



Italian Journal of Gynæcology & Obstetrics

March 2021 - Vol. 33 - N. 1 - Quarterly - ISSN 2385 - 0868

Grade of satisfaction and tolerability of a medical device based on *P. acnes* in adults waiting for destructive treatments for genital warts

A. Ciavattini¹, J. Di Giuseppe¹, L. Giannella¹, D. Tsiroglou¹, M. Palomba², M. Barbero³, V. Rabino³, C. Bocci³, M. Capodanno⁴, M. Sansone⁴, M. Barbieri Carones⁵, A. Agarossi⁵, P. Cattani⁶, F. Perolo⁷, R. Ribaldone⁸, V. Prestia⁹, G. Delli Carpini¹

¹Department of Woman's Health Sciences, Gynecologic Section, Polytechnic University of Marche, Ancona, Italy

²Department of Obstetrics and Gynecology, University of Cagliari, Cagliari, Italy

³Department of Obstetrics and Gynecology, Asti Community Hospital, Asti, Italy

⁴Specialist in Obstetrics and Gynecology, Public Colposcopy Unit, Naples, Italy

⁵Department of Obstetrics and Gynecology, University of Milan, Milan, Italy

⁶Center for Gynecologic Oncology Prevention, ULSS 20, Verona, Italy

⁷Department of Obstetrics and Gynecology, Pesaro, Italy

⁸Department of Obstetrics and Gynecology, Novara, Italy

⁹Department of Obstetrics and Gynecology, Melegnano, Milan, Italy

ABSTRACT

Vulvar and vaginal warts (genital warts – GW), also known as condylomata acuminata, are one of the clinical manifestations of human papillomavirus (HPV) infection. Oxidative stress may have an important role in the pathogenesis of GW. A preparate of bacterial lysate based on *Propionibacterium acnes* (*P. acnes*) showed a potent antioxidant activity *in vitro*, suggesting a potential role in the treatment of GW. The aim of the present study was to evaluate the grade of satisfaction of patients who were waiting for destructive treatment, prospective enrolled and treated for 60 days with a *P. acnes* lysate. The effect on the number, location of the lesions and the quadrants involved was also evaluated waiting destructive approach. Anamnestic data were collected and a vulvoscopy was performed with an accurate description of the lesions at the first visit and after 30-60-90 and 180 days of treatment. During the study period, 69 women, fulfilling the study inclusion/exclusion criteria, constituted the study cohort. *P. acnes* preparation showed a high tolerability and a high grade of satisfaction. Moreover, all patients included decided to wait at least 60 days before being subjected to any destructive treatment, which was then necessary only in 31.8% of cases. The results

SOMMARIO

La condilomatosi vulvare e vaginale (CV) è una delle manifestazioni cliniche dell'infezione da papillomavirus umano (HPV). Lo stress ossidativo può avere un ruolo importante nella patogenesi della CV. Un preparato di lisato batterico a base di *Propionibacterium acnes* (*P. acnes*) ha mostrato una potente attività antiossidante *in vitro*, suggerendo un potenziale ruolo nel trattamento della CV. Obiettivo dello studio è stato quello di valutare il grado di soddisfazione e la tollerabilità dopo somministrazione di un preparato contenente lisato di *P. acnes* in pazienti in attesa di trattamento distruttivo per condilomatosi. Le pazienti arruolate sono state trattate per 60 giorni consecutivi ed è stato valutato l'effetto sul numero, sulla sede delle lesioni e sui quadranti coinvolti, l'insorgenza di effetti collaterali, il grado di soddisfazione e la tollerabilità. Alla prima visita sono stati raccolti dati anamnestici ed è stata eseguita una vulvosopia con descrizione accurata delle lesioni. Le pazienti sono state rivalutate a 30, 60, 90 e 180 giorni dall'inizio del trattamento. La coorte di studio era costituita da 69 donne, che osservavano i criteri di inclusione/esclusione dello studio. La preparazione di *P. acnes* ha mostrato un'alta tollerabilità e un alto grado di soddisfazione. Tutte le pazienti incluse

obtained with this preliminary study enable to indicate this therapy as possible innovative option in the treatment of GW. A prospective blinded RCT will be necessary to evaluate the *P. Acnes* preparation efficacy in the treatment of condylomatosis.

hanno deciso di attendere almeno 60 giorni prima di essere sottoposte a qualsiasi trattamento distruttivo, che si è rivelato necessario solo nel 31,8% dei casi. Al termine del trattamento, è stata osservata una risposta completa, parziale o assente alla terapia rispettivamente in 37 (61.6%), 15 (25%) e 8 pazienti (13.4%). I risultati ottenuti con questo studio preliminare consentono di indicare questa terapia come possibile opzione innovativa nel trattamento della CV. Sarà necessario un RCT in cieco per valutare la potenziale efficacia della preparazione di *P. acnes* nel trattamento della condilomatosi.

Corresponding Author: Andrea Ciavattini

E-mail: ciavattini.a@libero.it

Copyright 2021

DOI: 10.36129/jog.33.01.04

Key words:

Genital warts; Propionibacterium acnes; condylomata acuminata; oxidative stress; therapy.

INTRODUCTION

Vulvar and vaginal warts (genital warts – GW), also known as condylomata acuminata, are one of the clinical manifestations of human papillomavirus (HPV) infection. According to their oncogenic potential, low-risk HPV types 6 and 11 are responsible for over 90 percent of the GW (1), which are one of the most common sexually transmitted diseases (2-4) worldwide.

Although the vaccination with quadrivalent and nonavalent vaccines reduce the incidence of GW in women and men (5), the vaccination coverage in Italy was in 2017 significantly below the optimal threshold set by the National Vaccinal Prevention Plan, with 56% estimated vaccine coverage among females aged 12 (6). In a large European survey conducted on general adult populations (18-45 years), the self-reported lifetime history of GWs was 10% (7).

Following initial clinical manifestation, approximately 30 percent of all warts will spontaneously regress within the first four months of infection (8). Unfortunately, long-term remission rates remain largely unknown, and most GW will recur within three months of infection, even after undergoing appropriate treatments (9). Significant risk factors for long-term persistence include host immunosuppression, infection with high-risk HPV subtypes, and an older patient age (9, 10). A prolonged infection with HPV leads to chronic inflammation which can locally cause oxidative stress (11). Oxidative stress occurs as a result of unbalance between the

oxidant and the antioxidant system (12) and constitutes the basis of many inflammatory skin disease and skin cancer (13, 14). Oxidative stress may also have an important role in the pathogenesis of genital warts, as previously described by Cockuk *et al.* (12). Briefly, the authors found that the activities of glutathione peroxidase and catalase and the level of malondialdehyde (MDA, a well-known indicator of oxidative stress), were significantly higher in patients with genital warts than in healthy subjects. The current options available for the treatment of GW are meant to eliminate or to reduce the warty growth, rather than to determine the clearance of the underlying viral infection (8). Wide ranges of therapies are currently used, with variability with respect to cost, side-effect profiles, dosing schedules, duration of treatment, and overall effectiveness (8). Several studies reported the successful use of topical or systemic zinc-based antioxidants for the treatment of non-genital warts (15, 16) and the efficacy of catechins-based formulations on the external genital and perianal warts via inhibitory effects of enzymes related to oxidative stress (17). Furthermore, a prepare of bacterial lysate based on *Propionibacterium acnes* (*P. acnes*), a gram positive, pleomorphic, strictly anaerobic bacteria, showed a potent antioxidant activity *in vitro*: in particular, such prepare counteract the increase of MDA and nitrites in hydrogen peroxide-stimulated murine fibroblasts culture (Cuzzocrea, Messina, Italy, data not published), suggesting a potential role in the treatment of GW.

Alternatively, GW can be removed by scalpel or scissor excision or they can be destroyed by electrosurgery or carbon dioxide laser ablation. However, not all these treatments have showed completely satisfactory results; a high recurrence rate after their utilization, as well as definitive scars and sequelae, are described with a recurrence rate of about 25% for destructive therapy too (8).

The aim of the present study was to evaluate the grade of satisfaction of patients treated with *P. acnes* lysate (Immunoderm®, Depofarma, Mogliano Veneto, TV, Italy), who were waiting for destructive treatment for GW; the effect on the number, location of the lesions and the quadrants involved was also evaluated waiting destructive approach.

METHODS

A prospective multicentric cohort study (January 2018-September 2019) was conducted on patients who were waiting for destructive treatments for vulvo-perineal condylomatosis, consecutively enrolled and treated for 60 days with a commercially available preparations based on *P. acnes* (Immunoderm®, Depofarma, Mogliano Veneto, TV, Italy). The *P. acnes* preparation used was a medical device with marketing authorization number AIC-972778029 of the Italian Medicines Agency (AIFA) and European Community certification mark approved for use in patients with symptoms related to GW or subjected to any treatment for GW.

At inclusion, all eligible patients signed an informed consent, showing the technical and scientific basis of the research project and granting their permission to data collection and to administration of *P. acnes* preparation. The study was conducted in accordance with the Declaration of Helsinki (1964). The information collected and the clinical observations from the clinical examination were in possession only of those involved with the project and the patients, if they want. All included patients were over 18 years old and had a first diagnosis of multiple genital warts (three or more), all with a diameter less than one centimeter. Patients with the presence of cervico-vaginal warts, HIV positivity, immunosuppression (transplant patients, steroid therapy or with autoimmune disease), pregnancy and the onset of lesions for more than three months from the potential recruitment were excluded. All the cases with diagnostic uncertainty, which did not allow for a clinical diagnosis (*e.g.*, pigmented,

indurated, affixed to underlying tissue, bleeding, or ulcerated lesions) or with suspicion of precancer or cancer were excluded.

Visit 1 (T_0)

At the first clinical evaluation, anamnestic data were collected (age, BMI, HIV positivity, smoking habit and number of cigarettes/day, number of previous partners, number of previous pregnancies, concomitant pathologies, ongoing therapies, period of onset of the lesions). A vulvoscopy was performed with an accurate description of the lesions and a cervico-vaginal examination was performed to exclude the presence of cervico-vaginal warts. Typical warts were identified according to the clinical features reported by the International Union Against Sexually Transmitted Infections (IUSTI) (18): superficial papular lesions of 1-5 mm diameter, flat or pedunculated, solitary or multiple (also forming larger plaques). GW were identified as soft, raised masses, with smooth, verrucous, or lobulated aspects that could appear as pearly, filiform, fungating, or plaque-like eruptions often with surface showing finger-like projections, generally nonpigmented.

In accordance with the recommendations of the IUSTI (18) and of the Centers for Disease Control and Prevention (CDC) (19), the diagnosis of anogenital warts was made by visual inspection in all the cases with typical anogenital warts. Biopsy was not necessary for typical anogenital warts as recommended by afore mentioned guidelines (18, 19). The location of warts and the number of lesions (near to clitoris, right labia majora, left labia majora, right labia minora, left labia minora, vestibule, perineum, anus and perianus) and the number of quadrants involved were recorded. At the end of the first evaluation, topical preparation based on *P. acnes* was prescribed, 2 applications per day for 60 days, to all included patients attending for destructive treatment for GW. During the 60 days period, unsatisfied patients were free to discontinue topical application and undergo immediately destructive treatment.

Visit 2 (T_1 : 30 days after recruitment)

A vulvoscopy was performed, reporting the number, location of the lesions and the quadrants involved, according to the modalities of the visit 1. The patient's satisfaction, also indicating resolution of specific symptoms, was assessed with a score from 1 to 5 corresponding to the following catego-

ries (insufficient; sufficient; discreet; good; excellent). Simultaneously, the response to the administration was categorized as complete (complete absence of warts), partial (persistence of at least one condyloma) or unchanged (number of warts unchanged from diagnosis). The possible occurrence of adverse events was recorded, also reporting the type, the period of onset and the need of any treatment. Local tolerability was assessed with a score from 0 to 5 corresponding to the following categories (no erythema; barely noticeable erythema; slight erythema without edema; moderate erythema and edema with or without papules; accentuated erythema or edema with or without papules; accentuated erythema or edema with blisters).

Visit 3 (T₂:60 days after recruitment), visit 4 (T₃:90 days after recruitment) and visit 5 (T₄:180 days after recruitment)

At visit 3, a vulvoscopy was performed with the same modalities of previous controls, and response to the *P. acnes* administration was also categorized. Patient's satisfaction and tolerability were recorded. Complete response patients were sent to follow-up, one month after the end of therapy (90 days from recruitment – visit 4/T₃) and four months from the end of administration (180 days from recruitment – visit 5/T₄), while patients with partial/unchanged response were subjected to destructive therapy, with subsequent follow-up 1 month (90 days from recruitment – visit 4/T₃) and 4 months from destructive treatment (180 days from recruitment – visit 5/T₄). The execution of destructive therapies in recurrence cases at T₃ or T₄ was recorded. The study protocol is shown in **table I**.

Outcome analysis

The degree of local tolerability, the patient's satisfaction and the possible occurrence of adverse events were analyzed. The rate of patients with complete, partial or unchanged response, the median number of GW and of quadrants involved after Immunoderm® topical administration at T₂, and the number of patients who needed destructive treatment were also recorded.

All the statistical analyses were performed using MedCalc for Windows version 12.7.0 (Medcalc®, MedCalc Software bvba, 2013, Ostend, Belgium). Continuous parametric variables were expressed as mean (\pm standard deviation); nonparametric variables were ex-

Table I. Study protocol.

Visit 1 (T₀)	1. First clinical evaluation with collection of anamnestic data 2. Vulvoscopy 3. Prescription of <i>P. Acnes</i> preparation	
Visit 2 (T₁) 30 days	1. Vulvoscopy 2. Evaluation of patient's satisfaction, local tolerability, response to therapy and occurrence of adverse events	
Visit 3 (T₂) 60 days	1. Vulvoscopy 2. Evaluation of patient's satisfaction, local tolerability, response to therapy and occurrence of adverse events	
	Complete response to <i>P. Acnes</i> therapy	Partial/unchanged response to <i>P. Acnes</i> therapy
Visit 4 (T₃) 90 days	1. Vulvoscopy	1. Destructive therapy
Visit 5 (T₄) 180 days	1. Vulvoscopy	1. Destructive therapy

pressed as median and range after testing for normal distribution. The significance of couples' comparisons between treatment sessions was analyzed using the Wilcoxon test for non-parametric data. A $p < 0.05$ was considered statistically significant.

RESULTS

During the study period, 69 women, fulfilling the study inclusion/exclusion criteria, constituted the study cohort. At T₀, the mean age was 35.0 ± 7.5 SD (range: 19.0-57.0) and the mean BMI was 23 ± 4.0 SD. Twenty-five patients (35.2%) were tobacco users with a median of 10 cigarettes (range 6-20) per day. The median number of sexual partners was 3 (range: 1-10); one patient suffered from epilepsy and one patient reported thyroid disorder, both taking medical therapy. Only the 28.9% of patients (20 patients) had almost one previous pregnancy (50% one pregnancy, 50% two pregnancies). The mean period of onset of the lesions before diagnosis was 40.6 days (± 34.6 SD). The incidence of at least one GW, according to sites, at the diagnosis (T₀) is reported in **table II**.

At T₀, the median number of lesions for each patient was 4 (range: 3-40) with a median number of quadrants involved of two areas (range: 1-5).

At T₁, data of two cases were not available. Median patient's satisfaction was 3 (discreet) (range: 1-5) and 51/67 (76.1%) of patients reported a discreet, good or excellent grade of satisfaction. A high local tolerability with no erythema or barely noticeable erythema was present in 85% of cases (57/67) with a median local tolerability of 0 (no erythema) (range: 0-2). No adverse side effects were recorded after 30 days of

Table II. Incidence of GW, according to sites at the diagnosis (T₀).

Sites	Number of patients
Near to clitoris	12 (17.4%)
Right labia majora	21 (30.4%)
Left labia majora	24 (34.8%)
Right labia minora	15 (21.7%)
Left labia minora	12 (17.4%)
Vestibule	24 (34.8%)
Perineum	30 (43.5%)
Anus and perianus	28 (40.6%)

therapies (T₁). The median number of lesions for each patient was 2 (range: 0-40) with a median number of quadrants involved of one area (range: 0-5). A complete, partial, or absent response to *P. acnes* administration was observed in 14 (20.9%), 37 (55.2%) and 16 (23.9%) patients, respectively. All patients, even with persistence of GW, decided to do not interrupt local therapy for another 30 days before undergoing a possible destructive treatment. No patients decided to be subjected to destructive therapy at T₁.

At T₂, at the end of 60 days of therapy, data about 60/69 patients (86.9%) are available; median patient's satisfaction was 4 (good) (range: 1-5) and 50/60 patients (83.3%) reported a discreet, good or excellent grade of satisfaction). A sufficient (5/60-8.3%) or insufficient grade (5/10-8.3%) of satisfaction was recorded only in the 8 patients with absent response to therapy and in 2 cases with partial response. No significant differences about patient's satisfaction was found after 30 or 60 days of therapy (p = 0.43). Local tolerability at T₁ was 0 (no erythema) (range: 0-2) with no erythema or barely noticeable erythema in 96.6% of cases (58/60). A significant improvement in local tolerability was found after 30 and 60 days of therapy (85% vs 96.6%, p = 0.05). No adverse effects were recorded after 60 days of therapies (T₂).

The median number of lesions for each patient was 0 (range: 0-9) with a median number of quadrants involved of one area (range: 0-5). A complete, partial, or absent response to therapy was observed in 37 (61.6%), 15 (25%) and 8 (13.4%) patients, respectively. A significant reduction of the median numbers of GW (4 vs 0 – IR: 3-5 vs 0-2; p < 0.001) and of the number of quadrants involved (2 vs 0 – IR: 1-3 vs 0-2; p < 0.001) were recorded (see figures 1, 2).

Among the 23 patients with partial or absent response after 60 days of therapy, 20 were subjected to destructive therapy (16 laser vaporization, 4 diathermocoagulation). Three patients decided to continue the follow-up.

Data about follow-up at 90 days after recruitment (T₃) are available in 43/69 cases (62.3%): no GW were observed in 40/43 cases (93%). Two cases with persistent GW at T₃ were the same cases with persistence at T₂ and were treated with destructive therapy (laser vaporization). One patient decided to continue follow-up. Data about follow-up at 180 days after recruitment (T₃) are available in 27/69 cases (39.1%) and showed 1 persistence of GW in one patient who refused therapy at the 90 days follow-up (T₃). No cases of relapse of GW were recorded at T₃ and T₄ follow-up.

DISCUSSION

Genital warts have quality of life (20-23) and significant socio-economic impact, as it is the most common

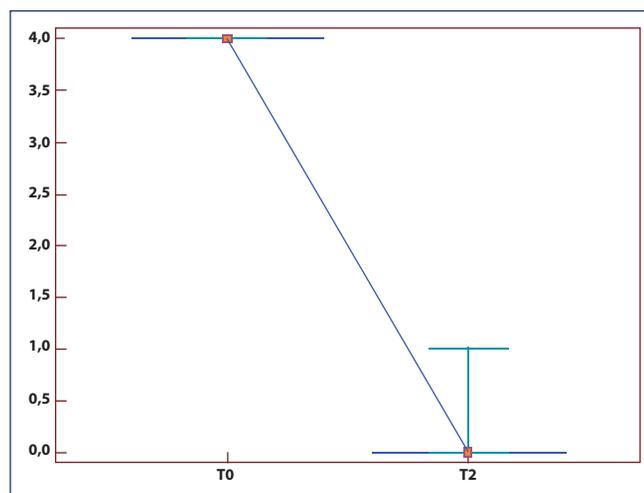


Figure 1. Trend of variation of median number of GW between treatment sessions.

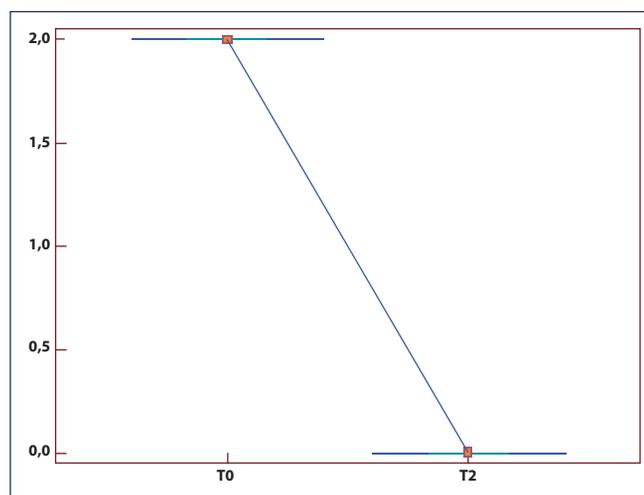


Figure 2. Trend of variation of median number of quadrants involved between treatment sessions.

sexually transmitted infections (2-4, 24), although the presence of national vaccination programs.

Various highly aggressive methods have been used for treatment of GW but can lead to sequelae like scars and deformations with a high recurrence rate (25) and can be associated with pain and HPV transmission, if HPV particles are present in the smoke plume produced by destructive therapies (26). Therefore, topical therapies offer some advantages as they can be used both by doctors and by patients at home and they can be useful for treatment of multiple lesions, which have a substantial risk of latent HPV presence in the clinically normal epithelium beyond the warts (26).

Topically applied therapeutic agents for external genital warts include imiquimod, podophyllotoxin, sinecatechins, trichloroacetic acid (TCA) and podophyllin and unconventional or newly emerging modalities, such as cidofovir gel, idoxuridine, polyhexamethylene biguanide, sodium nitrite with citric acid and SB206 12% (27).

The use of preparations based on *P. acnes* has been studied recently for treatment in skin warts (28), but there are not data for use in genital warts. Administered parentally, these preparations are highly immunogenic and are able to induce specific antibodies (29, 30) for immune response to HPV infection. There are no literature data to support the immunostimulating effect of topical bacterial lysate preparations, but, *in vitro*, preliminary studies have suggested an antioxidant activity of the *P. acnes* preparation subject of this study (data not shown), a well-recognized mechanism that results in the reduction of inflammatory process (31) and the resolution of the tissue damage (32).

The aim of the present study was to evaluate the grade of satisfaction, the local tolerability, and the effect on the number of GW and the number of quadrants involved in patients waiting for destructive therapy treated with *P. acnes* preparations. Our data showed a high satisfaction grade (discreet, good or excellent) after 30 and 60 days of topic application, without a significative variation during the study period. No incidence of side effects and a significative improvement in local tolerability after 30 and 60 days with high rates of patients with no symptoms (erythema or barely noticeable erythema) throughout the treatment period (85% and 96.6% after 30 and 60 days of treatment, respectively) was recorded. No patient decided to undergo destructive treatment after 30 days of therapy even in cases where there was a partial or absent re-

sponse. This may be due to a decrease in the symptoms perceived by the patients, to the absence of side effects and in most of the patients of the study, to the reduction of the number of warts. The gel formulation relieves itching and burning localized in the ano-genital area with genital warts; very often condylomatosis can be symptomatic at the time of diagnosis (20-23). Only two cases reported the onset of a slight erythema without edema after 60 days of therapy, without however determining the interruption of the treatment.

This level of tolerability is certainly higher than that reported in a recent meta-analysis (27), where many of the topical drugs used determined severe adverse events that led to patient withdrawal: the analysis of 17 studies showed that imiquimod 5% cream (OR: 8.68; 95% CI: 1.01-74.43), podophyllin 2.0% solution (OR: 38.43; 95% CI: 1.28-1156.07), podophyllotoxin 0.5% cream (OR: 5.98; 95% CI: 1.07-33.54), polyhexamethylene biguanide cream (OR: 55.87; 95% CI: 3.33-937.61) and sinecatechins 10% (OR: 8.03; 95% CI: 3.97-16.24) and 15% cream (OR: 8.54; 95% CI: 4.23-17.25) were associated with significantly higher numbers of patients with severe adverse events or patients who were lost to follow-up because of treatment-related side effects, compared to the placebo; Imiquimod 5% cream can determine the development of severe erythema and erosions even in the 40% of cases, podophyllin 2.0%, polyhexamethylene biguanide cream, and sinecatechins seems to determine severe local reaction or severe erythema in 4, 22 and 28% of cases, respectively.

The analysis of the rate of persistence or regression of GW after 60 days of therapy showed a significant decrease in the median number of GW and of quadrants involved and a complete response to therapy in 61.6% of patients that, therefore, they avoided a destructive therapy. This data is not comparable with other topical preparations for GW (27) because there is not a cohort treated with placebo and because, despite the number of our treated patients with *P. acnes* preparations is considerable, it would be necessary an efficacy studies or a RCT to evaluate their outcomes. When compared to placebo (25), all other treatments were significantly more efficacious: Podophyllotoxin 0.5% solution was significantly superior to imiquimod 5% cream for lesion clearance, although it was associated with a higher overall rate of adverse events. Sinecatechins were inferior to imiquimod 5% cream in wart clearance. For recurrence, all modalities did

not significantly differ from each other. Some unconventional agents were potentially better than conventional therapies regarding their efficacy or safety, although additional studies are required to confirm these results.

This study is not without limitations: the absence of a control group does not allow a real evaluation of efficacy but only of tolerability and grade of satisfaction. Moreover, among the 23 patients with partial or absent response after 60 days of therapy, 20 were subjected to destructive therapy, not allowing the evaluation of any subsequent spontaneous complete remission, as approximately 30 percent of all warts could regress within the first four months of infection (8). However, the homogeneity of the study cohort enrolled allow to consider assessable the grade of satisfaction of the patients. Immunoderm® could be then useful in patients who would like not to be subject to destructive treatments with related pain and risk of sequelae. Moreover, data available showed a long-term absence of relapse of GW (0 cases at T₃ and T₄ follow-up), also considering that most of GW will recur within three months of infection, even after undergoing appropriate treatments (9).

The real prevention of GW can be achieved by the use of the quadrivalent or nonavalent prophylactic HPV vaccines administered prior to sexual debut, as well as the meticulous use of condoms (1). Where coverage of the quadrivalent vaccine has been high, marked reductions in GW are being seen in young women of vaccine-eligible age, as well as in young males (1, 5).

A prospective single-center study (33) reported that recurrence for high grade cervical intraepithelial neoplasia (CIN2+) occurred in 6.4% of unvaccinated women and 1.2% of vaccinated women 30 days post LEEP. The effectiveness of vaccination in reducing recurrence after treatment of warts

should be assessed, also in association with immune stimulants substances.

P. acnes preparation has shown a high tolerability and a high grade of satisfaction in patients waiting for destructive treatment for GW. Moreover, even if this study does not allow conclusions regarding efficacy, all patients included decided to wait at least 60 days before being subjected to any destructive treatment, which was then necessary only in 31.8% of cases. A further study could evaluate its usefulness after destructive treatment to improve the symptoms experienced by patients.

According to literature, the uses of preparations based on *P. acnes* has been studied recently for treatment in skin warts (28), but there are not data for use in genital warts. Applied intradermally, these preparations resulted highly immunogenic and were able to induce specific antibodies (29, 30) for immune response to HPV infection. Nevertheless, the specific immunomodulatory properties of Immunoderm® are unpredictable, since there are still no evidences on the ability of such *P. acnes* preparation to penetrate the skin and acting as an immunomodulator.

However, the results obtained with this preliminary study enable to indicate the therapy with Immunoderm®, as possible innovative option in the treatment of GW. A prospective blinded RCT will be necessary to evaluate the *P. acnes* preparation efficacy in the treatment of condylomatosis. Currently, these results not allow a real evaluation of efficacy but show a good tolerability and acceptability profile of the Immunoderm®.

CONFLICTS OF INTERESTS

The authors declare that they have no conflict of interests.

REFERENCES

1. Steben M, Garland SM. Genital warts. *Best Pract Res Clin Obstet Gynaecol* 2014;28(7):1063-73.
2. Jardine D, Lu J, Pang J, et al. A randomized trial of immunotherapy for persistent genital warts. *Hum Vaccin Immunother* 2012;8:623-9.
3. Frazer IH. Interaction of human papillomaviruses with the host immune system: a well evolved relationship. *Virology* 2009;384:410-4.
4. Frazer I. Correlating immunity with protection for HPV infection. *Int J Infect Dis* 2007;11:S10-16.
5. Bergman H, Buckley BS, Villanueva G, et al. Comparison of different human papillomavirus (HPV) vaccine types and dose schedules for prevention of HPV-related disease in females and males. *Cochrane Database Syst Rev* 2019;2019(11):CD013479.
6. Cox JT, Palefsky JM, Hirsch MS, Bloom A, Human papillomavirus vaccination. UpToDate. Available at: https://www.uptodate.com/contents/human-papillomavirus-vaccination?search=human-papillomavirus-vaccination.&source=search_result&selectedTitle=1~111&usage_type=default&display_rank=1. Accessed: 26/02/2021.
7. Kjaer SK, Tran TN, Sparen P, et al. The burden of genital warts: a study of nearly 70,000 women from the general female population in the 4 Nordic countries. *J Infect Dis* 2007;196:1447-54.
8. Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. *J Clin Aesthet Dermatol* 2012;5:25-36.
9. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 1998;338(7):423-8.
10. Coleman N, Birley HD, Renton AM, et al. Immunological events in regressing genital warts. *Am J Clin Pathol* 1994;102(6):768-74.
11. Arican O, Ozturk P, Kurutas EB, Unsal V. Status of oxidative stress on lesional skin surface of plantar warts. *J Eur Acad Dermatol Venereol* 2013;27:365-9.
12. Cokluk E, Sekeroglu MR, Aslan M, Balahoroglu R, Bilgili SG, Huyut Z. Determining oxidant and antioxidant status in patients with genital warts. *Redox Rep* 2015;20:210-4.
13. Takci Z, Bilgili SG, Karadag AS, Kucukoglu ME, Selek S, Aslan M. Decreased serum paraoxonase and arylesterase activities in patients with rosacea. *J Eur Acad Dermatol Venereol* 2015;29:367-70.
14. Nishigori C, Hattori Y, Toyokuni S. Role of reactive oxygen species in skin carcinogenesis. *Antioxid Redox Signal* 2004;6:561-70.
15. Cokluk E, Sekeroglu MR, Aslan M, Balahoroglu R, Bilgili SG, Huyut Z. Determining oxidant and antioxidant status in patients with genital warts. *Redox Rep* 2015;20:210-4.
16. Sadighha A. Oral zinc sulphate in recalcitrant multiple viral warts: a pilot study. *J Eur Acad Dermatol Venereol* 2009;23:715-6.
17. Tyring SK. Sinicatechins: Effects on HPV-Induced Enzymes Involved in Inflammatory Mediator Generation. *J Clin Aesthet Dermatol* 2012;5(1):19-26.
18. Gilson R, Nugent D, Werner RN, Ballesteros J, Ross J. 2019 IUSTI-Europe guideline for the management of anogenital warts. *J Eur Acad Dermatol Venereol* 2020;34(8):1644-53.
19. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* 2015;64(RR-03):1-137.
20. Dominiak-Felden G, Cohet C, Atrux-Tallau S, et al. Impact of human papillomavirus-related genital diseases on quality of life and psychosocial wellbeing: results of an observational, health-related quality of life study in the UK. *BMC Public Health* 2013;13:1065.
21. Patel H, Wagner M, Singhal P, Kothari S. Systematic review of the incidence and prevalence of genital warts. *BMC Infect Dis* 2013;13:39.
22. Senecal M, Brisson M, Maunsell E, et al. Loss of quality of life associated with genital warts: baseline analyses from a prospective study. *Sex Transm Infect* 2011;87:209-15.
23. Drolet M, Brisson M, Maunsell E, et al. The impact of anogenital warts on health-related quality of life: a 6-month prospective study. *Sex Transm Dis* 2011;38:949-56.
24. Burchell AN, Coutlee F, Tellier PP, et al. Genital transmission of human papillomavirus in recently formed heterosexual couples. *J Infect Dis* 2011;204:1723-9.
25. Beutner KR, Ferenczy A. Therapeutic approaches to genital warts. *Am J Med* 1997;102:28-37.
26. Ferenczy A, Bergeron C, Richart RM. Carbon dioxide laser energy disperses human papillomavirus deoxyribonucleic acid onto treatment fields. *Am J Obstet Gynecol* 1990;163:1271-4.
27. Jung JM, Jung CJ, Lee WJ, et al. Topically applied treatments for external genital warts in

- nonimmunocompromised patients: a systematic review and network meta-analysis. *Br J Dermatol* 2020;183(1):24-36.
28. Nasser N. Treatment of common warts with the immune stimulant *Propionium bacterium parvum*. *An Bras Dermatol* 2012;87:585-9.
 29. Cantrell JL, Wheat RW. Antitumor activity and lymphoreticular stimulation properties of fractions isolated from *Corynebacterium parvum*. *Cancer Res* 1979;39:3554-63.
 30. Kalis C, Gumenscheimer M, Freudenberg N, *et al.* Requirement for TLR9 in the immunomodulatory activity of *Propionibacterium acnes*. *J Immunol* 2005;174:4295-300.
 31. Arulselvan P, Fard MT, Tan WS, *et al.* Role of Antioxidants and Natural Products in Inflammation. *Oxid Med Cell Longev* 2016;2016:5276130.
 32. Kisaoglu A, Borekci B, Yapca OE, Bilen H, Suleyman H. Tissue damage and oxidant/antioxidant balance. *Eurasian J Med* 2013;45:47-9.
 33. Ghelardi A, Parazzini F, Martella F, *et al.* SPERANZA project: HPV vaccination after treatment for CIN2. *Gynecol Oncol* 2018;151:229e34.