent infection with high-risk types of the human papillomavirus. Although human papillomavirus infections are 80%–90% transient and disappear spontaneously within 24 months, human papillomavirus infections that remain are at risk of developing cervical lesions. Different therapeutical approaches have been tested to promote the regression of low-grade lesions or prevent progression. They include the application of 5-fluorouracil, curcumin, imiquimod, interferons, Vitamin D, and others. Also, the effect of probiotics and vaginal therapy with carboxy-methyl-beta glucan was assessed. Review of the literature and presentation of the last study data are presented. Clearance of high-risk human papillomavirus seemed to be promoted by treatment with a new vaginal gel containing a highly disperse SiO_2 and an anti-oxidative combination of citric acid and sodium. This gel showed, after 6 months, an improvement of cytological Pap findings (ASC-US, LSIL, ASC-H, or HSIL) in 80.9% of the participants. Similarly, there was a clearing of hr-human papillomavirus in 53% of cases after 3 months of gel administration. The percentage increased slightly in the non-treated control group from 78.3% at baseline to 83% after 3 months. The percentage of patients who were tested positive for p16/Ki67 reduced from 75% at baseline to 5.3% in the treatment group after 6 months, while the percentage decreased only slightly in the non-treated group (baseline: 91.5%; 6 months: 75.2%). The examined vaginal gel may support the healing of conspicuous cytological findings (ASC-US, LSIL, ASC-H, or HSIL) and clearance of hr-human papillomavirus positive results.

Keywords

human papillomavirus clearance, Pap testing, silicon dioxide, vaginal gel

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Introduction

Cervical cancer is the third most common cancer in women, causing approximately over 300,000 registered deaths worldwide every year.[1] In many low- and middle-income countries (LMICs), it is the leading cause of cancer deaths in women and hence a significant burden in these countries, as nine out of ten women who die of cervical cancer worldwide lived in LMICs.[2] Despite this high number of deaths, cervical cancer is considered a preventable disease with a slow disease progression and a known cause.[2]

Human papillomavirus (HPV) is the most frequently diagnosed sexually transmitted infection, with more than 100 types of HPV identified.[2] They infect the skin with

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squamous epithelia and mucosa, and low-risk types of HPV cause benign papillomas or warts.[2] However, a persistent infection with oncogenic high-risk HPV (e.g. HPV16 and HPV18) is the cause of nearly 100% of cases of invasive cervical cancer,[3,4] most anal cancers, and a subset of vulvar, vaginal, penile, and oropharyngeal cancers.[5]

Although there is a strong link between HPV infection and cervical cancer, only 10%–20% of women display a persistent infection prerequisite for cervical carcinogenesis.[4,6,7] About 80%–90% of HPV infections are transient and clear spontaneously within 24 months after first detection.[4,7] Several cofactors that promote the persistence of HPV infection could be identified: high parity, number of sexual partners, genetic factors, smoking, and coinfection with other sexually transmitted infectious agents such as herpes simplex virus two and *Chlamydia trachomatis*.[8–11] Furthermore, based on epidemiological data, the use of oral contraceptives and their duration is linked to increased risk of invasive cancer, while the risk declines after cessation of oral contraceptive use.[12] Recent studies aim to elucidate factors contributing to HPV clearance and persistence in more detail. However, data are still incomplete and in part inconsistent concerning the cofactors that regulate these events.[13,14]

On a molecular basis, evidence emerges that cellular immune response is impaired in patients with persistent HPV infection. Cytokines like interleukin (IL)-10, IL-6, and transforming growth factor (TFG-)β1 are increased in these patients, indicating a shift toward Th2-type cytokines in the course of the development of cervical cancer. The local immune environment might be impaired and hence enables viral integration as well as cellular transformation and immortalization.[15–17]

Cellular lesions resulting from HPV infections are mostly transient as well. For example, when diagnosed with a cervical intraepithelial lesion (CIN) grade 1, 57% and 32% regress or persist, while 12% progress. Only about 5% of CIN2 lesions progress to invasion or 22% to carcinoma in situ.[18] However, with higher-grade lesions, the percentage of progression increases. In women diagnosed with CIN3, the cumulative incidence of invasive cancer was about 31% within 30 years.[19] Of note, age does influence the rate of persistence independently of CIN grade and type of HPV. Younger women do have a higher chance for regression than older women, and with every 5 years of age, the odd for regression decreases by about 20%.[20]

The development of a cervix carcinoma is a long-lasting process that is preceded by well-characterized dysplastic stages and hence offers the early detection and control of the disease. Therefore, cervical cancer prevention strategies have been implemented worldwide with the aim to prevent and reduce morbidity and mortality from cervical cancer. According to the WHO, the prevention strategies include the following steps: (1) HPV vaccination for girls aged 9–13 years to reduce HPV infections; (2) regular screenings of women >30 years of age to identify precancerous lesions by cytological methods and to identify women at risk due to an infection with high-risk HPV types; and (3) accurate and timely cancer diagnosis to provide appropriate treatment at each stage.[2]

Examination of cervical cell smears can be performed by Pap testing to distinguish between different cell types. Results are classified according to the international used the Bethesda nomenclature[21] or in Germany according to the Munich nomenclature[22] to differentiate between premalignant (NILM (negative for intraepithelial lesion or malignancy) or Pap I as well as Pap II-a), benign, and malign results. Lower-grade cytological findings like ASC-US (atypical squamous cells of undetermined significance, or Pap II-p) and LSIL (low-grade squamous intraepithelial lesions, or Pap IIID1) are able to regress spontaneously to an inconspicuous state within 1–2 years but may also progress to more severe conditions.[10,23] Unclear findings like ASC-H (atypical squamous cells cannot exclude high-grade squamous intraepithelial lesions or Pap III-p findings) or higher-grade cytological findings like AIS (adenocarcinoma in situ, or Pap IVa–g) require a diagnostic or confirmatory test (colposcopy or biopsy) as not all positive results on the cervical screening test is actual pre-cancer or cancer. This to ensure that women receive adequate treatment.[2] The exact course also depends on additional factors like age, persistence of high-risk HPV types, and further risk factors.[24–27] Hence, to prevent over-treatment of low-grade abnormalities, testing for hr-HPV is often included in screening strategies[2,28,29] to estimate the risk for the occluded presence or potential progression to higher-level lesions. However, screening for HPV is particularly recommended for older women[2] as hr-HPV persistent is more significant in older women. In comparison, younger women show a spontaneous high clearance rate of HPV infections.[30]

Due to the burden of HPV infection and cervical cancer, research is ongoing to develop novel strategies. Therefore, nanocapsules loaded with imiquimod are tested against HPV and for the treatment of cervical cancer by inducing cell deaths involving apoptosis and autophagy.[31,32] Therapeutic vaccines are still under investigation to treat HPV infection and its related epithelial lesions, but phase III clinical trials are still needed.[33] In addition, other therapeutic approaches have been tested to promote the regression of low-grade lesions or prevent progression. They include the application of 5-fluorouracil, curcumin, imiquimod, interferons, Vitamin D, and others.[34–36] Also, probiotics have been applied but did not show any influence on high-risk HPV clearance,[37] while vaginal therapy with carboxy-methyl-beta-glucan might positively impact

the risk of HPV persistence.[38] However, up to date, no effective strategy was established for those medical approaches.

DeflaGyn®

Recently, a vaginal gel (DeflaGyn®) was developed, which is based on a combination of citric acid and sodium selenite with antioxidant properties. The anti-oxidative capacity might lower the risk of viral persistence as oxidative stress is associated with the carcinogenesis induced by HPV.[39] In addition, the vaginal gel contains highly disperse siliceous dioxide particles that may bind proteinaceous particles. In a preliminary study, intravaginal application of the gel improved the cytological status of women with abnormal cell smears compared to non-users within a 16-week trial.[40]

In this first trial, the authors could show that upon 307 female patients who were included in the analysis at the time of the survey, 186 patients (60.6%) had Pap III and 119 (38.8%) had Pap III D finding. The spontaneous remission rate of untreated Pap III patients was 6%, and that of untreated Pap III D patients was 11%. The remission rates of patients treated with a vaginal gel were 77% for Pap III and 71% for Pap III D. In this first study, no data regarding HPV clearance were obtained.

A subsequent study[41] aimed to further characterize the effect of the gel. The open, prospective clinical trial was analyzed, focusing on women diagnosed with conspicuous cervical smears (ASC-US, LSIL, ASC-H, or high-grade squamous intraepithelial (HSIL)).[41] Extracting data from the trial of Major et al.[41] and excluding for the cytological analyses those patients with an NILM, 100 women were treated with the gel for 3 months (3×28 days), while a control group ($n = 106$) did not receive any treatment over the course of the study. Subsequently, there was a follow-up period with no treatment in both groups. Pap smear findings, high-risk HPV status, and expression of tumor markers p16/Ki67 (CINTec PLUS) were assessed at baseline and after 3 months. After the follow-up, CINTec PLUS and Pap smear testing was performed. Success was defined as either cytological regression, defined as an initial ASC-US, LSIL, ASC-H, or HSIL lesion, which disappeared or changed to a lower level and improvement of high-risk HPV status and tumor marker expression.

The results (excluding the cytological healthy patients for the first record) showed that from the 100 women with the abnormal cervical smear who received the treatment with the vaginal gel containing SiO2, selenite, and citric acid, 22% were diagnosed with ASC-US, 58% as LSIL, 9% as ASC-H, and 11% with HSIL diagnose. After treatment with the vaginal gel for 3 months, 75% of the participants had improved cytological findings (determined as complete resolution of lesions or change to lower-grade lesions). After 6 months, the improvement was seen in 80.9% of them. Fifty-six percent of cervical smears were classified negative for intraepithelial lesion or malignancy (NILM), 34% had low-grade lesions (ASC-US and LSIL), and 3% were classified as HSIL after 3 months with further improvements after 6 months. Improvements were found in 79.3% of LSIL and 76.2% of ASC-US cases, while 4.8% and 5.2% of them had progressed to higher-level findings after 6 months. 100% of ASC-H findings and 88.9% of HSIL improved after 6 months.[41]

In the non-treated group, baseline abnormal cervical smear displayed an equal distribution compared to the treated group: of the 106 women, 23.6% were diagnosed with ASC-US, 55.7% as LSIL, 16% as ASC-H, and 4.7% as HSIL. However, less pronounced changes were observed during the study. After completing the trial (6 months), 37.1% of the participants had improved Pap results. In detail, 16.2% had inconspicuous findings, while 71.4% still were diagnosed with lower-grade lesions (ASC-US or LSIL) and 12.4% with higher-grade lesions ASC-H or HSIL. From low-grade lesions at baseline, ASC-US and LSIL, 25% and 23.7% had improved, and 45.8% and 8.5% progressed to higher-grade. All the HSIL findings at baseline were improved, and 82.3% of ASC-H. However, one ASC-H had progressed to HSIL. According to statistical evaluation with Fisher's exact test of independence, the association between treatment with vaginal gel and overall improvement of cytological findings was highly significant when compared to the non-treated group ($p < 0.0001$).[41]

In the same study, the clearance of high-risk HPV was assessed to evaluate the efficacy of the vaginal gel. In the treated group, 87.0% of cytological samples were found to be high-risk HPV positive at baseline. The value declined to 41% high-risk HPV positive after 3 months, corresponding to a clearance rate of 53%. Most lesions that resolved to NILM or regressed to ASC-US also became HPV negative within 3 months. Most higher-grade lesions remained high-risk HPV positive.[41]

In the comparison group, no HPV clearance was observed. In contrast, the percentage of HPV positive findings increased by 6% within 3 months (83.0% vs 78.3% at baseline). This finding is consistent with the observation that there was a minor overall improvement in cytological findings. Also, 50% of the unsuspicious results (NILM) and 64.3% of ASC-US were diagnosed as high-risk HPV positive (vs 14.3% and 27.8% in the treated group, respectively). The effect of treatment with the vaginal gel on overall HPV clearance was highly significant according to Fisher's exact test ($p < 0.0001$).[41]

The results of CINTec PLUS were corresponding. In the treatment group, CINTec PLUS positive results decreased from 75% of all cases at baseline to 12% and 5.3% of all patients after 3 and 6 months, respectively, while in the non-treated group, CINTec PLUS positive results decreased from 91.5% at baseline to 74.5% and

75.2% after 3 and 6 months. The treatment effect was also statistically significantly different ($p < 0.0001$).[41]

This study reported regression of CIN lesions with the vaginal gel in a subset of subjects.[41] Of note, none of the women dropped out during the active treatment phase of the study. However, the 3 months follow-up period was not completed by six participants of the treatment group and one participant of the control group. In total, 42 adverse events were reported; most of them were mild or moderate. Adverse events were vaginal itching or burning, bloody discharge, increased vaginal bleeding, vaginal mycosis or herpes, or slight abdominal cramps. There were no serious adverse events reported. In addition, it was confirmed that no systemic absorption of selenium occurred.[41]

Conclusion

These results reaffirm the fact that HPV clearance is critical for all treatment strategies. Even when initial cytological findings are still non-pathological, women who tested positive for high-risk HPV are at risk of developing precancerous lesions.[42] Their clearance rate is described with 43% within 6 months[43] and a median duration of 224 days.[44] Up to 90% of HPV, infections are believed to resolve within 2 years.[4] In contrast, abnormal cytological findings are associated with high-risk HPV persistence,[42] and 2-year cumulative regression rates between 35% and 53%[45] are reported. The data indicate that a 3-month application of the vaginal gel containing disperse SiO_2 and an anti-oxidative combination of citric acid and sodium selenite promotes the clearance of high-risk HPV in 53% of cases while the control group displayed a slight increase of 6%. Furthermore, there is an improvement in cytological Pap findings in 80.9% of women using the gel, while in only 37.1% women of the control group. This is underlined as only 5.3% of women treated with the vaginal gel were tested positive for p16/Ki67 after 6 months compared to 75.2% in the non-treated group. Therefore, the examined vaginal gel may support the healing of conspicuous cytological findings and clearance of high-risk HPV positive findings.

Author contributions

P.-A.R., A.M., and M.S. were responsible for the design and writing of the manuscript. J.H. was responsible for the literature research and validation of data.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: P.-A.R. is an employee of Exeltis Healthcare. A.M.is an employee of Exeltis Germany GmbH. M.S. is an employee of Exeltis Germany GmbH. Professor J.H. declares no conflict of interest.

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