Italian Journal of
Gynæcology & Obstetrics
March 2017 - Vol. 29 - N. 1 - Quarterly - ISSN 2385 - 0868

Role of TIAGIN® vaginal formulation in cervical reepithelialization and high-risk HPV clearance in patients with low-grade cervical lesions

Caterina Ricci[1]

[1] Polo Salute della Donna e del Bambino, Fondazione Policlinico Universitario A. Gemelli - U.C.S.C.- Rome Director: Prof. Giovanni Scambia

ABSTRACT

Background: high-risk HPV infection, particularly when associated with a low-grade cervical lesion, is a very common problem, especially in young women. It is often associated with the presence of cervical ectropion/ectopy, which causes bleeding and consequent anxiety and discomfort for the patient. The use of a molecule able to trigger the reparatory processes of the cervical epithelium, while also providing antibacterial action and boosting the local physiological immune response, could be a valid aid for the clinical management of such cases.

Objective: to evaluate the reepithelialising action and efficacy of TIAGIN® vaginal formulation in a group of patients with low-grade cervical lesions (ASC-US/L-SIL) positive for high-risk HPV with cervical ectropion/ectopy, treated with TIAGIN® vaginal formulation, by analysing the cytological clearance percentage, the HPV clearance percentage, any regression of the lesions visible during colposcopy and the degree of ectropion/ectopy reepithelialisation at 6 months.

Results: data was collected from 19 patients, with a mean age of 31. Almost all the patients managed to complete the prescribed treatment. Only 1 of the 19 patients stopped treatment after the first cycle due to intolerance to the product and was therefore excluded from the analysis, conducted on 18 patients. The cytology check-up at 6 months after treatment with TIAGIN® vaginal formulation was negative in 12 out of 18 patients (66.7%), while the microbiological clearance rate at 6 months after treatment was 50% with 9 negative HPV tests out of 18. At 6 months, 9 out of 18 patients (50%) had negative colposcopy results following complete regression of the AT1. In the remaining 50%, the colposcopy results were unchanged or improved, without any progression or the need for a biopsy.

Bleeding had stopped in all patients at the 6-month check-up. In 5 patients (27.8%), the ectropion/ectopy was unchanged compared to T0. In 3 patients (16.6%), it was at least 25% smaller. In 10 patients (55.6%) it was resolved and completely reepithelialised.

Conclusions: in clinical practice, vaginal TIAGIN® vaginal formulation has shown itself to be a promising therapeutic aid in the management of low-grade cervical lesions caused by high-risk HPV, and is a valid option for the conservative management of bleeding ectropion/ectopy. Although this data is very interesting and promising, further evaluation and validation is required from prospective studies involving a larger number of subjects.

Keywords: Aloe Barbadensis, silver ions, Vaginal Health Index Score, Female Sexual Function Index (FSFI), vaginal disepithelization.hormone.

SOMMARIO

Introduzione: l'infezione da HPV ad alto rischio, in particolare associata a una lesione cervicale di basso grado è una problematica attualmente molto diffusa, specie nelle giovani donne. Ad essa spesso si associa la presenza di un ectropion/ectopia, causa di sanguinamento e conseguente ansia e sconforto per la paziente. L'utilizzo di una molecola che riesca ad innescare i processi riparativi dell'epitelio cervicale, svolgendo anche un'azione antibatterica, e a coadiuvare la risposta immunitaria fisiologica locale, potrebbe rappresentare un valido aiuto nella gestione clinica.

Obiettivi: valutare l'azione riepitelizzante e l'efficacia di TIAGIN® formulazione vaginale in un gruppo di pazienti con lesioni di basso grado della cervice uterina (ASC-US /L-SIL) positive ad HPV ad alto rischio con ectropion/ectopia cervicale, trattate con TIAGIN® per applicazione vaginale, analizzando la percentuale di negativizzazione della citologia, la percentuale di negativizzazione dell'HPV test, l'eventuale regressione delle lesioni colposcopicamente visibili e il grado di riepitelizzazione dell'ectropion/ectopia a 6 mesi,

Risultati: sono stati raccolti i dati relativi a 19 pazienti con età media di 31 anni. La quasi totalità delle pazienti è riuscita a portare a termine la terapia prescritta; solo 1 paziente su 19 ha sospeso il trattamento dal primo ciclo per intolleranza al prodotto ed è stata quindi esclusa dall'analisi, condotta su 18 pazienti. La citologia di controllo a 6 mesi dopo terapia con

Corresponding to: caterina.ricci@hotmail.it

DOI: 10.14660/2385-0868-XX

TIAGIN® formulazione vaginale è risultata negativa in 12 pazienti su 18 (66,7%). Il tasso di negativizzazione microbiologica a 6 mesi dopo terapia è risultato del 50% con 9 negativizzazioni dell'HPV test su 18. Al tempo 6 mesi 9 pazienti su 18 (50%) mostravano una negativizzazione del quadro colposcopico in termini di regressione completa della TA1. Nel restante 50% il quadro colposcopico è risultato invariato o ridotto in estensione, senza alcuna progressione o necessità insorta di prelievo bioptico. Tutte le pazienti hanno mostrato al controllo a 6 mesi una risoluzione del sanguinamento. In 5 pazienti (27,8%) l'ectropion/ectopia risultava invariato rispetto al T0. In 3 pazienti (16,6%) risultava ridotto in dimensioni di almeno il 25%. In 10 pazienti (55,6%) risultava risolto e completamente riepitelizzato. **Conclusioni**: TIAGIN® formulazione vaginale si è mostrato nella pratica clinica un promettente supporto terapeutico nella gestione delle lesioni di basso grado della cervice uterina causate da HPV ad alto rischio, e una valida opzione nella gestione conservativa dell'ectropion/ectopia sanguinante. Tali dati, seppur interessanti e promettenti, necessitano di valutazioni e ulteriori validazioni in studi prospettici su più ampio campione.

Parole chiave: Riepitelizzazione, ASC-US/L-SIL, Ectropion, HPV

BACKGROUND

High-risk HPV infection, particularly when associated with a low-grade cervical lesion, is a very common problem, especially in young women. These lesions are known to present a significant possibility of spontaneous regression, meaning that conservative and observational management is often an option.[1] The presence of cervical ectropion/ectopy, which causes bleeding and consequent anxiety and discomfort for the patient, is also very widespread and often occurs alongside the lesions. Gynaecologists and colposcopists are routinely required to manage these problems on an outpatient basis.

The role played by the local vaginal immune system in determining the regression/progression of HPV-related lesions having been amply demonstrated in literature[2-3], the use of a molecule able to trigger the reparatory processes of the cervical epithelium while also providing antibacterial action and boosting the local physiological immune response, could be a valid aid for the clinical management of such cases.

The TIAB® complex (titanium dioxide with covalently linked monovalent silver ions) is a nanotechnology product contained in TIAGIN® for vaginal application and foam for vulvar application. It kills the microorganisms in question, particularly fungi, bacteria and viruses, through a twofold mechanism: by blocking the enzymatic respiratory system through interaction with the ribosome; by damaging the cell wall and making it permeable. This complex has been shown to act on 650 microorganisms in the vagina and possesses considerable reepithelialising potential[4-5].

In vitro studies have particularly highlighted the antiviral potential of silver nanoparticles thanks to their interaction with membrane viral glycoproteins. In fact, by bonding to them and changing their three-dimensional structure by altering the S-S bonds, they reduce the opportunity for the virus to enter the host cell[6]. In greater detail, a study conducted in 2011 demonstrated the antiviral activity of silver nanoparticles on a cervical cell culture model with regard to the HIV-1 virus by means of various mechanisms: TNF-alpha reduction, stimulation of lymphocyte production and immune cell activation[7].

However, there are no studies in literature designed to establish the possible efficacy of this complex on cervical lesions caused by high-risk HPV.

OBJECTIVE

The study objective was to evaluate the reepithelialising action and efficacy of TIAGIN® vaginal formulation as an adjuvant in the resolution of HPV-related low-grade cervical lesions in a group of patients with low-grade cervical lesions (ASC-US /L-SIL) positive for high-risk HPV with cervical ectropion/ectopy. We particularly analysed the cytological clearance percentage, the HPV clearance percentage, the regression of lesions visible during colposcopy and the degree of reepithelialisation of the ectropion/ectopy at 6 months.

SETTING

Colposcopy Clinic, University Hospital.

MATHERIALS AND METHODS

Data was gathered on 19 patients with a mean age of 31 (20-62 years old), who attended the Colposcopy Clinic between December 2015 and August 2016, all of whom were suffering from low-grade cervical lesions (ASC-US /L-SIL) positive for high-risk HPV with cervical ectropion/ectopy, treated with TIAGIN® vaginal formulation. The patients, assessed during an initial visit (Time 0), all met the following criteria: Pap test indicative of low-grade lesions (ASC-US /L-SIL), colposcopy with evidence of bleeding ectropion/ectopy, HPV test positive for high-risk genotypes. The exclusion criteria were: pregnancy, use of other immune system adjuvant therapies, previous cervical treatments. The patients underwent a colposcopy at T0 and T6 months, performed by the same SICPCV-accredited colposcopists. At T0, all 18 patients showed an AT1 (abnormal transformation zone suggestive of a low-grade lesion in accordance with the SICPCV classification)[8] on the type 1 transformation zone (fully visible ectocervical squamocolumnar junction as per the IFCPC 2011 classification)[9] associated with bleeding ectropion/ectopy. The patients were treated on the basis of the following dosage regimen: TIAGIN® vaginal formulation 1/day for 10 days a month for 4 months. They were then reassessed after 6 months (Time 6m), when the Pap test, colposcopy and HPV test were repeated. Traditional cytology and Multiplex HPV PCR tests were used in the study, in keeping with routine clinical practice at the facility. The patients were permitted to replace TIAGIN® capsules with TIAGIN® vaginal softgel capsules when the product was launched on the market and replaced.

OUTCOMES

The outcomes we evaluated were the cytological clearance percentage, the HPV clearance percentage, any regression of lesions visible during colposcopy and the degree of reepithelialisation of the ectropion/ectopy at 6 months. This outcome was evaluated as: complete resolution, partial regression or unchanged appearance compared to T0.

RESULTS

Almost all the patients managed to complete the prescribed treatment. Only 1 of the 19 patients stopped treatment after the first cycle due to intolerance to the product in the form of localised itching and was therefore excluded from the analysis, conducted on 18 patients. All the patients demonstrated a preference for the TIAGIN® softgel formulation and found it easier to use than the TIAGIN® capsules used during the first treatment cycles.

At T0 the cytology results showed 13 patients with L-SIL and 5 patients with ASC-US. The follow-up cytology assessment at 6 months after treatment with TIAGIN® vaginal formulation was negative in 12 out of 18 patients (66.7%), with all the ASC-US cytology tests and 7 of the L-SIL cytology tests coming back negative. All the study patients had an HPV test at T0 that was positive for high-risk genotypes (the 18 patients were found to have 9 different genotypes, with 2 cases of multiple infection).

The microbiological clearance rate at 6 months after treatment was 50%, with 9 cases of clearance out of 18. The colposcopy examinations found all 18 patients to have an AT1 associated with bleeding ectropion/ectopy at T0. At 6 months, 9 of the 18 patients (50%) were found to be negative during the colposcopy due to complete regression of the AT1. In the remaining 50%, the colposcopy results were unchanged or improved, without any progression or the need for a biopsy.

Bleeding had stopped in all patients at the 6-month check-up. In 5 patients (27.8%), the ectropion/ectopy was unchanged compared to T0. In 3 patients (16.6%), it was at least 25% smaller. In 10 patients (55.6%) it was resolved and completely reepithelialised.

These results are summed up in **Table 1** and **Fig. 1**.

Table 1.
Cytological, colposcopic and microbiological response in 18 patients

Pap test negativisation No (%)	HPV clearance No (%)	Colposcopy negativisation No (%)
12 (66.7%)	9 (50%)	9 (50%)

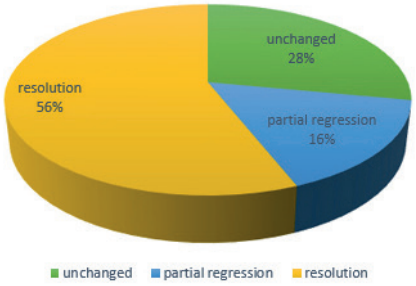

Figure 1
Degree of ectropion/ectopy reepithelialization

DISCUSSION

The findings in our study seem promising given the high rate of cytological, microbiological and also colposcopic regression of the HPV-related low-grade cervical lesions in the group analysed after treatment with TIAGIN® vaginal formulation. These results are more or less comparable with the spontaneous regression data present in literature and superior as regards the rate of spontaneous cytological and microbiological regression[10-12].

The findings regarding the rate of ectropion/ectopy reepithelialisation are also significant for clinical management purposes, with bleeding being resolved in all cases and complete reepithelialisation of the ectropion/ectopy being achieved in 55.6%.

These results also appear promising in consideration of the lack of studies reported in literature regarding a conservative, therapeutic approach to the medical management of ectropion/ectopy. This study is certainly limited by its small population and relatively short time scale, considering the natural history of HPV infection that underlies low-grade cervical lesions. On the other hand, it offers an interesting starting point for studies involving a larger population and tangible support for the clinical use of TIAGIN® in the analysed setting.

CONCLUSIONS

In its vaginal formulations TIAGIN® has shown itself to be a promising therapeutic aid in the clinical management of low-grade cervical lesions caused by high-risk HPV, thanks also to its good tolerability and ease of use, especially in the softgel formulation.

It has also been shown to be a valid option for the conservative management of bleeding ectropion/ectopy. Although this data is very interesting and promising, further evaluation and validation is required from prospective studies involving a larger number of subjects.

REFERENCES

1) **Natural history and epidemiology of HPV infection and cervical cancer**. Castellsaguè X. Gynecol Oncol 2008; 110(3 Suppl 2):S4-7.

2) **Role of Innate Immunity against Human Papillomavirus (HPV) Infections and Effect of Adjuvants in Promoting Specific Immune Response**. Alfredo Amador-Molina, et al. Viruses. 2013 Nov; 5(11): 2624-2642.

3) **Immune responses to human papilloma viruses**. Stanley MA. Indian J Med Res 2009;130:266-76.

4) **Evaluation of the efficacy of titanium dioxide with monovalent silver ions covalently linked (TIAB®) as an adjunct to scaling and root planning in the management of chronic periodontitis using pcr analysis: a microbiological study**. Lauritano D, et al. J boil regul homeost agents. 2015 jul-sep;29(3 suppl 1): 127-30.

5) **TIAGIN®** Capsule vaginali foglietto illustrativo

6) **Silver nanoparticles as Potential Antiviral Agents**. Galdiero S. et al. Molecules 2011, 16 8894-8918.

7) **Silver nanoparticles are broad-spectrum bactericidal and virucidal compounds**. Lara HH et al. Journal of Nanobiotechnology 2011, 9:30.

8) **SICPCV: gestione della paziente con pap-test anormale**. Linee Guida Edizione 2006. Anno XXI; N. 1 Dicembre 2006.

9) **2011 colposcopic terminology of the International Federation for cervical Pathology and Colposcopy**. Bornstein J et al. Obstet Gynecol. 2012 Jul; 120(1):166-72.

10) **Human Papillomavirus Infection and Time to Progression and Regression of Cervical Intraepithelial Neoplasia**. Nicolas F. Schlecht, et al. Jnl of Natl Cancer Inst. Volume 95, Issue 17 pp. 1336-1343.

11) **Natural history of dysplasia of the uterine cervix**. Holowaty P, et al. Jnl Natl Cancer Inst. 1999 Feb 3; 91(3):252-8.

12) **A long-term study of women with normal colposcopy after referral with low-grade cytological abnormalities**. Smith M.C. et al: BJOG. 2006; 113(11): 1321-8.