GYNECOLOGY

# The Paget Trial: topical 5% imiquimod cream for noninvasive vulvar Paget disease

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**BACKGROUND:** Vulvar Paget disease is an extremely rare skin disorder, which is most common in postmenopausal women. Most vulvar Paget disease cases are noninvasive; however, it may be invasive or associated with an underlying vulvar or distant adenocarcinoma. The current treatment of choice for noninvasive vulvar Paget disease is wide local excision, which is challenging because of extensive intraepithelial spread and may cause severe morbidity. Recurrence rates are high, ranging from 15% to 70%, which emphasizes the need for new treatment options. Imiquimod, a topical immune response modifier, has been shown to be effective in a few studies and case reports, and is a promising new treatment modality.

**OBJECTIVE:** To prospectively investigate the efficacy, safety, and effect on quality of life of a standardized treatment schedule with 5% imiquimod cream in patients with noninvasive vulvar Paget disease.

**STUDY DESIGN:** The Paget Trial is a multicenter prospective observational clinical study including 7 tertiary referral hospitals in the Netherlands. A total of 24 patients with noninvasive vulvar Paget disease were treated with topical 5% imiquimod cream 3 times a week for 16 weeks. The primary efficacy outcome was the reduction in lesion size at 12 weeks after the end of treatment. Secondary outcomes were safety, clinical response after 1 year, and quality of life. Safety was assessed by evaluation of adverse events and tolerability of treatment. Quality of life was investigated with 3 questionnaires taken before, during, and after treatment.

**RESULTS:** Data were available for 23 patients, 82.6% of whom responded to therapy. A complete response was reported in 12 patients (52.2%), and 7 patients (30.4%) had a partial response. A histologic complete response was observed in 10 of the 12 patients with a complete response. Patients experienced side effects such as fatigue (66.7%—70.9%) and headaches (16.7%—45.8%), and almost 80% needed painkillers during treatment. Eight patients (34.8%) adjusted the treatment protocol to 2 applications a week, and 3 patients (13.0%) stopped treatment because of side effects after 4 to 11 weeks. Treatment improved quality of life, whereas a slight, temporary negative impact was observed during treatment. Two patients with a complete response developed a recurrence within 1 year after treatment. Follow-up showed 6 patients with a noninvasive recurrence after a median of 31 months (14—46 months) after the end of treatment.

**CONCLUSION:** Topical 5% imiquimod cream can be an effective and safe treatment alternative for noninvasive vulvar Paget disease, particularly when compared with treatment with surgical excision.

**Key words:** clinical trial, imiquimod, quality of life, safety, vulvar Paget's disease

## Introduction

Vulvar Paget disease (VPD) is an extremely rare skin disorder, which is most common in postmenopausal women. It is the most common manifestation of extramammary Paget disease (EMPD). The incidence rate of EMPD is 0.11 per 100,000 person-years, based on an epidemiologic study with data from the Netherlands Cancer Registry.[1] Most VPD cases are noninvasive; however, VPD may be invasive or associated with an underlying adenocarcinoma or malignancies of the gastrointestinal or urologic tract.[2] In cases of invasive VPD, surgical excision is the treatment of choice.

Noninvasive VPD causes a skin lesion that can be described as a scaling, macerated erythematous plaque with typical cake-icing desquamation, which sometimes shows ulceration. Lesions can vary in size and may extend from the mons pubis to the buttock. They may cause pain or an itching or burning sensation, resembling eczematous skin lesions, which often results in delayed diagnosis of noninvasive VPD.[3] Histology confirms the diagnosis; the presence of so-called Paget cells in the basal layers of the epithelium is pathognomonic for the disease.

Historically, the treatment of choice for noninvasive VPD has been wide local excision with margins of 1 to 2 cm. Clear surgical margins can be difficult to achieve because of the wide histologic spread of Paget cells into microscopic lesions.[4,5] Moreover, the recurrence rates of noninvasive VPD are high at 15% to 70%, and are independent of margin status.[3,6] Margin-directed surgeries, such as Moh's surgery, have excellent negative margin rates and low recurrence rates.[7,8] However, the excision size may therefore be much larger.

Extensive vulvar surgery can cause permanent mutilation and functional impairment.[9—13] To address this problem, alternative treatment options such as photodynamic therapy, radiotherapy, chemotherapy, and laser treatment have been used in patients with noninvasive VPD, with varying but limited success rates.[14—21]

Topical 5% imiquimod cream is an immune response modifier. It binds to

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## AJOG at a Glance

### Why was this study conducted?

Topical 5% imiquimod cream is a promising treatment modality for noninvasive vulvar Paget disease, but limited data are available. Although this study had a small sample size, it is the largest prospective clinical study to date, investigating efficacy, safety, and quality of life in patients with noninvasive vulvar Paget disease.

### Key findings

The response rate was 82.6% in 23 patients, and a complete response was reported in 12 patients (52.2%). Mild side effects such as fatigue and the need for painkillers were reported. Quality of life improved after treatment. Two patients developed a recurrence within 1 year after treatment, and long-term follow-up showed 6 patients with a noninvasive recurrence after a median of 31 months (14−46 months).

### What does this add to what is known?

This was a prospective study reporting the efficacy and safety of topical 5% imiquimod using a standardized treatment schedule, with prospective data on quality of life. In addition, 2-year follow-up data were reported.

toll-like receptor 7, inducing an innate and cell-mediated immune response.[22] It has antiviral and antitumor properties and is registered for the treatment of condylomata acuminata, actinic keratosis, and superficial basal cell carcinomas. Imiquimod has also been shown to be effective for the treatment of human papilloma virus-induced vulvar high-grade squamous intraepithelial lesions (HSIL; previously usual vulvar intraepithelial neoplasia).[23,24] Thus far, the mechanism of action of imiquimod and local immunity in noninvasive VPD have not been fully understood.

More recently, a number of case reports, case series, and 2 observational trials reported on the use of topical 5% imiquimod cream for noninvasive VPD and showed that it was effective in some of the treated patients.[25,26] A systematic review also concluded that it is an effective treatment option for noninvasive VPD.[27] The review included studies with limited numbers of patients, various treatment schedules, and short follow-up periods. Therefore, it is difficult to draw firm conclusions about the use of imiquimod in noninvasive VPD.

This study aimed to assess the clinical efficacy of topical 5% imiquimod cream in patients with noninvasive VPD using a standardized treatment protocol and follow-up schedule. In addition, safety during treatment and quality of life were investigated.

## Materials and Methods

The detailed study protocol of this trial has been previously published.[28] Briefly, the Paget Trial was a multicenter, prospective, open-label observational cohort study in patients with histologically proven noninvasive VPD. The trial was performed in 7 tertiary referral hospitals with a vulvar clinic in the Netherlands and started in May 2015.

All consecutive patients with noninvasive cutaneous VPD were asked to participate in this study. Inclusion criteria were: histologically proven noninvasive VPD (primary or recurring after earlier surgery or imiquimod treatment >6 months ago), age ≥18 years, and being willing and able to comply with the protocol and provide informed consent in accordance with institutional and regulatory guidelines. Main exclusion criteria were: invasive VPD, underlying adenocarcinoma, and treatment of the vulva with topical 5% imiquimod cream during the previous 6 months. Invasive disease was ruled out by vulvar mapping (multiple biopsy samples) before enrolment in the study. All histologic samples were assessed by expert (gyneco)pathologists.

All patients were instructed on how to apply the imiquimod cream by their clinician, according to the leaflet provided by the manufacturer, and using a mirror.

On the basis of the estimated incidence of VPD in the Netherlands, viability was set at 20 inclusions. When 20 patients were treated with topical 5% imiquimod cream for at least 8 weeks, recruitment stopped.

All patients were treated with topical 5% imiquimod cream 3 times a week for 16 weeks. The healthy skin around the visible lesion could be protected with an indifferent ointment. Patients were allowed to use topical 3% lidocaine in Vaseline ointment when they experienced pain at the application site. There had to be a 1-hour interval between the applications of different topical agents. Patients were allowed to use paracetamol for pain relief. In case of severe pain, patients were allowed to reduce the frequency of imiquimod ointment application to twice a week or to stop the treatment for 1 week. Patients were allowed to stop or delay treatment for a maximum of 3 weeks within the assigned treatment period. An overview of the study visits is reported in the published study protocol.[28] Briefly: after inclusion, patients visited the clinic after 4, 12, 16, 28, 40, 52, and 68 weeks, and had a phone consultation 10 weeks after inclusion. Follow-up was completed on January 1, 2021.

### Primary outcome

The main study outcome was clinical response determined by the reduction in lesion size 12 weeks after the end of treatment. All measurements during the study were conducted by the same experienced treating clinician (gynecologic oncologist or dermatologist). Photographs for documentation were taken with a ruler alongside the lesions. On the basis of the van Seters et al[23] study on imiquimod for HSIL of the vulva, outcomes were grouped into the following categories according to lesion size at the start of treatment compared

with lesion size 12 weeks after the end of treatment:

- Complete response (CR): defined as disappearance of the lesion;
- Partial response (PR): defined as decrease by ≥50% of total lesion size;
- No response: defined as <50% decrease of total lesion size;
- Progressive disease: defined as ≥25% increase of total lesion size or progression into invasive disease and/or adenocarcinoma.

Biopsy samples were taken before and after treatment for histologic assessment by expert (gyneco)pathologists.

### Secondary outcomes

The response rates at 12 months after the end of treatment and on January 1, 2021 were presented in a descriptive manner. In addition, safety was analyzed in a descriptive manner and defined by any adverse events recorded during consultations or in the patient diary. During consultations, pain was measured using the visual analog scale (VAS) score. Pain, burning, and itching were recorded on a 4-point Likert scale. Quality of life was assessed by calculators provided by developers of 3 validated questionnaires: (1) the Crosswalk Index Value Calculator for the EQ-5D questionnaire, investigating general health[29]; (2) the Dermatology Life Quality Index (DLQI) results according to the instruction manual, investigating the impact of skin disease on the quality of life[30]; and (3) the Female Sexual Distress Scale (FSDS), investigating the effect of disease on sexual health in a descriptive manner.

This study was conducted according to the principles of the Declaration of Helsinki (2008) and the Medical Research Involving Human Subjects Act (Dutch: WMO). The protocol has been ethically approved by the Medical-Ethical Committee of Arnhem-Nijmegen for implementation in all 7 centers (NL51648.091.14). Before enrolment in the study, written informed consent was obtained from all patients.

### Statistics

An intention-to-treat analysis was performed, which included all patients that started treatment with topical 5% imiquimod cream. Per-protocol analysis would include patients that completed at least 8-week treatment with topical 5% imiquimod cream; all patients included in the trial were treated for over 8 weeks. Two-tailed $P$ values <.05 were considered statistically significant. The relation between treatment duration and dose vs response has been explored.

The sample size was set according to viability of inclusion based on the estimated incidence of VPD in the Netherlands. Briefly, assuming a CR rate of 80%, a cohort size of 20 patients is sufficient to estimate the CR rate with a standard error of 9%. At the time of establishing the protocol (2014), little data on topical 5% imiquimod for VPD were published—solely case reports and 1 observational trial in which the response rate was 90%.[26]

## Results

### Patient characteristics

A total of 24 patients were included between May 2015 and June 2017, whose characteristics are summarized in Table 1.

The median age was 67 (42−84) years. The median duration of symptoms experienced before VPD diagnosis was 24 (0−216) months. Symptoms were itching (20/24 patients, 83.3%), pain (11/24 patients, 45.8%), and burning sensations (17/24 patients, 70.8%). Seven patients (29.2%) experienced pain during urination. Of the 13 sexually active patients, 5 (38.5%) experienced pain during intercourse. Examination of the lesion showed erythema in all patients, scaling in 15 patients (62.5%), and ulceration in 6 patients (25%). The median size of the lesion before treatment was 16 $cm^2$ (3−130 $cm^2$).

There were 4 patients (12.5%) with a history of noninvasive VPD before enrolling in the trial. Two of these patients had 1 previous episode of VPD and were treated surgically. One patient had a partial vulvectomy 7 years earlier, and a recurrence after 2 years for which she underwent a vulvectomy. One patient had surgery for noninvasive VPD 18 years earlier, a recurrence 8 years later, which was excised, and a recurrence 2 years later for which she used topical 5% imiquimod cream.

### Primary outcome

#### Treatment efficacy

Data on the clinical response were available for 23 patients (Table 2). One patient was lost to follow-up immediately after inclusion, and data on treatment were therefore unavailable. Twelve weeks after the end of treatment, 12 patients (52.2%) had a CR, 7 (30.4%) a PR, and 4 (17.4%) no response. Of the 4 patients with a recurrent VPD lesion, 1 (25%) had a CR, 2 (50%) a PR, and 1 (25%) no response. Figure 1 shows pictures of 1 patient before and after treatment, showing a CR. Data on the lesion size after treatment were reported for 17 patients. The median lesion size was significantly reduced from 16 $cm^2$ before treatment to 1.0 $cm^2$ after treatment (0−130 $cm^2$; $t$-test, $P$=.001). Five of those 17 patients (29.4%) were reported to have a CR. Eight patients of those 17 (47.0%) had a PR, of whom 3 had a decrease of more than 95% in lesion size. Two patients (11.8%) had a decrease in lesion size of <50%, and 2 other patients (11.8%) had no response at all.

#### Follow-up

Data on follow-up of up to 1 year after the end of treatment were available for 17 patients; 6 patients were lost to follow-up or no longer attended consultations according to protocol. Of the 12 patients with a CR, 1 patient underwent surgery within 12 months because of increasing vulvar pain. Two patients had a visible lesion of 1 $cm^2$ but no symptoms 12 months after treatment (Table 2).

#### Long-term follow-up

Long-term follow-up was available for 20 patients. Three patients had persistent lesions after completing this trial, and 2 of them underwent additional surgery with complete removal of residual disease. Six patients with an initial CR and no recurrence within the duration of the

**TABLE 1**
**Baseline clinical characteristics of patients at inclusion**

| Patient characteristics | N=24 |
|---|---|
| Age, median | 67 (42–84) |
| Race: | |
| • White | 22 (91.8) |
| • Hispanic | 1 (4.2) |
| • Asian | 1 (4.2) |
| History of: | |
| • Breast cancer | 1 (4.2) |
| • Intestinal cancer | 0 |
| • Urologic cancer | 0 |
| Symptoms: | |
| • Itch | |
| ○ None | 4 (16.7) |
| ○ Mild | 6 (25.0) |
| ○ Moderate | 10 (41.7) |
| ○ Severe | 4 (16.7) |
| • Pain: | |
| ○ None | 13 (54.2) |
| ○ Mild | 4 (16.7) |
| ○ Moderate | 4 (16.7) |
| ○ Severe | 3 (12.5) |
| • Burning: | |
| ○ None | 7 (29.2) |
| ○ Mild | 8 (33.3) |
| ○ Moderate | 6 (25) |
| ○ Severe | 3 (12.5) |
| • Erythema: | |
| ○ None | 0 |
| ○ Mild | 7 (29.2) |
| ○ Moderate | 16 (66.7) |
| ○ Severe | 1 (4.2) |
| • Scaling: | |
| ○ None | 9 (37.5) |
| ○ Mild | 7 (29.2) |
| ○ Moderate | 7 (29.2) |
| ○ Severe | 1 (4.2) |
| • Ulceration: | |
| ○ None | 18 (75) |
| ○ Mild | 2 (8.3) |
| ○ Moderate | 4 (16.7) |
| ○ Severe | 0 |

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trial developed a recurrence after a median of 31 months (14–46 months) (Figure 2). Three of these patients underwent successful retreatment with topical 5% imiquimod, whereas the other 3 underwent additional complete surgery.

## Secondary outcomes

### Safety of treatment

In addition to local treatment effects causing pain, discharge, and/or ulceration, most common reported side effects of treatment were fatigue, headache, and nausea (Table 3).

Data on side effects were available for 23 patients; 1 patient was lost to follow-up. Of these patients, 19 (79.2%) used painkillers because of local pain during treatment; 10 patients (41.7%) used both paracetamol and lidocaine ointment or cream, 7 (29.2%) used paracetamol only, and 2 (8.3%) used lidocaine ointment only.

Pain was monitored using the VAS score. We found a significant difference between the mean VAS scores before and after treatment (at week 28, 3 months after finishing treatment): 3.70 vs 0.85 (mixed models, $P$=.002).

Eight patients (34.8%) adjusted the schedule to 2 applications a week, and 3 of these patients stopped treatment for 1 week. Of the 15 patients who completed the treatment according to protocol, 8 (34.8%) had a CR and 4 (17.4%) a PR. Of the 8 patients who adjusted the treatment schedule, 4 (17.4%) had a CR and 3 (13.0%) a PR. This difference was not statistically significant (chi-square test, 2-sided $P$=.827).

Three patients stopped treatment prematurely because of side effects and retracted from participation in this trial (2 patients after 4 weeks and 1 patient after 10 weeks), with the main reason being severe apathy preventing normal daily activities. All 3 had a CR.

### Quality of life

Before treatment, over 80% of the patients reported health problems, whereas 90% reported health issues during treatment, and 65% after treatment. Reported EQ-5D-5L index values showed no statistically significant effect

TABLE 2
**Response to treatment**

| Patient | Clinical response at end of treatment, week 28 | Histologic response at end of treatment, week 28 | Lesion size before treatment, week 0 ($cm^2$) | Lesion size after treatment, week 28 ($cm^2$) | Lesion size after treatment, week 68 ($cm^2$) | Additional treatment |
|---|---|---|---|---|---|---|
| 1 | CR | Negative | 13.5 | 0 | 0 | — |
| 2 | CR | Negative | 12 | 0 | 0 | — |
| 3 | CR | Positive | 18 | 0 | 1 | — |
| 4 | CR | Negative | 12 | 0 | 0 | — |
| 5 | CR | Negative | 3 | 0 | NA | — |
| 6 | CR | Negative | NA | 0 | 1 | — |
| 7 | CR | Negative | 30.5 | 0 | 0 | — |
| 8 | CR | Negative | 9 | 0 | NA | — |
| 9 | CR | NA | NA | 0 | NA | — |
| 10 | CR | Negative | 9 | 0 | NA | — |
| 11 | CR | Positive | 6.5 | 0 | 0 | Surgery 6 months after IMQ because of pain |
| 12 | CR | Negative | 9 | 0 | 0 | |
| 13 | PR | Positive | 46 | 0.3 | 9 | — |
| 14 | PR | Positive | 30 | 1 | 0 | Surgery |
| 15 | PR | Positive | 48 | 15 | 1 | Imiquimod |
| 16 | PR | Positive | 3 | 1 | 0 | Surgery |
| 17 | PR | Positive | 9 | 4 | 0 | Surgery |
| 18 | PR | Positive | 24 | 15 | 24 | — |
| 19 | PR | NA | 20 | NA | NA | — |
| 20 | NR | Positive | 4 | 1.4 | NA | Surgery |
| 21 | NR | Positive | 36 | 36 | 36 | — |
| 22 | NR | Positive | 130 | 130 | 130 | Surgery |
| 23 | NR | Positive | 21 | NA | 4 | Imiquimod |

Histologic response was positive or negative for Paget cells in biopsy.

*CR*, complete response; *IMQ*, imiquimod; *NA*, not available; *NR*, no response; *PR*, partial response.

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when we compared the values during and after treatment with the values before treatment.

Analysis of the DLQI showed that 11 patients reported no or small effect of VPD on their life before treatment. The number of patients reporting a very large or extremely large effect increased from 4 before treatment to 6 during treatment.

There was a reduction in the number of patients that experienced a moderate to extremely large effect after treatment compared with before treatment (chi-square, $P$=.018). Nine of the 14 patients (64.3%) who reported no to small effect had a CR after treatment.

Treatment with imiquimod was not associated with sexual health, as measured by the FSDS questionnaire. After treatment, none of the patients with no response or a PR to treatment reported that the disease had no effect on their sexual health. However, the effect was equal in patients with a CR to treatment: 2 reported no effect, 2 a small effect, and 3 a large effect.

## Discussion

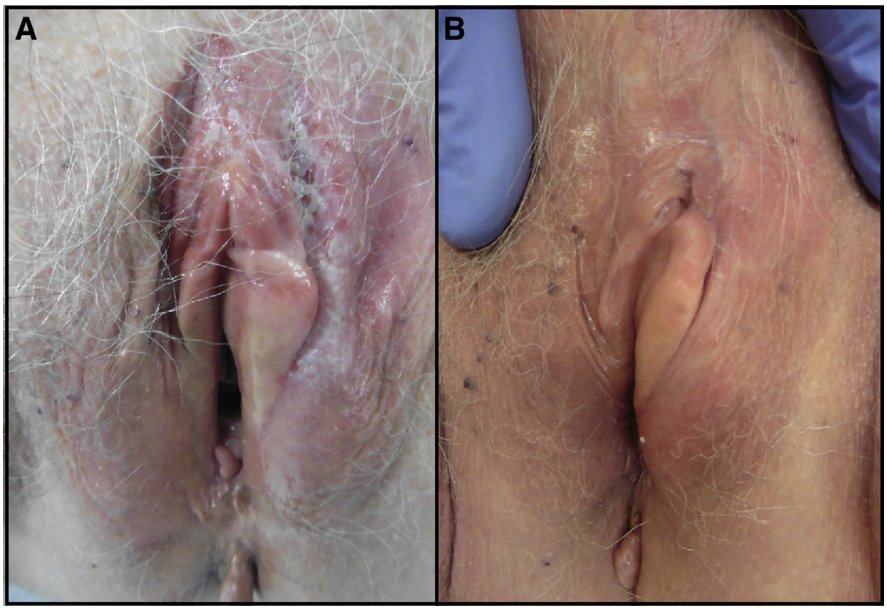
### Principal findings

This clinical trial showed a clinical response of over 80% in 3 months, after 16-week treatment with 5% imiquimod cream in patients with noninvasive VPD. Treatment with topical 5% imiquimod cream seems to be a reasonable alternative to surgery, and it is safe and improves quality of life.

### Results

The use of 5% imiquimod cream seems to be effective and safe. Many patients

FIGURE 1
**Complete response**




**A,** Taken before treatment, showing a lesion typical for VPD with an erythematosquamous lesion in the interlabial sulcus. **B,** Taken 12 weeks after 16 weeks of treatment with topical 5% imiquimod cream.

*VPD*, vulvar Paget disease.

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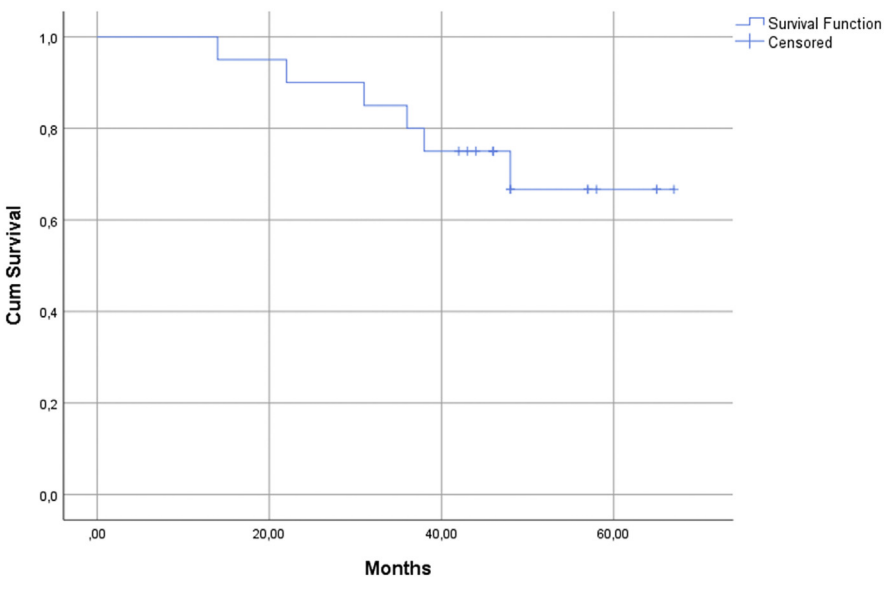
reported limited side effects. Three patients stopped treatment early because of many side effects, but all had a CR. We did not observe a difference in pain experienced before and during treatment. After treatment, most patients experienced no or little effect of their skin disorder on their lives. It is reported that vulvar surgery may contribute to decreased quality of life and sexual functioning compared with healthy patients.[31–34] Given that VPD has high recurrence rates, we assume that (repeated) surgical treatment may have significant psychosexual effects on the patients. Topical treatment with 5% imiquimod cream does not induce scarring nor alter the anatomy of the vulva. Our study confirms that the presence of vulvar disease, regardless of treatment benefits, affects quality of life and causes sexual distress.

To date, about 25 retrospective case series have been published on this topic, with high success rates. The effectiveness of topical 5% imiquimod cream for VPD in these retrospective cases might have been overrated because of publication bias. Moreover, most of the retrospective series and prospective series have used different treatment schedules.[26] Our aim was to investigate clinical efficacy with a standardized treatment schedule. We found that 82.5% of patients responded to treatment. In most case studies, treatment was continued until the patient exhibited a CR. A pilot study by Cowan et al investigated the clinical response after 12 weeks of treatment in 8 patients with noninvasive VPD, and reported a CR in 6 patients (75%).[25]

FIGURE 2
**Recurrence rate after topical treatment with 5% imiquimod cream**

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## Clinical implications

Topical 5% imiquimod cream can be considered as a treatment alternative to surgery for cutaneous noninvasive VPD. Clinicians should be aware of the sexual distress that vulvar disease may cause, and this topic should always be addressed during consultations.

## Research implications

Topical 5% imiquimod cream is registered by the European Medicines Agency with a maximum treatment duration of 16 weeks. The safety of longer treatment schedules with imiquimod is not clear yet and should be investigated further. If safety of longer treatment periods is guaranteed, the ideal treatment schedule could be until the patient exhibits a CR in cases in which the lesion responds to treatment. In addition, the hypothesis of

the mechanism of action of topical 5% imiquimod is that the immune system attacks the intraepidermal spread of Paget cells, which is not limited to the visible skin lesion. This leads to the further hypothesis that topical 5% imiquimod has lower recurrence rates than other treatment modalities. Moreover, further studies should investigate the long-term response and the reason behind the differences in treatment effect, which might be because of the tumor microenvironment of VPD.

## Strengths and limitations

The main strength of our study is that we treated the largest cohort of patients with noninvasive VPD so far in a prospective manner, with a standardized treatment schedule. We obtained vulvar biopsies before, during, and after treatment. Presently, we still cannot determine with certainty the mechanism of action of topical 5% imiquimod cream in VPD. We hypothesize that the effect of treatment can be ascribed to the local immune microenvironment of VPD. It is likely that imiquimod's immune-modulating effect induces a local immune response resulting in clearance of the Paget cells. Recently, we have shown that the local microenvironment in VPD varies between patients before and after imiquimod treatment.[35] We will analyze the tissue samples taken before, during, and after treatment in a separate analysis.

Given that VPD is extremely rare, we chose to perform an observational study. Although this is the largest trial treating VPD with topical 5% imiquimod, not all patients may have been counseled for participation because they had to be referred to 1 of the participating hospitals. Because of the small sample size, each hospital had a small number of inclusions. This confirms the need for centralized centers with experienced and specialized clinicians for rare diseases, as currently established in the Netherlands.

A limitation of this study is that data collection was done by multiple clinicians, and therefore might be subject to multiple interpretations. Our primary outcome was clinical efficacy, defined by the decrease in lesion size. We noticed that the effect of treatment reported by the clinician sometimes differed from the more objective measured decrease in lesion size. We presented both data because some patients still responded to therapy (a lesion was still present at the time of data collection that might have resolved completely if treatment was extended). In addition, there might have been measurement errors because of the differences between the percentages of lesion decrease and clinical observations.

Another limitation is that our main outcome was response at 12 weeks after the end of treatment. Therefore, we observed promising response rates shortly after treatment, but did not focus on rapid recurrences within 12 months after treatment.

**TABLE 3**
**Reported local and general side effects during treatment with topical 5% imiquimod cream**

| Side effect | Week 4 n, (%) N=24 | Week 10 n, (%) N=21 | Week 16 n, (%) N= 1 |
|---|---|---|---|
| Local | | | |
| Pain | | | |
| • Mild | 3 (12.5) | 3 (14.3) | 5 (23.8) |
| • Moderate | 8 (33.3) | 5 (23.8) | 2 (9.5) |
| • Severe | 4 (16.7) | 7 (33.3) | 5 (23.8) |
| Burning: | | | |
| • Mild | 3 (12.5) | 2 (9.5) | 5 (23.8) |
| • Moderate | 6 (25.0) | 3 (13.3) | 1 (4.8) |
| • Severe | 9 (37.5) | 7 (33.3) | 8 (38.1) |
| Ulceration: | | | |
| • Mild | 7 (29.2) | NA | 2 (9.5) |
| • Moderate | 5 (20.8) | NA | 0 |
| • Severe | 0 | NA | 0 |
| Systemic | | | |
| • Fatigue: | 17 (70.9) | 16 (66.7) | 16 (66.7) |
| • Headache: | 6 (16.7) | 9 (45.8) | 9 (45.8) |
| • Nausea: | 7 (29.2) | 8 (33.3) | 6 (25.0) |
| • Other: | Dizziness (1), no appetite (1), apathy (1), sore muscles (2) | Diarrhea (1), apathy (1), dizziness (2), no appetite (1), malaise (1) | Malaise (1), diarrhea (1) |

*NA*, not applicable.
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## Conclusions

Topical 5% imiquimod cream seems to be a viable treatment alternative for noninvasive VPD, with response rates of >80%. Treatment with topical 5% imiquimod seems safe, with most common side effects being temporary local pain and fatigue. Vulvar disease affects quality of life, but treatment with topical 5% imiquimod cream seemed to improve patients' own appreciation of it. We suggest topical 5% imiquimod cream as a treatment option for noninvasive VPD. ■

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Data sharing:

All of the individual participant data collected during the trial after deidentification, the study protocol, and informed consent form will be available immediately after publication and ending 36 months after publication for researchers who provide a methodologically sound proposal to achieve aims in the approved proposal. Proposals should be directed at Michelle.vanderLinden@radboudumc.nl.

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