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Prevention and treatment of low-grade cervical lesions caused by HPV: evidence for a vaginal gel based on Coriolus versicolor

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INTRODUCTION

Scientific and technological advances have resulted in the detection of more high-risk human papillomavirus (HPV) infections and women with associated cervical intraepithelial neoplasia (CIN) than ever before though, hitherto, the traditional options remain as either masterly inactivity or surgery.

We know that nearly all sexually active adults will acquire HPV at some point in their lifetimes[1]. The vast majority of these infections are transitory and 90% are spontaneously cleared or become inactive within 12 to 24 months of exposure to the virus[2,3,4]. Nonetheless, in some women the infections persist and in these women there is a risk of developing precancerous.

It is recognised that the likelihood of persistence is related to the type of HPV. More than 150 subtypes of HPV have been identified which can be classified into 2 groups depending on their oncogenic capacity, namely, viruses with a low risk of progression to cancerous lesions (LR-HPV) and viruses with a high risk of progression to cervical cancer (HR-HPV). The main serotypes in this group are 16, 18, and 31, which are more directly associated with persistence of the virus. Persistent infection with an oncogenic or HR-HPV type is the main risk factor for detecting a CIN that may range from CIN1 to CIN3 and, ultimately, cancer[3,5,6].

The potential health burden caused by HPV is immense. In Europe, approximately 60,000 women are diagnosed with cervical cancer every year of whom about 26,000 will die from the disease[7] yet this represents but a tiny proportion of those who have been infected with HPV. In only a fraction of those infected will the virus persist and go on to develop CIN. Even then, a significant proportion of cases will resolve, particularly in young women. Up to 70% of women aged 30 or less with CIN2 will regress spontaneously[8] and colposcopists are increasingly reluctant to subject young women to potentially harmful cervical treatment with the recognised associated obstetric morbidity[9].

These considerations pose a real problem for cervical screening programmes, particularly if primary HPV testing is used. Many well and asymptomatic women will screen positive and experience with the associated anxiety[10,11], yet still be at a relatively low risk of developing cervical cancer or requiring treatment of CIN. In some cases, particularly if further tests are normal or low grade, conservative management will be advised even if referred for colposcopy. Given that such an approach may last for months this can be challenging both for the patient and clinicians. It follows that in these circumstances there is a demand for a safe, non-surgical treatment that might enhance viral clearance.

HPV infection alone is not the only determinant of outcome. Other factors, such as host immunity, histological structure of the ectocervix and transformation zone, plus the state of the vaginal microbiota all play a role, which is still poorly defined, but which may be essential for progression or regression of the infection[12]. Influencing some of these factors may provide an opportunity for improved clearance of the virus and reduction in risk.

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Original

Prevention and treatment of low-grade cervical lesions caused by HPV: evidence for a vaginal gel based on Coriolus versicolor

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INTRODUCTION

Human papillomavirus (HPV) and cervical lesions currently have a major impact in Spain, where, every year, around 370,000 low-grade lesions (low-grade squamous intraepithelial lesion [LSIL] or atypical cells of uncertain significance [ASCUS]) and 2,500 cases of cervical cancer are diagnosed. However, the most striking finding is that HPV testing is positive in approximately 2 million women[1]. The magnitude of the problem of HPV

for society as a whole is seen clearly in Figure 1, where the pyramid shows that cervical cancer is a rare yet preventable complication of a very common infection.

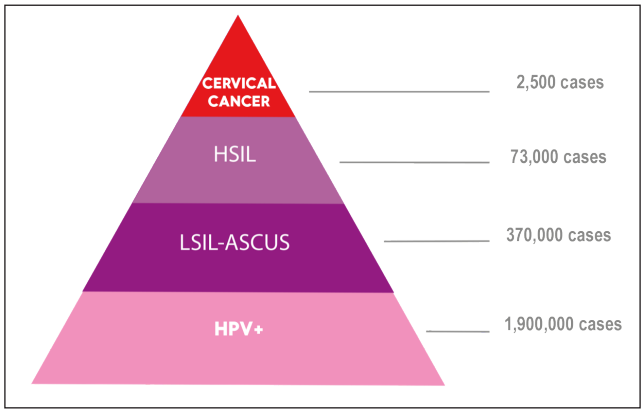

Fig.1. Pyramid illustrating the incidence of HPV in Spain (adapted from the vaccination guide of AEPCC 2014)[2]

HPV infection is the most common sexually transmitted infection in the world, and cervical cancer is the second most common type of cancer in women[2]. More than 150 subtypes of HPV have been identified; of these, 40-50 can produce genital lesions. According to Bouvard, these viruses can be classified into 2 groups depending on their oncogenic capacity, namely, viruses with a low risk of progression to cancerous lesions (LR-HPV) and viruses with a high risk of progression to cervical cancer (HR-HPV). The main serotypes in this group are 16, 18, and 31, which are more directly associated with persistence and with cervical cancer[3].

HPV is very prevalent and has a high clearance rate in women aged <30 years. However, the rate of clearance of HR-HPV at 6 and 18 months stands at 29% and 41%, respectively; in the case of HPV-16 in particular, the clearance rate is only 9% at 6 months and 19% at 18 months, which is much lower than rates for the other serotypes and is highly consistent with the potential malignant transformation of this serotype[4].

Today, we know that HPV infection is a necessary but not the only condition for developing the disease and that identification of the HPV serotype responsible for the disease is not the only determinant of outcome. Other factors, such as host immunity, histological structure of the exocervix and transformation zone, and the state of the vaginal microbiota also play a role, which is still poorly defined, but which may be essential for progression or regression of the infection[5].

VAGINAL GEL BASED ON CORIOLUS VERSICOLOR

Given this initial situation, we began to evaluate a vaginal gel, Papilocare® (Procare Health Iberia), which is composed of ingredients that act synergistically to enable a positive effect on modifiable factors. The gel aims to enhance epithelialization of the cervix in order to minimize the window of opportunity for viral entry, to improve the microbiota and thus create a less favorable state for persistence of the virus, and to generate favorable conditions for natural immunity that would enable viral clearance and healing of lesions.

The clinical development of this product comprises several trials and studies performed during recent years, including an initial study in HPV-infected patients that revealed a significant improvement in cervical epithelialization and vaginal health[6]. The first study of HPV-positive women was the EPICERVIX pilot study[7], which included a sample of 21 patients with no lesions in cytology, and a normal colposcopy result. Patients underwent an exploratory investigation to determine the effect of applying vaginal gel daily for 21 days on cervical epithelialization and on vaginal microbiota.

The degree of ectopia was evaluated using colposcopy and then assessed by an investigator using a Likert-type scale ranging from 1 (severe ectopia and bleeding) to 5 (no ectopia). The composition of the microbiota was determined using pyrosequencing of the 16S rRNA gene (Illumina MiSeq sequencing). Changes in biodiversity were evaluated using the Shannon index (<2, low biodiversity; 2-3, normal biodiversity; and >3 high biodiversity) and based on the proportion of microorganisms in the vagina.

Epithelialization of the cervix improved in 52.6% of patients and remained stable in 47.7%. No patients worsened. At the end of the study, 63.2% of patients had normal cervical epithelialization compared with 38.1% at baseline. In addition, significant changes in vaginal microbiota were observed at the end of the study. Biodiversity decreased significantly as the concentration of autochthonous species increased and that of pathogenic species decreased (Figure 2).

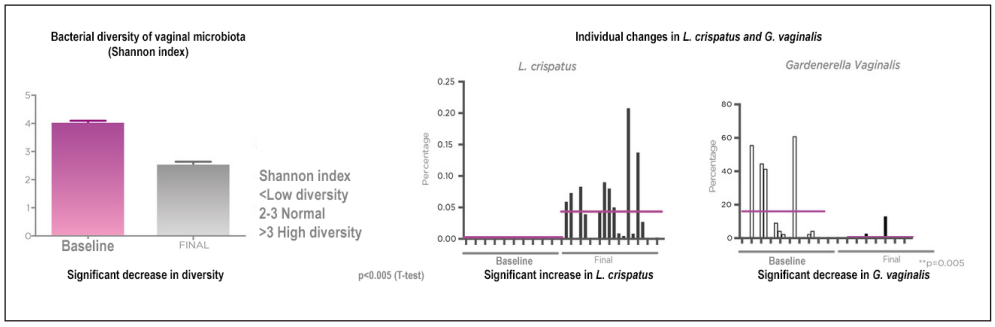

Fig.2. Results for vaginal microbiota in the Epicervix study[7]

The EPICERVIX study revealed a significant improvement in epithelialization of the cervix in HPV-infected persons in the absence of lesions and confirmed that it was possible to modify the composition of the microbiota, thus reducing the considerable biodiversity associated with vaginal dysbiosis and increasing the concentration of lactobacilli.

A more wide-ranging study, the PALOMA trial, was started to advance the development of the product and to confirm these findings.

THE PALOMA CLINICAL TRIAL

Methods

The PALOMA clinical trial[8-10] is a multicenter, open-label, parallel-group randomized clinical trial with a control group that was designed to explore the efficacy of Papilocare® gel for treatment of lesions of the cervical mucosa caused by HPV.

We included HPV-positive patients aged between 30 and 65 years with a cytology indicating ASCUS or LSIL and a compatible colposcopy image.

The exclusion criteria were previous HPV vaccination and clinically relevant abnormalities such as pregnancy, immunosuppression, and abnormal genital bleeding.

The patients included were randomized to 1 of 3 arms: 2 arms with the vaginal treatment in different regimens and 1 control arm (routine clinical practice, ie, wait and see approach). Fig.3.

The primary endpoint was the percentage of patients with repair of cervical lesions according to cytology and compatible colposcopy image 6 months after starting treatment.

The secondary endpoints analyzed included the percentage of patients with clearance of HPV according to a PCR genotyping assay (Clart HPV4®) and stress perceived by the patient using a questionnaire (14-item Perceived Stress Scale [PSS-14]).

Other variables evaluated included tolerability, satisfaction, and adherence to treatment with Papilocare® gel.

Detection and identification of HPV and evaluation of cytology findings was centralized under triple-blind conditions at the Instituto de Estudios Celulares y Moleculares (ICM), Lugo, Spain.

The main analysis was performed between 2 groups: the treatment group (both arms) and the control group. The intention-to-treat population was analyzed: patients who received at least 1 application of the investigational product and had at least baseline values and a posttreatment value for the primary endpoint.

A subanalysis was performed to assess the repair of lesions and viral clearance in patients with HR-HPV by any of 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

Results

We recruited a total of 91 patients, of whom 84 attended the final visit after 6 months of treatment. The mean age of the patients was 41.3 years in the treatment group and 39.2 years in the control group. The frequency of HR-HPV was 75% in both groups and the baseline characteristics were similar.

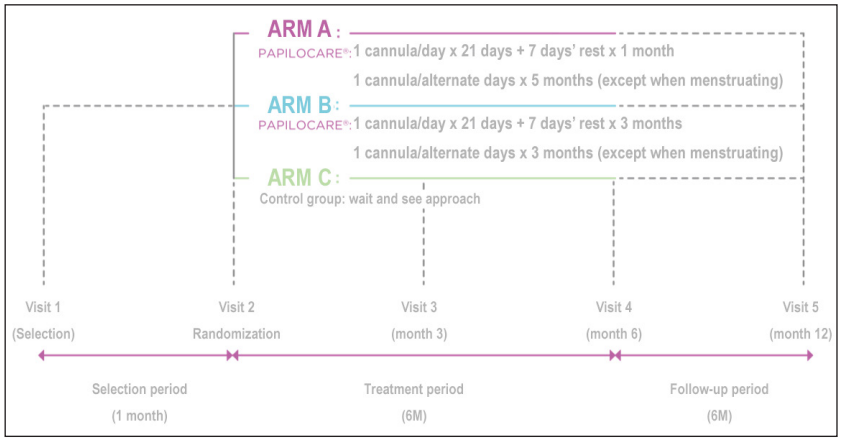

Fig.3. Design of the PALOMA trial[8]

Of the 84 patients who attended the final visit, the lesions had healed (normalization of ASCUS/LSIL cytology findings together with a concordant colposcopy image) in 85% of patients in the treatment group compared with 65% in the control group. In the HR-HPV population (n=66), the lesions had healed in 88% of the Papilocare® group and in 56% of the control group. The differences were significant in both cases. Fig.4.

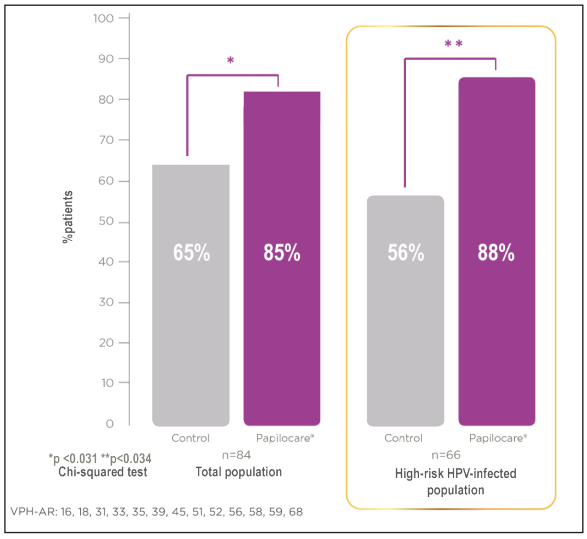

Fig.4. Repair of lesions affecting the cervix at 6 months in the PALOMA trial[9]

As for clearance of HR-HPV, it was noteworthy that the group treated with Papilocare® cleared 63% of the virus at 6 months compared with 40% in the control group, that is, a 57% higher rate of clearance. Fig.5.

Stress during the 6-month period was also very important. The sensation of stress tended to decrease more in terms of the mean PSS-14 score in both groups and in terms of the percentage of patients whose score on the questionnaire improved: 58% vs 39% of patients improved with respect to the sensation of stress in the Papilocare® and control groups, respectively.

Similarly, the study showed the tolerability of the product to be favorable and its safety to be adequate: no severe or unexpected adverse effects associated with the product were recorded. The most frequent adverse effect was itching or irritation. Patients were generally satisfied with the product (87%), and adherence was very good (93.4% at 6 months).

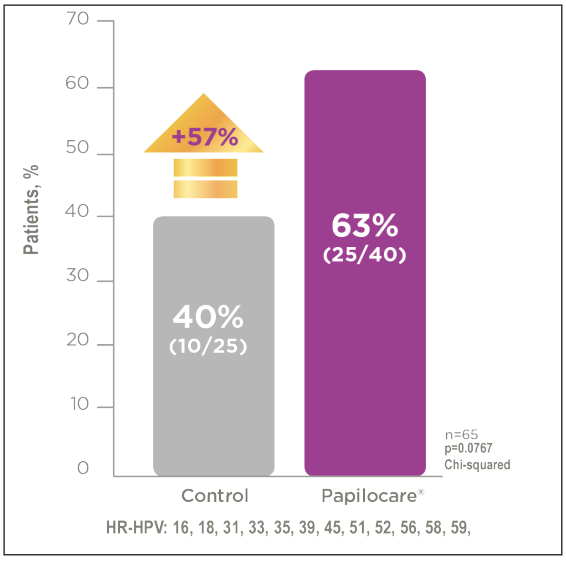

Fig.5. Clearance of high-risk HPV at 6 months in the PALOMA trial[9]

REAL-WORLD DATA

In line with the product development plan, the PAPILOBS study was designed to assess Papilocare® in daily clinical practice[11].

The study, which is currently under way, is a noncomparative observational multicenter study whose main objective is to evaluate the effectiveness of Papilocare® for treatment of low-grade cervical lesions caused by HPV (normalization of the cytological ASCUS or LSIL with compatible colposcopy findings) in women aged >25 years who tested positive for HPV. Similarly, total or partial clearance of HPV was set as a secondary objective. Patients are treated with the standard schedule of Papilocare® (1 cannula per day for the first month and 1 cannula on alternate days for 5 months). The patient is evaluated at 6 months and, if the expected results are not achieved, a second cycle of treatment can be offered with a further evaluation after 6 months.

We currently have interim results for 97 patients. The mean age of the population analyzed was 38.6 years; HR-HPV was detected in 92.1% of patients. After 6 months of treatment, 66% had normal cytology findings and a concordant negative colposcopy result, with normalization of findings in 91% of patients at 12 months. This last finding is particularly relevant, since continuing treatment for 6 months made it possible

to achieve normal results for a larger number of cervical lesions.

In addition, HR-HPV cleared in 63% of patients at 6 months and in 82% at 12 months.

In this interim analysis, Papilocare® proved to have a notable effect for treatment of low-grade HPV-dependent cervical lesions and on clearance of HPV under real-world conditions. The objective of therapy was reached after 6 months' treatment in most patients, and at 12 months, it was achieved in 91%.

The effectiveness of Papilocare® in clearance of HR-HPV has also been evaluated in independent observational clinical studies, some of which were prospective, in 3 public hospitals in Spain[12-14] and in a private center in Italy[15]. Fig 6. As seen in Figure 7, the results for clearance with Papilocare® are especially coherent and reproducible, both under clinical trial conditions and under real-world conditions: clearance was recorded in 50% to 70% of cases of HR-HPV at 6 months in more than 700 patients[16,17].

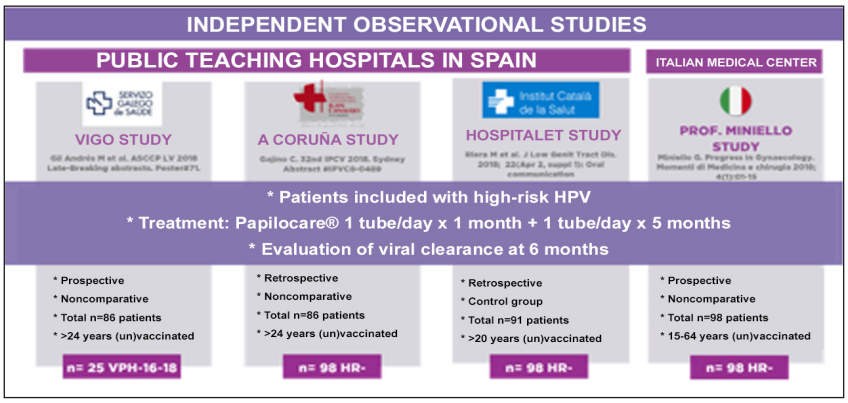

Fig.6. Design and characteristics of independent observational studies carried out with Papilocare®[17]

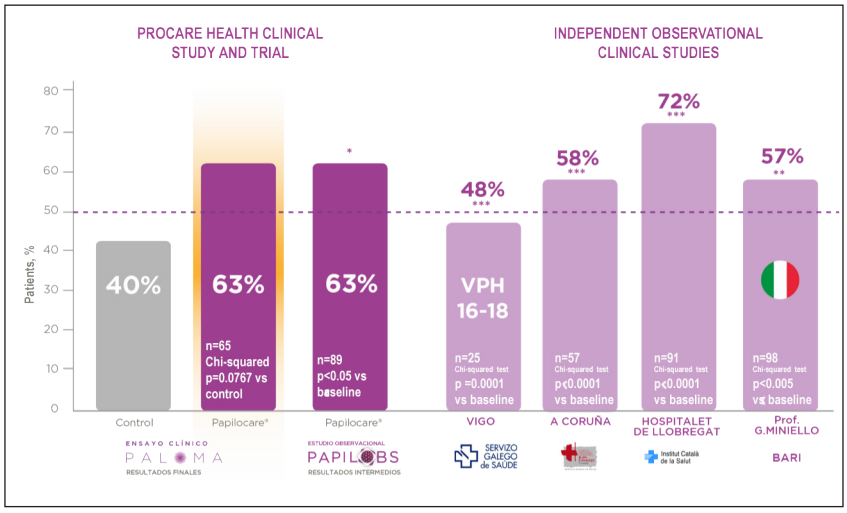

Fig.7. Results for clearance of high-risk HPV in the PALOMA trial and observational studies with Papilocare®[17]

CONCLUSIONS

In conclusion, Papilocare® is the first and only treatment in Europe that is indicated for the prevention and treatment of low-grade HPV-dependent lesions.

The gel is a unique combination of natural ingredients selected to act on 3 modifiable factors in viral clearance.

The 6-month rates for healing of lesions and viral clearance in patients with HR-HPV, together with the reduced the sensation of stress and high degree of satisfaction and tolerability of treatment in the abovementioned studies, favor offering vaginal gel to HPV-infected patients with low-risk cervical lesions (ASCUS or LSIL) as opposed to the wait-and-see approach used in routine clinical practice.

With the aim obtaining more in-depth knowledge and determining the extent of the effects of Papilocare® vaginal gel, a major international clinical development plan is under way, with more than 1000 patients in various ongoing studies.

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CLINICAL TRIAL

PALOMA

ClinicalTrials.gov NCT04002154

PAPILOCARE®

1st TREATMENT TO PREVENT AND TREAT HPV-DEPENDENT CERVICAL LESIONS◊

Phase II, randomised, open-label, parallel-group, controlled clinical trial on the efficacy of **PAPILOCARE®** vaginal gel in repairing the cervico-vaginal HPV-dependent lesions[1,2]

NEW PRESENTATION

21% OFF

21 cannulas of 5 ml presentation

7 cannulas of 5 ml presentation

NORMALIZATION OF HPV-DEPENDENT CERVICAL LESIONS IN

88%**

of High-Risk HPV+ patients at 6 months vs 56% in the control group

FINAL RESULTS on High-Risk HPV

HPV CLEARANCE IN

63%

of High-Risk HPV+ patients at 6 months vs 40% in the control group

**p=0,0034

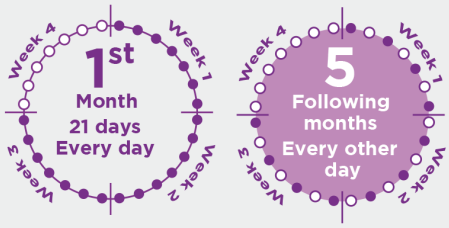
HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68

x21 CANNULAS

- **COMPLIANCE**
- **CONVENIENCE**
- **PRICE**

RECOMMENDED TREATMENT DURATION: 6 MONTHS

Instructions for use:



- Start treatment after period.
- Insert a single-dose cannula into the vagina, preferably before bedtime.
- Stop during the period, if exists.

◊Low-grade lesions: ASCUS/LSIL

Procare Health
Naturally woman

References:

1. Serrano L, López A, González S, Palacios P, Dexeus D, Centeno C, Coronado P, de la Fuente J, López Fernández JA, Vanrell C, Combalia J and Cortés J. EP274 Effect of a Coriolus versicolor-based vaginal gel in HPV infected women: normalizing HPV-dependent cervical lesions (ASCUS/LSIL) and high-risk HPV clearance. International Journal of Gynecologic Cancer 2019;29:A206. 2. Seydoux G, Cortés J, Serrano L, López AC, González S, Palacios S, Dexeus D, Centeno C, Coronado P, de la Fuente J, López JA, and Vanrell C. Efficacy of a Multi-Ingredient Vaginal Gel in Normalizing HPV-Dependent Cervical Lesions and HR-HPV Clearance. J Low Genit. Tract Dis. 2020 April; 24(1S):S16. doi:10.1097/LGT.0000000000000538 3. Gaslain Y, Cortés J, Dexeus D, Palacios S, Serrano L, Seydoux G, Gajino C, Marín E, and Riera M. Effect of a Multi-Ingredient Vaginal Gel in High-Risk HPV Infected Patients: Results of Different Studies. J Low Genit. Tract Dis. 2020 April; 24(1S):S15-S16. doi:10.1097/LGT.0000000000000538. 4.Miniello G. Prevenzione e trattamento coadiuvante delle lezione della cervice uterine indotte da HPV: un'experienza di Real Life. Progress in Gynaecology. Momenti di Medicina e chirurgia 2018; 4 (1): 0 1-15.

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