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ORIGINAL RESEARCH

Therapeutic Efficacy of a *Coriolus versicolor*-Based Vaginal Gel in Women with Cervical Uterine High-Risk HPV Infection: A Retrospective Observational Study

Anna Angela Criscuolo · Francesco Sesti · Emilio Piccione · Pasquale Mancino · Elena Belloni · Cetty Gullo · Marco Ciotti

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ABSTRACT

Introduction: A *Coriolus versicolor*-based vaginal gel is available for treating women with cervical uterine high-risk human papillomavirus (HPV) infection through re-epithelizing and re-balancing microbiota actions.

Methods: A longitudinal retrospective observational study was performed to evaluate efficacy and safety of the gel. Women treated with *Coriolus versicolor*-based vaginal gel were compared with women not treated with the gel. Both groups were monitored for HPV infection by an HPV DNA test, Pap smear (cytology) and colposcopy at baseline and after 6 months.

Results: Overall, 183 high-risk HPV positive women were enrolled (97 treated and 86 controls). After 6 months, the HPV DNA test became negative in 67.0% versus 37.2% of treated and controls, respectively ($p < 0.0001$). Furthermore, 76.1% versus 40.8% registered a colposcopy improvement ($p = 0.0005$) and 60.4% versus 40.8% showed a remission ($p = 0.05$), for treated versus controls, respectively. Regarding to cytology, 78.5% of treated versus 37.7% of controls registered an improvement, while 70.8% of treated versus 34.8% of controls had a remission ($p < 0.0001$ for both variables). At multivariate analyses adjusted for age, smoking habit, and use of estroprogestinic pill, compared to controls, women treated with the gel showed a significantly higher likelihood to experience the clearance of HPV DNA (OR 4.81; 95% 2.43–9.53), and remission at colposcopy (OR 2.30; 95% 1.00–5.31), and cytology (OR 5.13; 95% 2.40–10.96) at 6 months. No adverse event was reported during the follow-up.

Conclusions: The use of a *Coriolus versicolor*-based vaginal gel in high-risk HPV patients is safe and effective based on all examined tests.

Keywords: Colposcopy; *Coriolus versicolor*; Cytology; HPV-DNA; Human papillomavirus; Vaginal gel

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A. A. Criscuolo · F. Sesti · E. Piccione · E. Belloni · C. Gullo
Section of Gynecology and Obstetrics, Department of Surgical Sciences, University of Rome Tor Vergata, Rome, Italy

P. Mancino
Department of Obstetrics Gynecology and Neurology, University La Sapienza, Rome, Italy

M. Ciotti (✉)
Virology Unit, Laboratory of Clinical Microbiology and Viroloy, Polyclinic Tor Vergata, Rome, Italy
e-mail: marco.ciotti@ptvonline.it

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Key Summary Points

Why carry out this study?

Human papillomavirus (HPV) infection is the most frequent sexually transmitted disease, which has been shown to be a necessary cause for the development of cervical cancer.

Effectiveness and safety of a *Coriolus versicolor*-based vaginal gel for treating women with cervical uterine high-risk HPV infection have been assessed.

What was learned from the study?

The use of the *Coriolus versicolor*-based vaginal gel significantly improved results of HPV-DNA, cytology and colposcopy tests.

Therapy was associated with from 2 to 5 times higher likelihood to obtain remission or improvements as compared to controls.

These findings suggest the possibility to avoid more aggressive treatments, such as destructive and/or excisional interventions in a relevant number of women.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13326362.

INTRODUCTION

Human papillomavirus (HPV) infection is the most frequent sexually transmitted disease. More than 140 genotypes are known, of which around 40 are responsible for genital and anal tract infections [1–4]. HPV infection has been shown to be a necessary cause for the development of cervical cancer. In particular, 12 high-risk (HR) strains cause approximately 90% of cases of cervical cancer [5]. It is estimated that up to 80% of sexually active women become infected with HPV virus of any type during their lives, and more than 50% are infected with a high oncogenic risk type [6]. The carcinoma of the cervix was the first tumor to be recognized by the World Health Organization as totally attributable to an infection [7]. Other related HPV tumors are found at the anal, vaginal, vulvar, penile, and oropharynx levels. HPV infections appear to be responsible for 99% of malignant tumors of the cervix, 97% of anal malignancies, 70% of malignant tumors of the vagina, 47% of malignant tumors of the penis, 40% of malignant tumors of the vulva, 47% of cases of malignant tumors of the oropharynx, and 11% of malignant tumors of the oral cavity [8, 9].

National and international guidelines provide recommendations regarding the management of persistent infection of HR HPV, associated or not with cervical intra-epithelial neoplasia grade 1 (CIN 1), and regarding the immediate treatment or the watchful waiting, with close cytological and colposcopic controls, to monitor regression or any progression of the lesions towards forms of atypia of higher degree [10, 11].

The percentage of spontaneous regression of HR HPV infection without treatment is around 50%; for this reason, a watchful waiting approach is usually adopted in patients under 35 years and a conservative treatment is preferred in patients over 35 years with persistent and large lesions or poor compliance to follow-up [12].

The role of the immune system in determining the regression/progression of cervical lesions is acknowledged [13, 14]. To date, there are effective ablative or excisional methods to treat evident lesions produced by the persistence of HPV [10]. However, there is still no therapy capable of improving the immune response and facilitate the lesion regression.

Recently, a non-hormonal vaginal gel has been approved in Europe as a medical device

(Papilocare®; Procare Health Iberia, distributed by Shionogi, Rome, Italy). The gel combines ingredients of known properties, such as moisturizing, tissue regenerating, healing, and balancing of vaginal microbiota (hyaluronic acid, Asian centella, *Aloe vera*, and alpha-glucan oligosaccharide), with other ingredients having demonstrated positive effects on both HPV-dependent cervical lesions and HPV clearance (*Coriolus versicolor*, *Azadirachta indica*, and carboxymethyl-β-glucan) [15–17]. The gel acts as a moisturizer and lubricant because of strong hydrating properties, also enhancing and accelerating repair of atrophic or injured cervicovaginal mucosa. However, evidence of its effect on HR HPV infection is scant.

Given these premises, a pilot study was designed to assess the clinical benefits of the gel on the epithelization and repair of cervical lesions.

The study aimed to evaluate the efficacy and safety of the gel as re-epithelizing and repairing therapy in women positive to HR HPV infection with normal or abnormal cytology.

Therapeutic outcomes were compared with those obtained in women not receiving re-epithelizing therapy.

METHODS

This was a longitudinal retrospective observational study involving women admitted to the Clinic of Colposcopy and Cervical-Vaginal Pathology of the University Hospital Tor Vergata, Rome, Italy, between October 2017 and July 2018.

The study was approved by the Independent Ethics Committee of Polyclinic Tor Vergata Foundation, protocol n. 167/19. All participants signed informed consent for being included in the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Inclusion criteria were: women aged between 18 and 49 years, positive to a HR HPV desoxyribonucleic acid (DNA) test, and with normal or abnormal cytology [atypical squamous cells of undetermined significance (ASCUS), low grade squamous intra-epithelial lesion (LSIL), and high-grade squamous intraepithelial lesion (HSIL)].

Exclusion criteria were other sexually transmissible diseases, congenital or acquired immunodeficiency, pregnancy, or CIN grade 2 or 3 lesions. CIN2 and CIN3 were excluded because patients with such lesions usually undergo conization.

All participants underwent the HPV DNA test, cervical cytological examination (Papanicolaou test), and colposcopy at baseline and after 6 months.

Women treated with *Coriolus versicolor*-based vaginal gel were compared with women not treated with the gel, according to the guidelines of the Italian Society of Colposcopy and Cervical-Vaginal Pathology (SICPCV), and to the availability on the market of the vaginal gel at baseline.

Treatment scheme of *Coriolus versicolor*-based vaginal gel included 1 cannula/day for 21 consecutive days in the first month of therapy; then, 1 cannula to be used in every other day (except in the presence of the menstrual cycle) during the next 2 months.

At cervical cytology, exo- and endocervical cells were collected using the Ayre's spatula and cytobrush, respectively. The cells were streaked on two different sections of a glass slide, spray-fixed, and sent to the Pathology Department for examination. Smears were classified according to the 2001 Bethesda System: negative for intraepithelial lesion, ASCUS, atypical squamous cells which cannot exclude high-grade squamous intraepithelial lesion (ASC-H), LSIL, and HSIL [18].

For detection of HPV DNA and typing, cervical cells collected from the transition zone were suspended in PreservCyt solution (Hologic, Marlborough, MA, USA), and stored at room temperature according to the manufacturer's instructions until analysis. Then, an aliquot of 5 ml was transferred to a collection tube and centrifuged at 1200 rpm for 5 min. The supernatant was discarded, and the pellet resuspended in 1 ml buffer before DNA extraction on an eMAG™ extractor (BioMerieux, Marcy l'Etoile, France). HPV detection and

typing were performed with an AnyplexTM II HPV28 Detection kit (Seegene, Seoul, South Korea) [19].

Statistical Analysis

Being a pilot study, no formal sample size estimation was performed. All consecutive eligible women were included. Descriptive analyses were carried out, and the results were reported as mean ± standard deviation and percentages for continuous and categorical variables, respectively. Mann–Whitney and chi-squared tests were performed to compare baseline characteristics between the two treatment groups. The Fisher Exact test was adopted where appropriate.

Treatment efficacy was evaluated after 6 months in terms of HPV DNA test (negative, partial negativization, positive), colposcopy (negative, ectopy, positive), and cytology (negative, ASCUS, LSIL, HSIL). For each endpoint, the proportion of women with a negative test (i.e., clearance/remission) was evaluated, as well as the proportion of women with at least one category reduction (i.e., improvement: e.g., cytology from LSIL at baseline to ASCUS after 6 months).

For each endpoint, the distribution of patients with different test results at baseline and after 6 months was calculated in both groups of interest. Percentage histograms were plotted.

For inferential purposes, patients with negative test at baseline for each outcome were not considered in the analyses. The comparison between treatment arms was based on the chi-squared test. Results are also expressed odds ratios (OR) and their 95% confidence intervals (95% CI).

Multivariate analyses adjusted for baseline characteristics (age, smoking habit, and previous and/or current use of estroprogestinic pill) were applied to evaluate the likelihood of remission and improvement associated with the therapy versus control for each test. Results are expressed as OR and their 95% CI.

Incidence of adverse events was also assessed.

Table 1 Baseline characteristics of the two groups of women enrolled in the study

	Control group (Not treated)	***Coriolus versicolor*-based vaginal gel group**	***p* value**
n	86	97	
Age (mean years and standard deviation)	30.1 ± 7.4	32.3 ± 8.4	0.09
Smokers *n* (%)	9 (10.5)	6 (6.2)	0.29
History of taking estroprogestins, *n* (%)	11 (12.8)	9 (9.3)	0.45
Caucasian race, *n* (%)	86 (100)	97 (100)	–
Colposcopy, *n* (%)			
Negative	37 (43.0)	51 (52.6)	**< 0.0001**
Ectopy	0 (0.0)	18 (18.5)	
Positive	49 (57.1)	28 (28.9)	
Cytology, *n* (%)			
Negative	17 (19.8)	32 (33.0)	0.11
ASCUS	37 (43.0)	31 (32.0)	
LSIL	32 (37.2)	33 (34.0)	
HSIL	0 (0.0)	1 (1.0)	

Data are means and standard deviations or frequency and proportion

Mann–Whitney test, chi-squared test or Fisher Exact test were performed, as appropriate

p value in bold is statistically significant ($p < 0.05$)

A p value < 0.05 was considered statistically significant. Statistical analyses were performed with the Statistical Package for the Social Sciences Windows, ve.5.0 (SPSS, Chicago, IL, USA).

The data associated with the paper are not publicly available, but are available from the corresponding author upon reasonable request.

Table 2 Test results in the two groups of women investigated after 6 months

	Control group (Not treated)	*Coriolus versicolor*-based vaginal gel group	*p* value
n	86	97	
HPV-DNA, *n* (%)			
Negative	32 (37.2)	65 (67.0)	**< 0.0001**
Partial negativization	0 (0.0)	3 (3.1)	
Positive	54 (62.8)	29 (29.9)	
Colposcopy, *n* (%)			
Negative	48 (55.8)	77 (79.4)	**< 0.0001**
Re-epithelization phase	0 (0.0)	8 (8.3)	
Ectopy	0 (0.0)	4 (4.1)	
Positive	38 (44.2)	8 (8.3)	
Cytology, *n* (%)			
Negative	41 (47.7)	75 (77.3)	**0.0002**
ASCUS	19 (22.1)	11 (11.4)	
LSIL	25 (29.0)	10 (10.3)	
HSIL	1 (1.2)	1 (1.0)	

Data are frequency and proportion. Chi-squared test or Fisher Exact test were performed, as appropriate
p values in bold are statistically significant ($p < 0.05$)

RESULTS

Overall, 183 women were enrolled in the study, of whom 97 treated with the gel and 86 controls. Baseline characteristics are reported in Table 1.

After 6 months, the HPV DNA test became negative in 37.2% of controls and 67.0% of treated patients (Table 2; Fig. 1) ($p < 0.0001$ between groups); additionally, among treated women, 3.1% showed partial negativization (Table 2; Fig. 1). The proportion of women with

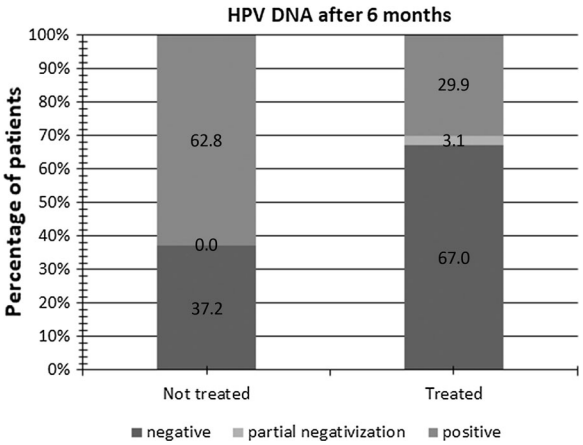

Fig. 1 Efficacy of *Coriolus versicolor*-based vaginal gel. Changes in the distribution of diagnostic test categories by treatment group and time

negative colposcopy increased from 43.0% at baseline to 55.8% after 6 months in the control group, and from 52.6 to 79.4% in women treated with *Coriolus versicolor*-based vaginal gel ($p < 0.0001$ between groups at 6 months). Among treated women with ectopy, 8.3% were in re-epithelization phase (Table 2; Fig. 2). The percentage of women with negative cytology increased from 19.8% at baseline to 47.7% after 6 months in the control group, and from 33.0% to 77.3% in treated women (Table 2; Fig. 2) ($p < 0.0001$ between groups at 6 months).

After the exclusion of women with a negative test at baseline, remission and improvement at 6 months versus baseline were examined for colposcopy and cytology, and the results are shown in Table 3 and Fig. 3. After 6 months, 76.1% of treated women versus 40.8% of controls registered a colposcopy improvement ($p = 0.0005$), while 60.9% versus 40.8% showed a remission, respectively ($p = 0.05$). Regarding cytology, after 6 months 78.5% of treated women versus 37.7% of controls registered an improvement, while 70.8% versus 34.8% had a remission, respectively ($p < 0.0001$ between groups, for both comparisons). Treated women were from 2.26 to 6.02 times more likely than controls to experience improvement or remission at the different diagnostic procedures (Table 3).

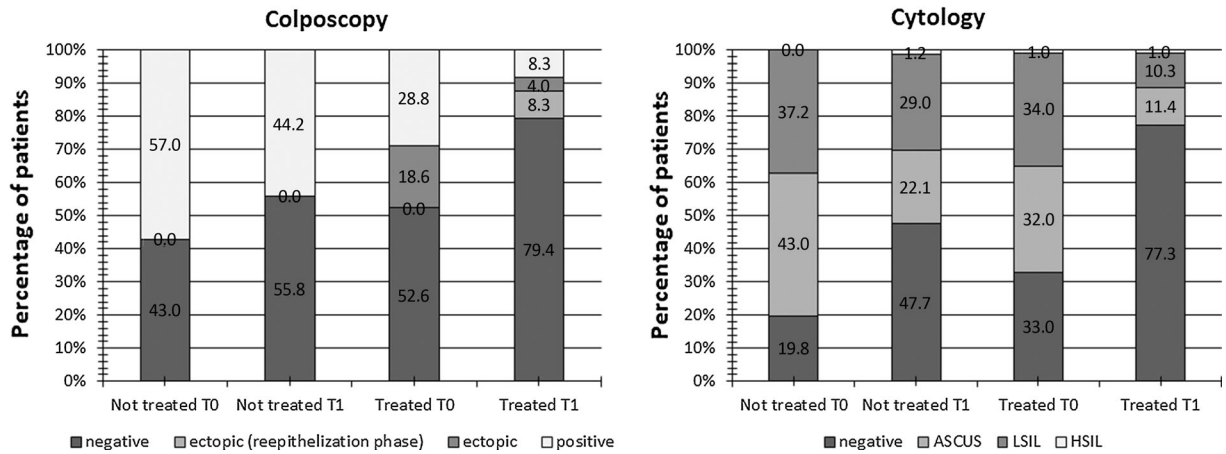

Fig. 2 Efficacy of *Coriolus versicolor*-based vaginal gel. Changes in the distribution of diagnostic HPV-DNA categories by treatment group at 6 months; *T0* baseline, *T1* after 6 months

In multivariate analyses, compared to controls, women treated with the gel showed:

- In HPV DNA test, an almost five-fold higher likelihood to experience viral clearance (OR 4.81; 95% CI 2.43–9.53) and a five-fold higher likelihood to experience improvement (OR 5.28; 95% CI 2.67–10.44).
- In colposcopy, a two-fold higher likelihood to experience remission (OR 2.30; 95% 1.00–5.31) and a four-fold higher likelihood to experience improvement (OR 4.61; 95%CI 1.87–11.38).
- In cytology, a five-fold higher likelihood to experience remission (OR 5.13; 95% CI 2.40–10.96) and a seven-fold higher likelihood to experience improvement (OR 7.12; 95% CI 3.16–16.04).

Multivariate models are reported in Online Appendix 1. Age was also significantly associated with viral clearance or improvement at HPV DNA test, with increasing age associated with a decrease in the likelihood of remission/improvement.

No adverse event was registered and no concomitant adjuvant therapies (e.g., lubricants) were used in either group during follow-up.

DISCUSSION

A clear beneficial effect of the *Coriolus versicolor*-based vaginal gel on epithelization of the ectocervix was found. The therapeutic scheme was based on 21 consecutive days of therapy in the first month plus every other day during the subsequent 2 months.

At the end of the 6-month observation period, among the controls, women documenting a spontaneous improvement or remission ranged from 34.8 to 40.8% in the different screening methods, while over 2/3 of treated women were in remission from HPV-infection in the HPV-DNA test, and from 60.9 to 78.5% achieved remission or improvement in the different screening methods.

Multivariate analyses documented that therapy was associated with from 2 to 7 times higher likelihood to obtain remission or improvements as compared to controls.

Previously, another pilot study assessed the effect of a 12-day treatment using the *Coriolus versicolo*r-based vaginal gel in 21 women showing a positive effect on epithelization of the cervical mucosa [20]. To the best of our knowledge, no other studies have been published on this topic, although several data presented at international gynecology congresses consistently documented treatment-related benefits, which may include cervix re-epithelization among HPV-positive women, normalization of

Table 3 Proportions of patients experiencing remission and improvements after 6 months based on each diagnostic procedure (patients with negative test at baseline were not considered)

	n^a	Not treated *n* (%)	n^b	*Coriolus versicolor*-based vaginal gel *N* (%)	*p* value	OR (95% CI)
Improvement						
HPV-DNA	86	32 (37.2)	97	68 (70.1)	< **0.0001**	3.96 (2.14–7.33)
Colposcopy	49	20 (40.8)	46	35 (76.1)	**0.0005**	4.61 (1.90–11.18)
Cytology	69	26 (37.7)	65	51 (78.5)	< **0.0001**	6.02 (2.80–12.96)
Clearance/remission						
HPV-DNA	86	32 (37.2)	97	65 (67.0)	< **0.0001**	3.43 (1.86–6.30)
Colposcopy	49	20 (40.8)	46	28 (60.9)	0.05	2.26 (0.99–5.13)
Cytology	69	24 (34.8)	65	46 (70.8)	< **0.0001**	4.54 (2.19–9.41)

Definitions: *Clearance/remission* negative test at 6 months, *Improvement* at least one category reduction (for example, cytology from LSIL at baseline to ASCUS after 6 months)

OR Odds ratio, *95% CI* 95% confidence intervals

n^a Evaluable not treated women after the exclusion of those with negative test at baseline for each diagnostic procedure

n^b Evaluable treated women after the exclusion of those with negative test at baseline for each diagnostic procedure

p values in bold are statistically significant ($p < 0.05$)

cervix low-grade lesions, improvement in vaginal dysbiosis favoring the natural process of vaginal immunity, and clearance of the virus after 6 months of treatment [21–27]. These findings suggest the possibility to avoid more aggressive treatments, such as destructive and/or excisional interventions in a relevant number of women.

Previous publications support the evidence of moisturizing and re-epithelizing action of the main components of the vaginal gel. In fact, *Coriolus versicolor* and beta glucan are incapsulated inside niosomes and phytosomes, which ensure an effective penetration into the basal layers of the cervical epithelium. The gel has a targeted action and re-epithelizes the cervical transformation zone (i.e., the area where the HPV integrates), preventing the formation and progression of cervical intraepithelial lesions [20, 28].

Regarding the properties of the vaginal gel, several studies have highlighted the positive effects of the substances present in the gel on re-epithelization, balancing the vaginal microbiota besides the effects on the immune system and HPV clearance [29–34]. In particular, the tissue-regenerating effect of *Centella asiatica* as well as the re-epithelizing effect of *Azadirachta indica* has been reported in several studies [20, 32, 35]. Re-epithelization at the transitional zone of cervix will hamper the entry of the virus inside the cells.

Positive effects on the vaginal microbiota has been reported by Palacios et al. [20], and restoration of vaginal ecosystem protects from HPV infection [36].

The study has strengths and limitations. The major strengths are the novelty of the study and the large sample size. The major limitations are the potential bias derived from the non-experimental study design. However, the characteristics influencing the response to the treatment were balanced between groups, with the only exception being the colposcopy results at baseline. Information on socioeconomic status and sexual or reproductive history were not available in the retrospective database. To take into consideration systematic differences, multivariate models were applied. Furthermore, no

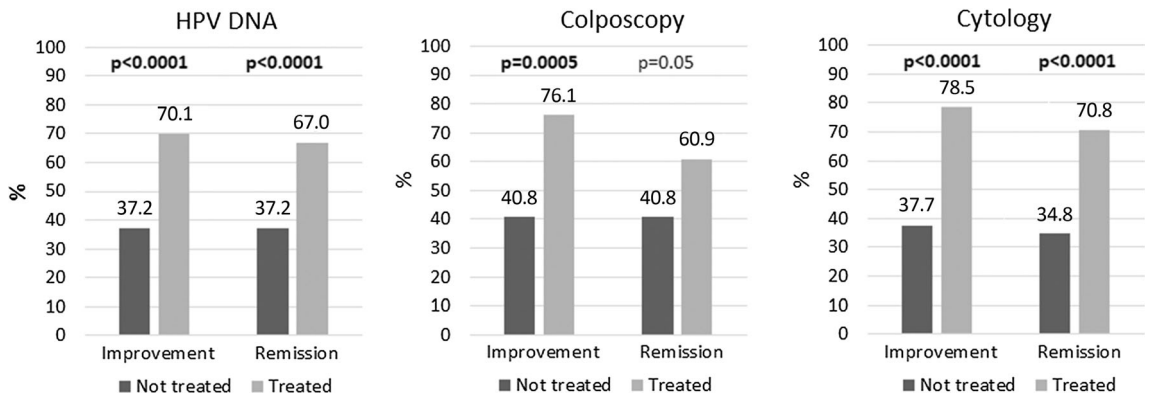

Fig. 3 Proportions of patients experiencing remission and improvements after 6 months based on each diagnostic procedure (patients with negative test at baseline were not considered)

additional therapies were used during the follow-up in either group.

CONCLUSIONS

In this proof-of-concept study conducted among HR HPV women, the use of a *Coriolus versicolor*-based vaginal gel significantly improved results of HPV-DNA, cytology, and colposcopy tests, aligned with the most recent data presented. This was a pilot study based entirely on routine clinical experience with the *Coriolus versicolor*-based gel versus no treatment (standard of care). The extremely marked benefits obtained in our study need to be confirmed by appropriate randomized double-blinded clinical trials to address any possible bias associated with the retrospective design of the study. However, the novelty of the data and the documentation of marked benefits of the new treatment option deserve consideration.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Compliance with Ethics Guidelines. The study was approved by the Independent Ethics Committee of Polyclinic Tor Vergata Foundation, protocol n. 167/19. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

Disclosures. The authors Anna Angela Criscuolo, Francesco Sesti, Emilio Piccione, Pasquale Mancino, Elena Belloni, Cetty Gullo and Marco Ciotti have nothing to disclose.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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