

# Treatment for Vulvar Intraepithelial Neoplasia II/III Bowenoid or Basaloid with Imiquimod 5% cream.

**Authors:** Marchitelli C; Secco G; Perrotta M; Lugones L; Pesce R; Testa R

**Claudia Marchitelli:** Vulvar Pathology Section Coordinator. Gynecology Department.  
Hospital Italiano .  
Buenos Aires, Argentina.

**Mail address:** 4239 Pavon Ave. (1253) Buenos Aires, Argentina  
Phone/Fax: 54 01 4992-9503

**E-mail:** [claudia.marchitelli@hospitalitaliano.org.ar](mailto:claudia.marchitelli@hospitalitaliano.org.ar)

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## **Synopsis**

Imiquimod proved to be effective when used in young women with multifocal undifferentiated VIN.

## **Abstract**

**Objectives:** To evaluate efficacy and safety of Imiquimod 5% for the treatment of VIN II/III Bowenoid or Basaloid.

To evaluate recurrences following treatment.

**Material and method:** Eight patients less than 55 years (32-51), mean (39.7), with VIN II/III Bowenoid or Basaloid diagnosed by biopsy were treated with Imiquimod 5%.

Patients with other intraepithelial neoplasia (IEN) of the lower genital tract, immunodepressed individuals, pregnant women or patients with other vulvar pathology, were excluded.

Two patients, previously treated for VIN III (surgical resection, resection by method of LEEP) were recurrent.

Patients applied Imiquimod cream three times a week until the complete disappearance of the lesions or up to a maximum of 16 weeks.

Responses were categorized as complete, when there was no colposcopic evidence of lesion; partial, when the lesion area diminished more than 50%; and progressive, when there was an increase of the lesion area.

A biopsy was performed at the end of treatment.

Follow-up was carried out monthly (10-30 months)

**Results:** Complete disappearance of lesions was observed in 6 patients after 10-16 weeks. Two patients had a partial response (one with 75% and the other with 50% reduction of the lesions).

Post-treatment histopathology showed the absence of precancerous lesions in 7 patients (87.5%).

Biopsy was positive for VIN III (12.5%) only in the patient showing a clinical response of 50%.

Of the 7 patients with negative biopsies for VIN, 2 (25%) were positive for viral infection; one gave a negative reading after two months of treatment and the other remained positive for HPV.

The patient with persistent VIN received surgical treatment.

Adverse effects were as follows: eritema in 8 patients (100%), erosions in 1 patient (12.5%) and edema in 1 patient (12.5%).

No relapses occurred after treatment during a 10-30 months follow-up.

**Conclusions:** In this initial series Imiquimod proved to be effective for the treatment of VIN Bowenoid or Basaloid in a group of young women, being a less aggressive treatment than the surgical ones.

2. Treatment was well tolerated, presenting local reactions that enabled the proposed therapeutical scheme to be completed.

The beginning of a prospective series of patients undergoing this treatment is presented in this study.

## **INTRODUCTION:**

During the three past decades, there was a significant increase in the incidence of the VIN (1-2-3). This increase is mainly observed in young women, under 40 years old and smokers (1). This can be correlated with an increase in the incidence of genital infections by the Human Papillomavirus (HPV), mainly in this population group.

On the other hand, during these decades of life there was an increase in the incidence of the VIN which agrees with the opening of doctor's offices specialized in vulvar pathology, using diagnostic methods like vulvoscopy and biopsy, which allow to detect injuries that in the past were unnoticed (4). It would be possible questioned if this is a true increase in the incidence or if it is really a slant search that confuses a greater incidence with a better capacity to diagnose injuries that in the past were unnoticed.

This increase in the incidence of intraepithelial neoplasias (IEN) of lower genital tract seems to be associated with the viral infection by HPV. Some viral types (specially the 16) are strongly implied like causal agents (5). Other cofactors suggested in the pathogenesis of IEN are multiple sexual partners, habit of smoking, wrong washing, immunosuppression and pregnancy (6). There is a strong association between VIN and sexual transmitted diseases (STD) with rates of 20-60% according to different authors (7).

Two well-defined types of VIN are recognized, each one has differences in etiology, pathogenesis and clinical evolution. One is the undifferentiated VIN or classic VIN, associated with HPV infection, which mostly happens in young women, this tends to be pigmented and multifocal. This is associated with other intraepithelial neoplasias of the lower genital tract, generally with CIN 3 in over the 30% of the patients. Another one is the differentiated VIN, not associated with the HPV, but related to non-neoplastic epithelial disorders (Lichen sclerosus – Squamous hyperplasia). It appears most frequently in post-menopausal women, it tends to be unifocal, leucoplastic and it is not associated with other IEN from the lower genital tract (LGT) (8-9).

This differentiation is hardly reflected in literature since most of the series do not differentiate the histological types of VIN. The undifferentiated type (classic VIN), related to the HPV is the most frequent one but no way, the unique one.

The natural history of the VIN is still unpredictable, but young women show a stationary condition during a long period of time, and in some cases, a spontaneous regression is observed (10).

On the other hand, in aged patients these lesions have a greater malignant potential, related to the age of appearance of the vulvar carcinoma, predominantly in aged women (11). In this group of patients, the vulvar squamous carcinoma is frequently associated with non-neoplastic epithelial disorders and rarely with the undifferentiated VIN (12).

The age of appearance is an epidemiologically important factor.

The present treatments for the VIN are based on the destruction of affected tissues, carrying out a great deterioration of the vulvar anatomy and its functioning. This is translated to a great physical, psychological and sexual morbidity. They have high relapse rates, possibly due to the lack of

elimination of HPV reservoirs present in the vulvar skin. Relapses between 30-70% were described after resections by means of LEEP, laser or surgical practice (13-14).

The Imiquimod, a modifier of the immune response, stimulates the body's immune system by inducing cytokines (Interferon alpha Interleukin 12), to fight against viral infection (17). Undifferentiated VIN, related to the HPV, is the most frequent among young women population. Due to the mechanism of action of the Imiquimod and its effectiveness in the treatment of external genital warts (15-16), this treatment for the VIN 2-3 Bowenoid and /or Basaloid is proposed, which are the positive HPV intraepithelial neoplasias.

Knowing that these lesions remain stationary or years are needed so that they advance to another more serious injury, we have time to evaluate the effectiveness of the Imiquimod during their treatment. On the other hand, the VIN appears in younger women who would be benefited when receiving this type of treatment, comparing to the destructive ones applied up to now.

Next, the effectiveness and security of IMIQUIMOD 5% cream for the treatment of the 2/3 VIN Bowenoid and/or Basaloid are evaluated, as well as the rates of post-treatment relapses.

### **Materials and methods:**

The approval of the Ethics Committee of the Hospital Italiano of Buenos Aires (Argentina) was obtained in order to carry out this observational and prospective work.

Eight (8) patients under 55 years old, average 39.7 (32-51 years), with VIN 2-3 Bowenoid and/or Basaloid diagnosed by biopsy were included in this work.

All of them were older than 18 years and they signed up an informed consent so to be included in this work.

Vulvoscopy was made and photographs from all the lesions were taken to be able to compare the response with the treatment. The characteristics of the patients are shown in Table I. The biopsies were made with dermatological punch of 6 mm. and in case of multifocal injuries, several biopsies from the different lesions and locations were taken. In patients with perianal VIN, an anoscopy was performed to them so as to discard injury of the anal channel.

Patients with another IEN of the TGI, immunosuppressed, pregnant or with another vulvar pathology (including the differentiated VIN) were excluded from this work.

Two(2) (25%) of the eight (8) patients had received previous treatments due to VIN. In one patient, the injury was dried up by means of LEEP, being recurrent 5 months after treatment; the other patient, a local surgical resection was performed with a recurrence 4 months post treatment.

The application methodology was, previous instruction to the patient, the topical placing of the preparation three-times-a-week in alternating days and night schedule, and washing up the area in the morning. The treatment ends when the lesions disappear completely or after a maximum of 16 weeks. The response was considered as complete when vulvoscopic evidence of lesion could not be demonstrated; as partial, when the injured area diminished more than 50% and as progressive, when

an increase of the same one was observed. Every month patients have come to evaluate the treatment and to search for adverse reactions.

The follow-up lasted 22 months (10-30 months).

Table I

### **Results:**

Eight (8) patients were included in this work. The main reason for consultation was itching (62.5%) (see Table II). Seventy-five percent (75%) of the patients presented injuries in more than one location (Table III). In the two patients with perianal lesions, the anoscopy was negative. From the eight (8) patients, two (2) had history of vulvar condyloma acuminata treated with local topics; three had associated cervical lesions (two (2) had a previous viral condyloma plane (CVP) treated with criosurgery two and one years ago); and the last one presented a CVP at that moment and three (3) did not present associated injuries.

The complete disappearance of the lesions was observed in six (6) patients after 10-16 weeks of treatment.

Two (2) patients had a partial response, one (1) presented a decrease of 75% of the lesion (case 2) and the other one, a 50% of the same one (case 8). The post-treatment hystopathology showed absence of VIN in seven (7) patients (87.5%). The positive biopsy for VIN 3 corresponded to the patient with a 50% decrease of the lesion (case 8). Among seven (7) patients with negative biopsies for VIN, two (2) of them were positive for viral infection. One (1) belonged to the patient with residual injury of 25% (case 2), which became negative spontaneously after two months once treatment was completed and the other one belonged to a patient in which residual vulvoscopic injury was not observed (case 3) after treatment.

The patient with persistent VIN received surgical treatment of the residual lesion.

The adverse effects were well-tolerated local reactions. Being a small number of patients, they were orally interrogated about the presence of symptoms like burning, itching, pain and dyspareunia. These symptoms were evaluated monthly and they are shown in Graphic 4. In spite of not referring dyspareunia as an important symptom, when making a more exhaustive interrogation about the sexuality, 87.5% of the patients referred to a decrease in the sexual desire and the frequency of sexual relationships.

These symptoms reverted after a month once the treatment was completed.

Only in two patients the treatment had to be interrupted for a week. One (1) presented vulvar erosions and the other one, vulvar edema. After resting for a week, they respectively continued with the treatment until 16 weeks. Eritema in the 100% of the patients was verified. Table of Adverse Effects.

Post-treatment relapses were not observed during a 10-30 months follow-up.  
(average: 22)

Table II

Table III

## Graphic 1

### **Discussion:**

There are not many reported series of patients with VIN 2-3 treated with Imiquimod.

Davis et al reported four cases of VIN-3 treated with Imiquimod. All four patients experienced clearance of the lesions, but two relapsed (18). There were no comments about the adverse effects.

Diaz-Arrastia reported eight cases of recurrent intraepithelial neoplasia of the lower genital tract: 2 cervical, 2 vaginal and 4 vulvar. Four (4) patients experienced a complete answer, two (2) partial answer, one (1) patient progressed to a vagina microcarcinoma and another one left the treatment. From the four (4) patients with complete answer: two (2) came back three and fifteen months after treatment, being these patients HIV positive (19).

Todd reported one of the longest series of patients with VIN 3 treated with Imiquimod. Fifteen (15) patients received treatment, four (4) of them had clinical improvements with three negative biopsies for VIN. Due to the important adverse effects only two (2) patients could complete the scheme of application of the cream three-times-a-week. This could be the cause of the reduced answer to the treatment (29).

Jayne Christopher, retrospective review the charts of 13 patients with VIN2/3 treated with Imiquimod. Eight (8) had a complete regression of the VIN, four (4) demonstrated 75% regression; in two (2) of them invasive Carcinoma was found in the area of residual disease (21).

Van Seters studied the clinical response of fifteen (15) patients with VIN 2-3. Four (4) had a complete response and nine (9), a partial response. Two (2) patients did not tolerate treatment (22).

G. Champagne treated one (1) patient with Imiquimod on account of high grade VIN in the vulva and other locations. Later biopsies to the treatment informed absence of VIN. In this patient the adverse effect of the medication was the appearance of vulvar pemphigus (23).

The frequency with which VIN 3 progressed to carcinoma is not clear. The increase in the incidence of the VIN in young women made us think that it would be a parallel increase in the incidence of the vulvar carcinoma in this population group. However, this has not been observed for invasive carcinoma; the age-corrected incidence of vulvar cancer has remained unchanged during the past two decades (24). This can be due to two factors: first, the early diagnosis of these lesions entailed their treatment with decrease of the progression of the vulvar Ca, and secondly, these VIN that appear in young women (those that increased in incidence) would not be the true precursor of the vulvar cancer (11-24). There are some works which explained about an increase of the vulvar cancer in young women, but they are still isolated reports (25-26-27). Most of the vulvar carcinomas have injuries of lichen sclerosus or squamous hyperplasia around the injury (greater than 50%) (28-29).

Although this work has its limitations since it was not randomized with a small sample and lesions of different sizes and locations, as far as we know it is the only one that considers the histological type of VIN. The patients who had biopsies with differentiated or mixed VIN (in those cases that the pathologist could not define a particular histological type) were excluded. Because the etiology is not related to the viral infection; therefore, the immunomodulator treatment would not be indicated.

It is possible that the good response to the treatment in this series must be due to that only viral VIN were treated: the majority (75%) had not received previous treatments and once the diagnosis was made, the therapeutic was quickly applied. Only one (1) patient took a year to make an appointment with a doctor. This presented positive post-treatment biopsy for VIN.

Important adverse effects as stated in other works were not observed.

The patients had been appointed by the doctor and they were instructed in the use of the cream, showing them how and where it had to be placed. This could be a cause of decrease in the adverse effects. It is important to remark that our patients well-tolerated the local reactions. Two (2) patients had to suspend the treatment under medical indication, because in the clinical examination, edema or erosion were observed even though they were well tolerated, the administration protocol did not allow to continue with the treatment.

Vulvar eritema was observed in the 100% of our patients; in some cases, it was intense. The mechanism of action of Imiquimod releasing cytokines entails the presence of eritema by the local inflammatory reaction. Due to this, we consider not only the intensity of eritema but also the symptoms reported by the patients, who in all the cases, these symptoms did not correlate with the intensity of the eritema.

In all cases, the patients were young women with multifocal disease. If they had received surgical treatment, the resections would have been extensive with a great destruction of the vulvar anatomy and with a great psychological and sexual deterioration.

A patient with positive biopsy for VIN presented a decrease of the affected area of more than 50%, which allowed the resections to become smaller, with acceptable cosmetic results.

In this work this Imiquimod turned out to be effective for the treatment of viral VIN 2-3. We considered important to know the histological type before making this treatment, so as to achieve greater therapeutic success and to deal injuries with smaller risk of progression. Imiquimod proved to be effective when used in young patients with multifocal undifferentiated VIN. If the etiology of VIN is not related to viral infection therefore the immunomodulator treatment will not be indicated.

In one (1) patient, spontaneous disappearance of residual viral injury was observed after the treatment.

Imiquimod represents an alternative for the treatment of the VIN in young women with multifocal lesions. It is effective, well-tolerated and less aggressive than the surgical treatments.

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