Self-administered Topical 5% Imiquimod Cream for External Anogenital Warts

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Objective: To compare the safety and effectiveness of 5% and 1% imiquimod cream with vehicle cream in the treatment of external anogenital warts.

Design: Randomized, double-blind, placebo-controlled comparison that evaluated patients for total clearance of their warts. Patients who experienced total clearance were evaluated for recurrence in a 12-week follow-up.

Setting: Eleven ambulatory offices, including both private physician offices and referral medical centers.

Patients: Three hundred eleven healthy men and women aged 18 years or older with 2 to 50 external anogenital warts were recruited from the practices of investigators, referring physicians, and advertisements. Eighty-two additional patients were screened but did not qualify. Four patients discontinued use of the medication because of adverse effects.

Interventions: Five percent imiquimod (Aldara) cream, 1% imiquimod cream, or vehicle cream was applied to all external warts overnight 3 times each week for 16 weeks, or until all treated warts disappeared, whichever occurred first.

Main Outcome Measurements: The number of patients experiencing the elimination of all baseline warts and the recurrence rate of these warts. In addition, the reduction in baseline wart area, the duration of therapy required to eliminate warts, and the frequency and severity of adverse reactions were principal measurements.

Results: In the intent-to-treat analysis, 54 (50%) of 109 patients who received 5% imiquimod cream, 21 (21%) of 102 of those who received 1% imiquimod cream, and 11 (11%) of 100 patients treated with vehicle cream experienced eradication of all treated baseline warts. The difference between the effectiveness of 5% imiquimod cream and the vehicle cream was statistically significant (P<.001). Of those patients whose warts cleared during therapy, 13% of patients who received 5% imiquimod experienced a recurrence of at least 1 wart. Recurrences occurred in none of the patients who used 1% imiquimod cream and in 10% of patients who used the vehicle cream. Local erythema was the most common adverse reaction, but the majority of patients in each group experienced no or only mild local inflammatory reactions. There were no differences in incidences of flulike symptoms among treatment groups.

Conclusions: Five percent imiquimod cream is an effective and safe self-administered therapy for external anogenital warts when applied 3 times a week overnight for up to 16 weeks. The recurrence rate is low.

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Although genital warts are common, therapy is generally painful, prolonged, variably effective, and characterized by recurrence. One reason for these therapeutic problems is that most current therapies depend on physical destruction of the tumor rather than direct antiviral activity against the causative agent, human papillomavirus. A treatment for anogenital warts that is specifically antiviral and nondestructive would represent a significant advancement.

Imiquimod is a recently developed imidazoquinolin heterocyclic amine that is an immune response modifier. It has been shown to exhibit antiviral and antitumor properties in animal models, at least partly on the basis of its ability to induce the production of interferon alpha. Interferon alfa is known to be effective in the treatment of anogenital warts, but therapy with this medication is expensive and unwieldy. Interferon alfa is not

The names and affiliations of members of the HPV Study Group are listed in the acknowledgment section at the end of the article.

This article is also available on our Web site: www.ama-assn.org/derm.
PATIENTS AND METHODS

PATIENTS

Healthy men and women aged 18 years or older participated in this trial. Patients had a diagnosis of anogenital warts, with a minimum of 2 and a maximum of 50 external lesions. The total wart area was no less than 10 mm².

Patients were enrolled only when judged to be healthy after a medical history taking, physical examination, and laboratory testing yielded no significant positive or abnormal findings.

Laboratory tests included a complete blood count, a serum screening multiphasic chemistry panel, serum pregnancy test (women), a urinalysis, and a determination of human immunodeficiency virus status. A Papanicolaou smear was performed on all women, and patients with abnormalities underwent colposcopy. Those patients found to have high-grade squamous intraepithelial lesions (greater than moderate dysplasia) were excluded. Patients immunosuppressed by virtue of disease or use of medication were excluded, as were pregnant or lactating women, and women not using contraception. Patients with current chemical or alcohol dependency were not enrolled.

Patients underwent a baseline skin biopsy test that was interpreted as diagnostic or suggestive of anogenital warts and without evidence of dysplasia.

Patients could not have treated their warts within 4 weeks before enrollment, and the skin must have returned to normal following any previous therapy. Patients with skin disease in the area to be treated, including frequently recurrent herpes simplex virus infection, were excluded. Patients having used any local medications for any purpose, including topical corticosteroids, in the target area during the 2 weeks prior to enrollment were excluded.

Patients signed consent forms approved by the respective institutional review boards.

STUDY DESIGN

At the initiation visit, anogenital warts were photographed, measured, and mapped and patients were randomized to use 1 of 3 treatments: 1% imiquimod cream, 5% imiquimod cream, or vehicle cream. Patients were instructed carefully in the use of the test medication, and they were asked to maintain diaries to record dosing and to ensure compliance. They were told first to clean and dry the area. They were then to apply test cream to all external lesions in an amount that could be rubbed in until the cream disappeared. They were instructed to allow the cream to dry before dressing, and to leave the medication on during their normal sleeping time. The test medication was to be washed off with soap and water after an allowable application time of 6 to 10 hours. The medication was to be used 3 times each week until all baseline warts were confirmed to have disappeared or for 6 weeks, whichever occurred first. Medication was to be applied every other day for 3 doses per week with individual applications separated by no less than 36 hours and no more than 96 hours. After the third dose, there was a 2-day pause (60-120 hours) before the next week’s dosing. No other topical preparations of any kind were allowed during the treatment period.

At any time during the treatment phase that warts were no longer visible, use of the test cream was stopped, and the patient was entered into the follow-up phase of the study to investigate recurrence. Patients whose warts did not disappear during the 16-week treatment phase did not enter the follow-up phase. New warts appearing during the treatment period could be treated with the study drug; however, those new warts were tracked separately and were not included in the analysis of baseline warts.

During the treatment phase of the trial, patients were seen weekly for 2 weeks and then biweekly until their warts cleared or for the remainder of the 16-week treatment period. At these visits, patient diaries were checked and patients were questioned for the development of adverse reactions. Warts were measured and photographed, and the area was examined for signs and symptoms of local inflammation.

Patients whose initially identified and treated warts disappeared by 16 weeks were entered, as clearing of the warts occurred, into a 12-week treatment-free follow-up phase. New warts that had appeared during the follow-up phase in these patients could be treated with conventional wart therapy. During this follow-up phase, patients were then seen biweekly to evaluate for recurrence of warts. Similar procedures were performed as were done during the treatment phase. Participation in the study was ended at completion of the 12-week follow-up period or on recurrence of a baseline wart, whichever occurred first.

EFFICACY MEASUREMENTS

Anogenital warts were measured, mapped, and photographed after the biopsy procedure but before institution of therapy, and every 2 weeks during the treatment and follow-up phases. Wart size was expressed as total area in square meters and determined by the product of the 2 longest perpendicular dimensions.

Patients who had lesions remaining after therapy underwent biopsy if there was any suspicion that the remaining lesion(s) may not have represented a wart.

SAFETY MEASUREMENTS

Laboratory testing consisting of a complete blood cell count, serum multiphasic screening chemistry panels, and a urinalysis was performed at the beginning of the study and again after 8 weeks of therapy. These laboratory tests, as well as a second physical examination, were performed at the conclusion of each patient’s participation. A Papanicolaou smear and, if indicated, colposcopy were repeated at the end of treatment if the time elapsed since the baseline testing was longer than 1 month. These were again repeated at the end of participation in the follow-up period if the time elapsed since the most recent Papanicolaou smear was longer than 1 month.

Patients were interviewed at each visit to identify symptoms possibly caused by use of study medication, and the treatment site was examined for local inflammation. Local reactions were graded independently by the patient and the investigator using the following scale: none, mild (visible irritation with minimal or no discomfort that did not disrupt daily activity), moderate (caused considerable discomfort but did not disrupt normal activities), or severe (substantially interfered with the patient’s normal daily activities).
therapy to a maximum of 5 warts concurrently. In addition, adverse effects generally limit therapy to a maximum of 5 warts concurrently. Because interferon is active against these warts and because imiquimod is active when applied topically, imiquimod has been examined as a potential treatment for anogenital warts with encouraging preliminary results."}

**RESULTS**

A total of 311 patients at 11 clinical centers were enrolled in this trial, including 131 women (42%) and 180 men (58%). One hundred nine patients were randomized to receive 5% imiquimod cream, 102 patients to receive 1% imiquimod cream, and 100 patients to receive vehicle cream. Patient characteristics can be seen in **Table 1**. There were no significant differences among the 3 groups for age, sex, race, height, weight, smoking habits, or extent of disease. Although the baseline wart area tended to be smaller for women in each group than for men, there was not a statistically significant difference among treatment groups for either sex (men, P>.50; women, P>.50). Also, the reported duration of the current outbreak of anogenital warts in women in each group was shorter than that of men; the difference in duration of warts among treatment groups for men was statistically significant (P=.01). Median duration of warts in the current outbreak for women was 3.4 months (5% imiquimod group), 4.4 months (1% imiquimod group), and 19 months (vehicle group). The reported median duration of warts for men was 6.7 months (5% imiquimod group), 7.9 months (1% imiquimod group), and 5 months (vehicle group).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>5% Imiquimod Cream (n=109)</th>
<th>1% Imiquimod Cream (n=102)</th>
<th>Vehicle Cream (n=100)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F, No. (%)</td>
<td>46 (42)</td>
<td>45 (44)</td>
<td>40 (40)</td>
<td>&gt;.50*</td>
</tr>
<tr>
<td>M, No. (%)</td>
<td>63 (58)</td>
<td>57 (56)</td>
<td>60 (60)</td>
<td>&gt;.50*</td>
</tr>
<tr>
<td>Mean±SD age, y</td>
<td>32±12</td>
<td>30±10</td>
<td>31±10</td>
<td>&gt;.50†</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>85</td>
<td>81</td>
<td>83</td>
<td>&gt;.50*</td>
</tr>
<tr>
<td>Black</td>
<td>13</td>
<td>17</td>
<td>17</td>
<td>&gt;.50*</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>&gt;.50*</td>
</tr>
<tr>
<td>Using tobacco, %</td>
<td>52</td>
<td>58</td>
<td>48</td>
<td>.37*</td>
</tr>
<tr>
<td>Duration of current warts, mo</td>
<td>4.2 (0.4-375)</td>
<td>6.6 (0-182)</td>
<td>5.8 (0-270)</td>
<td>.23†</td>
</tr>
<tr>
<td></td>
<td>3.4 (0.7-168)</td>
<td>3.1 (0.2-90)</td>
<td>4.4 (0-220)</td>
<td>&gt;.50†</td>
</tr>
<tr>
<td></td>
<td>6.7 (0-375)</td>
<td>25.4 (0-270)</td>
<td>2 (0-10)</td>
<td>&gt;.50†</td>
</tr>
<tr>
<td>Baseline wart area, mm²</td>
<td>69 (8-5525)</td>
<td>74 (10-4271)</td>
<td>77 (7-5000)</td>
<td>&gt;.50†</td>
</tr>
<tr>
<td></td>
<td>58 (15-2294)</td>
<td>58 (10-4271)</td>
<td>71 (7-1468)</td>
<td>&gt;.50†</td>
</tr>
<tr>
<td></td>
<td>92 (8-5525)</td>
<td>75 (10-2164)</td>
<td>87 (10-5000)</td>
<td>&gt;.50†</td>
</tr>
</tbody>
</table>

* Fisher exact test.
† Kruskal-Wallis test.
‡ Pairwise P values are 5% imiquimod cream vs vehicle cream, P=.38; 5% imiquimod cream vs 1% imiquimod cream, P=.006; and 1% imiquimod cream vs vehicle cream, P=.03.

Seventy-seven patients discontinued use of medication during the study, and the discontinuation rate was similar for each group. Nineteen patients (17%) in the 5% imiquimod group stopped use of medication, compared with 31 patients (30%) in the 1% imiquimod group and 27 patients (27%) in the vehicle group. Of the 77 patients who withdrew participation in the study, 4 patients discontinued participation because of adverse reactions and 18 patients for lack of therapeutic effect. These patients were classified as treatment failures. The treatment failures included 6 patients (6%) in the 5% imiquimod group, 8 patients (8%) in the 1% imiquimod group, and 19 patients (8%) in the vehicle group. Fifty-five participants did not complete the study because of noncompliance, personal reasons, or unavailability for follow-up. Because these patients were removed for reasons assumed to be unrelated to adverse reactions or lack of efficacy, they were not included in the treatment failures analysis of clearance rates. In this analysis, 13 patients (12%) in the 5% imiquimod group, 23 patients (23%) in the 1% imiquimod group, and 19 patients (19%) in the vehicle group were excluded. The intent-to-treat analysis included all randomized patients.

A total of 33 (31%) of 106 patients using 5% imiquimod cream developed new warts (not present at baseline) during the study. This rate compares with 44 (42%) of 97 patients using 1% imiquimod cream and 41% of patients using vehicle cream (P=.20).

**EFFICACY**

An intent-to-treat analysis was performed (Table 2). In this analysis, 54 (30%) of 109 patients using 5% imiquimod cream achieved total wart clearance, compared with 21 (21%) of 102 patients using 1% imiquimod cream and 11 (11%) of 100 patients using vehicle cream (P<.001). Thirty-three (72%) of 46 female patients experienced complete clearance, as did 21 (33%) of 63 men.
In the treatment failures analysis, 54 (56%) of 96 patients who received 5% imiquimod cream experienced clearing of all original warts, compared with 21 (27%) of 79 of those using 1% imiquimod cream and 11 (14%) of 81 patients who received vehicle cream (Table 3). The difference between the groups using 5% imiquimod and vehicle cream was statistically significant (P<.001), as was the difference between the groups using 5% and 1% imiquimod cream (P<.001), but there was no significant difference between the groups using 1% imiquimod cream and the vehicle cream. In addition to those patients whose warts were completely eradicated by using the 5% imiquimod cream, many other patients experienced a significant decrease in wart area. A 50% or greater reduction in total wart area occurred in 81% of these patients. Of those patients whose warts disappeared while using 5% imiquimod cream, 44% were clear by 8 weeks of therapy and 69% were clear by 12 weeks.

Seventy-seven percent of women and 40% of men using 5% imiquimod cream experienced complete wart clearance. A higher response in women was present in the groups using 1% imiquimod and vehicle cream as well. Recurrence of at least 1 wart in the treated area occurred in 6 (13%) of 45 patients using 5% imiquimod cream. This rate is conservative since those who discontinued participation were not included in either the numerator or the denominator. A total of 54 patients using 5% imiquimod cream had their warts cleared and 9 discontinued participation during follow-up, leaving 45 assessable patients. Six of these patients had recurrences; thus, the recurrence rate was 13%. Recurrence rates for patients using 1% imiquimod cream and vehicle cream were 0 (0%) of 18 and 1 (10%) of 10, respectively. These were not significantly different, and recurrence rates did not differ by sex.

**SAFETY**

There was no difference in incidences of flulike symptoms among groups by interview, laboratory testing, or physical examination. One patient was removed from the study because of rhabdomyolysis that was later found to be familial, and another patient for symptoms of lightheadedness, insomnia, and fatigue. This patient received a total dose of topical imiquimod far below that known to produce adverse reactions even when given systemically. Local inflammatory reactions were the most common adverse events but these were generally well tolerated (Table 4). There was good correlation between the investigators’ and the patients’ descriptions as to the presence and severity of local inflammation, although patients tended to assess their reactions as less severe. The investigators’ and the patients’ descriptions as to the presence and severity of local inflammation, although patients tended to assess their reactions as less severe. The most common local inflammatory reaction was erythema, occurring, by investigators’ judgment, in 71 (67.0%) of 106 patients treated with 5% imiquimod cream. The erythema was severe at some point in 6 patients (5.7%) and moderate in 36 patients (34.0%). There was
Anogenital warts are benign tumors induced by any of multiple different types of the human papillomavirus. During the last decade, the prevalence has increased dramatically so that now an estimated 2% of sexually active people are reported to have clinically visible anogenital warts, although far more have evidence of the human papillomavirus when evaluated by the polymerase chain reaction technique.\(^8,9\)

Rapidly effective therapies such as cryotherapy, laser vaporization, electrocautery, and excision are painful as well as expensive to varying degrees and although efficient, recurrences are common. Less destructive therapies include the application of podophyllin, and bichloroacetic and trichloroacetic acids. These medications require multiple applications in the office and regularly produce local inflammation that includes erythema, erosion, edema, scabbing, induration, vesicles, or ulceration. Only 2 patients (both using 5% imiquimod cream) were excluded from the study by investigators because of local reactions.

### Table 4. Local Inflammatory Reactions at the Wart Site as Assessed by the Investigator*

<table>
<thead>
<tr>
<th>Reaction</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>57.9</td>
<td>29.8</td>
<td>12.4</td>
<td>0.9</td>
<td>94.8</td>
<td>4.1</td>
<td>1.0</td>
<td>0.0</td>
<td>91.6</td>
<td>6.3</td>
<td>2.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Erosion</td>
<td>75.5</td>
<td>17.9</td>
<td>5.7</td>
<td>0.9</td>
<td>95.9</td>
<td>4.1</td>
<td>0.0</td>
<td>0.0</td>
<td>97.9</td>
<td>2.1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Excoriation or flaking</td>
<td>84.0</td>
<td>13.2</td>
<td>1.9</td>
<td>0.9</td>
<td>96.9</td>
<td>3.1</td>
<td>0.0</td>
<td>0.0</td>
<td>98.9</td>
<td>1.1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Edema</td>
<td>84.9</td>
<td>10.4</td>
<td>4.7</td>
<td>0.0</td>
<td>96.9</td>
<td>1.0</td>
<td>1.0</td>
<td>0.0</td>
<td>97.9</td>
<td>2.1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Scabbing</td>
<td>91.5</td>
<td>6.6</td>
<td>1.9</td>
<td>0.0</td>
<td>95.9</td>
<td>4.1</td>
<td>0.0</td>
<td>0.0</td>
<td>96.8</td>
<td>2.1</td>
<td>1.1</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*All values are percentages. In addition, fewer than 5% of patients in the 5% imiquimod cream, 1% imiquimod cream, or vehicle cream groups experienced ulceration or vesicles.

The introduction of interferon alfa for the treatment of anogenital warts raised hopes for a therapy that would eliminate both the wart tumor and the virus itself by immunological enhancement or a precise antiviral mechanism rather than nonspecific destruction. However, use of this medication requires administration by multiple injections, and, although producing clearing rates of 36% to 62% without destruction of underlying skin, it is also associated with a significant recurrence rate of visible warts.\(^5,6\) In addition, this therapy is expensive, produces systemic adverse effects, and requires multiple office visits.

If interferon alfa could be applied topically, some of the practical obstacles would be eliminated. The interferon molecule, however, is not well absorbed. Imiquimod, developed by 3M Pharmaceuticals, St Paul, Minn, is an immune response modifier. It is an inducer of interferon alfa that is active when applied topically. Interferon alfa subtypes 1, 2, 5, 6, and 8 are produced by human peripheral blood mononuclear cells in vitro in response to imiquimod.\(^11\) In addition, imiquimod induces the production by monocytes and macrophages of other immunologically active cytokines independent of induction by interferon.\(^15\) These cytokines include the following: interleukins 1, 6, and 8; interleukin 1 receptor antagonist; and tumor necrosis factor \(\alpha\).\(^16\) Although the exact mechanism of action of imiquimod is not known, imiquimod apparently exerts its in vivo antiviral, immune-enhancing, and antitumor effects by 1 or a combination of these immune mechanisms, and not by nonspecific tissue destruction.

This study confirms the data from preliminary clinical trials indicating that topical 5% imiquimod cream exerts a beneficial effect on anogenital warts and is well tolerated when applied 3 times a week overnight for up to 16 weeks. The complete eradication of baseline warts in 56% of patients and the dramatic reduction of wart area in even more patients compares well with the effects of more destructive and irritating existing therapies on anogenital warts. Reports include eradication of all treated warts in 32% to 80% of patients receiving podophyllin and 45% to 88% of those using podophyllin,\(^13\) 69% to 79% of those receiving cryosurgery,\(^12,17,18\) and up to 80% of those using bichloroacetic and trichloroacetic acids.\(^12,18\) Reported wart recurrence rates are 30% to 60% following therapy with topical chemotherapies such as podophyllin and bichloroacetic and trichloroacetic acids.\(^13\) Although excision, electrocautery, and laser vaporization can be used to remove warts quickly, these are painful, destructive therapies and recurrences are common (ie, occurring in 9%-72% of warts treated with...
ablative laser therapy). In comparison, imiquimod produces much less local tissue destruction and inflammation and has the great advantage of home use over all treatments except podophylox. Although recurrences occur with imiquimod, these rates are lower than those historically associated with other therapies for genital warts. The extremely low recurrence rates in patients whose warts were eliminated while using 1% imiquimod cream and vehicle cream are not surprising, since these warts were probably eradicated by the patient's own immunological mechanisms. The higher clearing of anogenital warts in women in each group compared with men may be attributable to the shorter duration of the warts.

This study shows that 5% imiquimod cream is effective in the treatment of anogenital warts when applied overnight 3 times weekly for up to 16 weeks, and it is associated with a lower recurrence rate than those found with other existing standard therapies. Use of this medication is safe, producing well-tolerated local inflammatory reactions in up to 70% of patients at some time during therapy. Five percent imiquimod cream represents a significant addition to the available armamentarium for the treatment of anogenital warts.

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REFERENCES