Treatment of Undifferentiated Vulvar Intraepithelial Neoplasia With 5% Imiquimod Cream

A Prospective Study of 12 Cases

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Objective: To assess the efficacy of 5% imiquimod cream on undifferentiated vulvar intraepithelial neoplasia (VIN), a disease caused by high-risk human papillomavirus.

Design: Prospective, uncontrolled study.

Setting: University hospital vulvar clinic.


Intervention: Self-application of 5% imiquimod cream, initially 3 times a week, then adjusted according to tolerance, for up to 7 months according to clinical response.

Main Outcome Measures: Therapeutic response, clinically assessed by successive photographs and histologically confirmed for complete responders, was scored as complete, partial (≥50% decrease in lesion size), or failure. Tolerance was evaluated at each visit.

Results: A total of 3, 4, and 5 patients achieved complete response, partial response (≥75% reduction in lesion size for all such cases), and failure, respectively. Mean duration of treatment was 3.6 months (37.3 applications), 5.0 months (50.7 applications), and 3.4 months (25.2 applications) for complete responders, partial responders, and failures, respectively. Follow-up after treatment was 5 to 18, 14 to 32, and 2 to 28 months, respectively, with 1 partial responder lost to long-term follow-up. No patient developed invasive carcinoma. All but 2 patients experienced vulvar discomfort, resulting in treatment withdrawal for 3. Two patients had flulike symptoms.

Conclusions: Imiquimod cream could be a therapeutic option for undifferentiated VIN. Although poorly tolerated, this self-applied treatment could spare patients, either totally or partially, the classic painful and sometimes mutilating treatments of VIN. Controlled, randomized studies are needed to evaluate its efficacy and tolerance.

Arch Dermatol. 2004;140:1220-1224

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vulva. Current treatments for undifferentiated VIN consist of physical destruction of the lesions by partial vulvectomy, cryotherapy, laser vaporization, or electrocautery. These painful, sometimes mutilating, treatments do not protect the patients from recurrences, which occur in 12% to 58% of women after treatment.4,6

Imiquimod, an imidazoquinoline amine, is an immune-response modifier that induces monocytes and macrophages to produce interferon-α and other cytokines (interleukins 1, 6, 8, 10, and 12 and tumor necrosis factor α). It inhibits viral replication and promotes stronger cell-mediated immune responses.7 Self-administered 5% imiquimod cream (Aldara; Laboratoire 3M Santé, Division 3M Pharma, Cergy-Pontoise, France) is currently approved for treating anogenital warts (AGWs), a condition related to low-risk HPV infection, with complete responses achieved in 35% to 52% of immunocompetent patients.8,9 In addition, phase 2 studies have shown that 5% imiquimod cream can be an effective treatment of superficial basal cell carcinoma, actinic keratoses, and extragenital Bowen disease.10,11

We postulated that 5% imiquimod cream could represent a conservative alternative to the current destructive treatments of undifferentiated VIN, both because this condition is HPV related and because it carries a low risk of invasive SCC. Therefore, it was acceptable to postpone the classic destructive treatment of the lesions until failure or partial response to 5% imiquimod cream.

METHODS

From March 1, 1999, to May 31, 2001, 5% imiquimod cream was prospectively prescribed to all patients with histologically confirmed, noninvasive, undifferentiated VIN who consulted the vulvar clinic of our university hospital. During that period, 3 other patients with thick, monolocal, erythroplastic lesions were treated surgically, because we were not sure that the local biopsy findings excluded SCC. The study followed the principles outlined in the Declaration of Helsinki. All patients gave informed oral consent.

The initial evaluation consisted of an inspection of the vulva and the anal margin, first with the naked eye and then with a magnifying lens (original magnification ×2), followed by a detailed, written description of the lesions, photographs, and drawn diagrams. Because of its lack of sensitivity and specificity, the acetoc acid test was not used. Biopsy specimens were obtained from all ulcerated, leukoplasic, thick, and infiltrated areas before treatment to exclude invasive SCC. All patients who had not had a Papanicolaou smear during the preceding year were advised to have one performed by their gynecologist. Patients with lesions of the anal margin underwent anoscopy. The diagnosis of undifferentiated VIN was made based on histologic examination of the biopsy specimens by an experienced pathologist (T.C.). The women were offered HPV typing by polymerase chain reaction performed on a biopsy specimen of a representative lesion. Patients were instructed to apply 5% imiquimod cream (each dose of 12.5 mg supplied in individual packets) 3 times a week overnight, as recommended for the treatment of external genital warts. The areas involved by the VIN were shown to the patient using a mirror. She was then instructed to apply the cream on these specific areas with the fingers. When the lesions involved more than 50% of the surface of the vulvar mucosa, the patient was told to apply 1 complete packet of cream. In case of less extended lesions, she was instructed to apply a small quantity of cream. In these latter patients, we did not quantify the amount of cream applied. The cream was applied at bedtime and was removed by washing with water and a gentle soap in the morning. The patient was asked neither to wash nor to have sexual intercourse during the time the cream was in contact with the mucosa. The frequency of the applications was adapted as a function of the tolerance to the cream.

Follow-up evaluations consisted of physical examination of the vulva, with detailed description of the lesions, photographs, and drawn diagrams made by 2 experienced physicians (M.M.-B., S.B.-L.). The number of applications, the duration of treatment, and tolerance of the cream were also recorded. Responses were evaluated clinically monthly, and 2 authors (J.W., M.M.-B.) reviewed successive photographs after completion of the study. A complete response was defined as histologically confirmed complete disappearance of the lesions. Partial response was defined as decrease of 50% or more in the lesion size, whereas a decrease of less than 50% of lesion size or progression was considered a failure. At the end of treatment, patients returned to usual follow-up and treatments by the same physicians.

RESULTS

Twelve consecutive patients fulfilled our criteria for inclusion (Table 1). Their ages ranged from 27 to 53 years (mean age, 41.4 years). Patients 6, 7, and 8 tested positive for human immunodeficiency virus (HIV) 1 and were undergoing highly active antiretroviral therapy (HAART) for more than 1 year with satisfactory responses (CD4 lymphocyte count of >350/μL, no detectable HIV-1 RNA in the serum for 2 of these patients, and 9000 copies/mL of plasma for the third). The VIN was recurrent in 8 patients. Four patients had histories of cervical intraepithelial neoplasias, and 1 had previously undergone surgery for anal intraepithelial neoplasia. All 12 patients had normal Papanicolaou smear results within the year preceding the 5% imiquimod cream treatment. Seven of 12 patients had multifocal lesions, which involved more than 50% of the vulvar mucosa in 3 of them. In 5 women, the lesions were monofocal. Lesions were predominantly pink papules or macules. Patient 6 had a typical bowenoid papulosis. Ten patients underwent an additional biopsy for HPV testing: HPV-16 was found in 9 patients and HPV-33 in 1.

Five percent imiquimod cream led to 3 complete responses, 4 partial responses, and 5 failures. None of the lesions progressed to invasive SCC. Patients 1, 2, and 3, who experienced biopsy-confirmed complete response and were not immunocompromised, initially had limited macular or papular pink lesions that involved less than 20% of the vulvar mucosa surface. Patients 2 and 3 had recurrent VIN. Imiquimod had been applied for a mean duration of 3.7 months (mean number of applications, 37.3). The HPV was no longer detected in a new biopsy specimen at the site of the pretreatment lesions in patient 1. Persistent HPV infection was not sought in the 2 other complete responders. No recurrence was observed during a mean follow-up of 9.7 months after the end of the treatment.

Patients 4 to 7 experienced partial response, with regression of more than 75% of the lesion area in all of them. Their lesions at inclusion were polymorphous: macular, papular, or warty; pink or pigmented; multifo-
These symptoms appeared 8 to 12 hours after every topical application and disappeared within 1 hour with paracetamol or within 16 hours without any treatment. Patient 1 had a monofocal VIN that involved less than 20% of the vulvar mucosa, and patient 11 had an extensive VIN that involved almost the entire surface of the vulvar mucosa; both had superficial topical ulcers. The flulike symptoms decreased after 5 or 6 applications. Patient 8, who was HIV positive, developed cytolytic hepatitis during the treatment. This hepatitis relapsed after the end of the imiquimod treatment and was eventually attributed to HAART.

Seven of 12 patients with undifferentiated VIN treated with 5% imiquimod cream experienced either complete remission or partial remission. In the patients who experienced partial remission (initially defined as a reduction of >50% in lesion size), the decrease in lesion size was at least 75%. Imiquimod could be a valid alternative to the classic destructive treatment methods, because it can be self-applied by the patients and, theoretically, because it represents an immunologic approach to the management of this HPV-associated condition. Indeed, conventional treatments of undifferentiated VIN are painful and sometimes mutilating, and recurrences frequently occur. Considering the low risk of transformation of undifferentiated VIN into SCC, the cost of conventional treatments most frequently exceeds their benefit.

### Table 1. Main Characteristics of the 12 VIN Patients

<table>
<thead>
<tr>
<th>Patient No./Age, y/HIV Status</th>
<th>Clinical Features of the Lesions</th>
<th>Location of VIN (% of the Vulvar Mucosa Involved)</th>
<th>Recurrent VIN</th>
<th>No. of Months Undergoing Treatment</th>
<th>No. of Applications</th>
<th>Response</th>
<th>Follow-up After Treatment, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/51/−</td>
<td>Pink; macular</td>
<td>Multifocal (&lt;20); fourchette, posterior vestibule, anal margin</td>
<td>No</td>
<td>4</td>
<td>28</td>
<td>Complete</td>
<td>18</td>
</tr>
<tr>
<td>2/44/−</td>
<td>Pink; papular or verrucous</td>
<td>Multifocal (&lt;20); labia minora</td>
<td>Yes</td>
<td>3</td>
<td>36</td>
<td>Complete</td>
<td>6</td>
</tr>
<tr>
<td>3/53/−</td>
<td>Pink; macular</td>
<td>Multifocal (&lt;20); fourchette</td>
<td>Yes</td>
<td>4</td>
<td>48</td>
<td>Complete</td>
<td>5</td>
</tr>
<tr>
<td>4/27/−</td>
<td>Pink or pigmented; papular</td>
<td>Multifocal (&lt;20); left labium minus, posterior vestibule, fourchette</td>
<td>No</td>
<td>6</td>
<td>41</td>
<td>Partial</td>
<td>14</td>
</tr>
<tr>
<td>5/40/−</td>
<td>Pink; papular or verrucous</td>
<td>Monofocal (20-50); left labium minus</td>
<td>Yes</td>
<td>7</td>
<td>78</td>
<td>Partial</td>
<td>LFU</td>
</tr>
<tr>
<td>6/39/+</td>
<td>Pigmented; papular</td>
<td>Multifocal (&lt;20); labia majora, fourchette, right labium minus, perineum, anal margin</td>
<td>No</td>
<td>6</td>
<td>72</td>
<td>Partial</td>
<td>15</td>
</tr>
<tr>
<td>7/40/+</td>
<td>Pink; macular or papular</td>
<td>Multifocal (20-50); clitoris, labia majora and minora, perineum anal margin</td>
<td>Yes</td>
<td>1</td>
<td>12</td>
<td>Partial</td>
<td>32</td>
</tr>
<tr>
<td>8/40/+</td>
<td>Pink, white, or pigmented; papular, macular, or verrucous</td>
<td>Multifocal (&gt;50); labia majora and minora, perineum anal margin</td>
<td>Yes</td>
<td>3</td>
<td>24</td>
<td>Failure</td>
<td>13</td>
</tr>
<tr>
<td>9/32/−</td>
<td>Pink or pigmented; macular or papular</td>
<td>Multifocal (&gt;50); labia majora and minora, perineum anal margin</td>
<td>Yes</td>
<td>3</td>
<td>36</td>
<td>Failure</td>
<td>28</td>
</tr>
<tr>
<td>10/47/−</td>
<td>Pink; verrucous</td>
<td>Monofocal (&lt;20); right labia minora and majora, fourchette</td>
<td>No</td>
<td>3</td>
<td>36</td>
<td>Failure</td>
<td>2 Then LFU</td>
</tr>
<tr>
<td>11/40/−</td>
<td>Pink or white; verrucous</td>
<td>Multifocal (&gt;50); labia minora and majora, anal margin</td>
<td>Yes</td>
<td>5</td>
<td>12</td>
<td>Failure</td>
<td>14</td>
</tr>
<tr>
<td>12/44/−</td>
<td>Pink, white, or pigmented; papular</td>
<td>Monofocal (30); left labium minus</td>
<td>Yes</td>
<td>3</td>
<td>18</td>
<td>Failure</td>
<td>11</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; LFU, lost to follow-up; VIN, vulvar intraepithelial neoplasia.
Our study included only 12 patients and was uncontrolled. However, it was prospective and used strict criteria to evaluate response to treatment. This study provides additional information about the efficacy and tolerance of imiquimod in undifferentiated VIN. Only 1 of 7 patients (patient 6) who responded to treatment, either completely or partially, had multifocal, pigmented, papular lesions, a clinical form of VIN for which spontaneous regression has been reported. Therefore, we favor the hypothesis that our patients' good outcomes were more likely due to the treatment than to spontaneous regression of the lesions.

So far, to our knowledge, 6 studies concerning the treatment of VIN with self-applied 5% imiquimod cream have been published (Table 2). These studies, either case reports or uncontrolled trials, included in total 52 patients. Twenty-two (42%) of them achieved complete remission, 15 (29%) achieved partial remission, and 15 (29%) were deemed treatment failures or were lost to follow-up. Our findings are in agreement with those results, although no definitive conclusion can yet be drawn, because all these studies are uncontrolled and each includes no more than 15 patients. It is worth noting that, as opposed to our study, none of the previously published studies specified whether the VIN treated with imiquimod were differentiated or undifferentiated. Indeed, patients with differentiated VIN could have been included in those studies and that form of VIN could respond to imiquimod in a different way.

The response in the 3 HIV-positive patients (all 3 undergoing HAART and with a CD4 T-lymphocyte count of >350/µL) did not seem different from that obtained in the HIV-negative population, although the number is too small to draw a definitive conclusion.

Table 2. Imiquimod for Treatment of VIN: Review of the Literature

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Type</th>
<th>No. of Patients</th>
<th>Complete</th>
<th>Partial (Regression ≥50% of the Lesion(s))</th>
<th>Failure and LFU</th>
<th>No. of Recurrences After Complete Response</th>
<th>Mean Follow-up After Treatment, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Seters et al, 2002</td>
<td>Prospective, uncontrolled</td>
<td>15</td>
<td>4</td>
<td>9</td>
<td>2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Jayne and Kaufman, 2002</td>
<td>Retrospective</td>
<td>13</td>
<td>8</td>
<td>4*</td>
<td>1</td>
<td>NS</td>
<td>5.5</td>
</tr>
<tr>
<td>Todd et al, 2002</td>
<td>Prospective, uncontrolled</td>
<td>15</td>
<td>3</td>
<td>1</td>
<td>11</td>
<td>3 (at 5 mo)</td>
<td>5</td>
</tr>
<tr>
<td>Petrow et al, 2001</td>
<td>Case report</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1 (at 15 mo)</td>
<td>31</td>
</tr>
<tr>
<td>Diaz-Arrastia et al, 2001</td>
<td>Retrospective</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>None</td>
<td>18</td>
</tr>
<tr>
<td>Davis et al, 2000</td>
<td>Case reports</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>2 (at 12 mo)</td>
<td>12</td>
</tr>
</tbody>
</table>

Abbreviations: LFU, lost to follow-up; NS, not specified; VIN, vulvar intraepithelial neoplasia.

* In this study, partial response was defined as at least 75% regression of the lesions.

In future studies, response to treatment should be assessed according to the vulvar area initially involved. However, it remains difficult to measure the area of multifocal lesions, and a feasible and reproducible method still needs to be validated. In our study, VINs that responded to the treatment were almost equally distributed between monofocal and multifocal lesions and among papular, macular, and verrucous forms. In the absence of a validated clinical classification of VIN, an analysis of the response to imiquimod according to the morphologic features of the lesions would not be reliable.

The VIN recurrence rates following partial vulvectomy or carbon dioxide laser vaporization ranged from 12% to 58%. None of our 3 patients who obtained complete remission experienced a recurrence of the disease (follow-up range, 5-18 months). In the published studies on imiquimod-treated VIN, follow-up for recurrence after complete remission was performed in only 10 of 52 patients (Table 2). Additional studies are needed to determine if, compared with other treatments, imiquimod reduces the recurrence rate of undifferentiated VIN as observed in the treatment of AGWs. Indeed, according to the literature, recurrence rates of AGWs treated with 5% imiquimod vary from 13% to 19%, whereas recurrence rates of those treated with podophyllin vary from 30% to 70% and from 58% to 70% with topical fluorouracil.

Local tolerance was poor in our study, as in the published reports, with burning, itching, and/or ulcers described. Patients frequently either stopped treatment or applied the cream less often. These results are in agreement with those of Todd et al, who reported that 11 of the 13 patients whom they followed up (2 patients were lost to follow-up) developed local adverse effects. In the other published studies, topical intolerance was frequently reported but rarely led to treatment withdrawal. Local intolerance is a well-known adverse effect of treating AGWs with 5% imiquimod cream. In published controlled trials, erosions occurred in 10% to 58% of the patients, and treatment withdrawal because of adverse effects ranged from 1% to 5%. Additional studies should determine whether imiquimod is more irritating in the treatment of VIN than in the treatment of AGWs. Indeed, the tolerance of imiquimod could be related to the type of condition treated. Although there are...
no controlled studies about this subject, to our knowledge, it seems that topical irritation is more frequently observed in imiquimod-treated actinic keratosis (16% to 53% of severe reactions requiring a rest period)22 and basal cell carcinomas (13% of severe local reactions leading to treatment withdrawal)23 than in imiquimod-treated genital warts. Because of the high rate of local irritation in this study, we now start treatment at a lower frequency (once a week) and then adapt the regimen to local tolerance. Another way to improve local tolerance could be to shorten the duration of each application (<6 hours) and reduce the quantity of cream applied.

Flulike symptoms, similar to those reported during interferon therapy, occurred in 2 of our patients and had previously been observed in a phase 1 clinical trial of oral imiquimod in patients with refractory cancer.24 As far as topical treatment is concerned, flulike symptoms did not occur with a significant frequency in the controlled trials concerning AGWs.3 Among the studies concerning VIN treatment with imiquimod, only Todd et al25 mentioned flulike symptoms in 2 of the 13 patients whom they followed up. These symptoms could result from imiquimod-induced cytokine release by responding cells within the lesion25 and/or in the bloodstream. This flulike syndrome did not seem to be associated with the extent of the lesion or the presence of particularly severe ulcerations.

In conclusion, 5% imiquimod cream was completely or more than 75% effective in 7 of 12 patients with undifferentiated VIN. These results, which are in agreement with most of the published data, support the hypothesis that imiquimod could be a therapeutic option for VIN, provided that previous biopsy specimens excluded the presence of SCC. However, additional controlled studies are needed to evaluate the efficacy of this treatment, to identify factors predictive of therapeutic response, and to decide whether imiquimod could be prescribed as conservative first-line treatment for undifferentiated VIN.

Accepted for publication May 17, 2004.

This study was presented in part at the Journées Dermatologiques de Paris: December 6, 2001; Paris, France.

We thank Janet Jacobson, BS, and Luis Perez, PhD, for editing our English; Eric Julian, PhD, for the HPV typing; and Bernard-Jean Paniel, MD, for providing surgical or laser treatment to the patients in whom imiquimod treatment failed.

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