Treatment of Cervical Intraepithelial Neoplasia With Topical Imiquimod

A Randomized Controlled Trial

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OBJECTIVE: Alternatives to surgical therapy are needed for the treatment of high-grade cervical intraepithelial neoplasia (CIN 2–3). We aimed to estimate the efficacy of a treatment with imiquimod, a topical immune-response modulator, in patients with CIN 2–3.

MATERIALS AND METHODS: Fifty-nine patients with untreated CIN 2–3 were randomly allocated to a 16-week treatment with self-applied vaginal suppositories containing either imiquimod or placebo. The main outcome was efficacy, defined as histologic regression to CIN 1 or less after treatment. Secondary outcomes were complete histologic remission, human papillomavirus (HPV) clearance, and tolerability. Assuming a two-sided 5% significance level and a power of 80%, a sample size of 24 patients per group was calculated to detect a 35% absolute increase in CIN 2–3 regression.

RESULTS: Histologic regression was observed in 73% of patients in the imiquimod group compared with 39% in the placebo group (P=.009). Complete histologic remission was higher in the imiquimod group (47%) compared with the placebo group (14%) (P=.008). At baseline, all patients tested positive for high-risk HPV. Human papillomavirus clearance rates were increased in the imiquimod group (60%) compared with the placebo group (14%) (P<.001). In patients with HPV-16 infection, complete remission rates were 47% in the imiquimod group compared with 0% in the placebo group (P=.003). Microinvasive cancer was observed in three of 59 (5% [1–14%]) patients, all within the placebo group. Topical imiquimod treatment was well tolerated, and no high-grade side effects were observed.

CONCLUSION: Topical imiquimod is an efficacious and feasible treatment for patients with CIN 2–3.

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Cervical intraepithelial neoplasia (CIN) is a common disease with the highest prevalence in women of reproductive age.[1] High-grade lesions (CIN 2–3) represent a precancerous condition, which can progress to cervical cancer, the second most common cancer among women worldwide.[2,3] Persistent high-risk human papillomavirus (HPV) infection is the most important risk factor for the development of CIN and the subsequent progression to cervical cancer.[4]

Cervical intraepithelial neoplasia 2–3 is usually treated by an excisional or, in selected cases, a destructive procedure.[5] In most countries, the excisional procedure, ie, conization, is the preferred treatment. Conization is associated with a low rate of short-term complications.[5,6] However, conization is associated with clinically relevant long-term sequelae such as preterm birth in subsequent pregnancies.[7,8] Because conization is often performed in reproductive-aged women, it may effect future fertility and pregnancy outcome. This risk for subsequent pregnancies is of special interest in young women with CIN 2–3, who still want to conceive.[5,9,10] Therefore, an effective conservative treatment of CIN is needed. Nonetheless, no medical therapy has been implemented into clinical practice so far.[11]

Imiquimod represents one of the most promising agents in the conservative treatment of HPV-related conditions.[12] Imiquimod, a topical immune response modulator, is a Toll-like 7 receptor agonist, which exerts its effect through the upregulation of interferon-α and the activation of dendritic cells.[13] Recently, a study reported on the efficacy of topical imiquimod therapy against HPV-related vulvar intraepithelial neoplasia.[12]

The aim of the present trial was to estimate the therapeutic efficacy of vaginal, self-applied imiquimod in women with high-risk HPV-positive CIN 2–3.

MATERIALS AND METHODS

Eligible women were aged 18 years or older with untreated, histologically proven, high-risk HPV-positive, and newly diagnosed CIN 2–3, satisfactory colposcopy (ie, fully visible transformation zone and fully visible lesion), and safe contraception, who were seen at the outpatient genital dysplasia clinic of the Department of General Gynaecology and Gynaecological Oncology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, between July 7, 2009, and August 6, 2010. Exclusion criteria were presence of cancer, pregnancy or lactation, immune deficiency, known hepatitis or human immunodeficiency virus infection, known hypersensitivity to imiquimod, or significant language barrier. All eligible patients were informed that conization was the current standard treatment for persistent CIN 2–3 and were asked to participate in the present trial. Patients were asked to provide written informed consent before study inclusion. A Consolidated Standards for the Reporting of Trials flow diagram is provided (Fig. 1).

A randomized, double-blind, placebo-controlled phase II trial was conducted (ClinicalTrials.gov Identifier: NCT00941252). The Ethics Committee of the Medical University of Vienna (EK No. 700/2008) and the Austrian Agency for Health and Food Safety

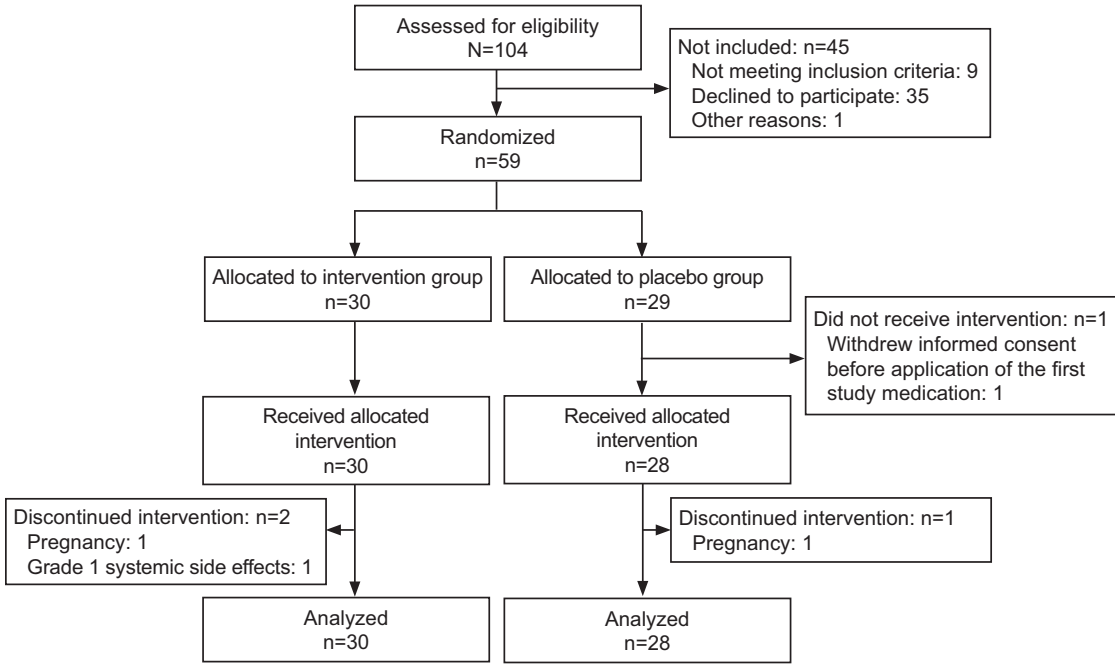

Fig. 1. Flow diagram showing the progress through the trial.
Grimm. Topical Imiquimod Compared With Placebo for CIN 2–3. Obstet Gynecol 2012.

(EudraCT-No. 2008-007763-16) approved the study before initiation.

Patients, who were eligible for the study and agreed to participate, were randomly assigned to one of two parallel groups receiving either treatment with self-applied vaginal suppositories containing 6.25 mg imiquimod or placebo for 16 weeks. At the inclusion visit, a gynecologic examination including a urine pregnancy test, a high-risk HPV test, a type-specific HPV test, and a colposcopically guided biopsy were performed. Participants were instructed about the correct method of self-application and storage of vaginal suppositories, possible side effects, and all additional treatment-related issues and were handed out a diary to record vaginal suppository application and side effects. At all study visits, a urine pregnancy test was performed, the correct use of the study medication was monitored, and patients were asked to report local and systemic side effects using a standardized case report form. After patients were included in the study, visits were scheduled every 2 weeks for the first 4 weeks and from then on every 4 weeks until week 20. After 8 weeks, a colposcopy with a colposcopically guided biopsy of the initially noted lesion was performed to rule out presence of invasive disease. In case of the presence of any new, colposcopically suspicious, previously not described lesions, additional biopsies were performed. At the final visit, ie, week 20, outcome measures were assessed with two HPV tests and colposcopically guided biopsies of each quadrant of the cervix in addition to biopsies of any suspicious lesion. Remaining study medication and patients' diaries were collected. Patients with a persistence of CIN 2–3 diagnosed at the final visit were treated with conization. Patients with no evidence of disease or CIN 1 were followed up in our outpatient clinic.

All study investigators are experienced in colposcopy and colposcopically guided biopsy. They are either gynecologic oncologists or registrars with a national diploma for colposcopy. All of the investigators work regularly in our outpatient genital dysplasia clinic and perform at least 100 colposcopies per year. All histologic and cytologic specimens were analyzed by two board-certified pathologists specialized in gynecologic pathology. The results were blinded between the two pathologists. In case of discordance, pathologists were unblinded to each other's results and had to agree on a common result. Patients, physicians, and outcome assessors were blinded to the patients' study group allocation.

All vaginal suppositories consisted of 2 g of Adeps solidus. Vaginal suppositories of the imiquimod group contained in addition to 6.25 mg imiquimod (1.0 vaginal suppository). The treatment regime was as follows: in treatment weeks 1 and 2, patients applied one vaginal suppository per week; in treatment weeks 3 and 4, patients applied two vaginal suppositories per week; and from then on until week 16, patients applied three vaginal suppositories per week. Vaginal suppositories were self-applied by the patients in the evening right after going to bed. Patients were advised not to have sexual intercourse during the nights in which they applied vaginal suppositories and to perform a vaginal douche in the morning. Patients were instructed to suspend the application of vaginal suppositories during the first 3 days of their menses. Patients were advised to store the study medication at room temperature. In case of persistent side effects in patients of the imiquimod group, the dose of the study medication was modified and participants received vaginal suppositories containing only 50% of the original imiquimod dose (vaginal suppositories containing 3.125 mg imiquimod, referred to as 0.5 VS). To ensure blinding, patients of the placebo group with persistent side effects also received vaginal suppositories labeled 0.5 VS containing placebo. A medication score was calculated to evaluate the actual dosage of imiquimod received: 1.0 VS accounted for 1 point and 0.5 VS for 0.5 points, resulting in a maximum possible medication score of 42.

The main outcome was treatment efficacy, defined as histologic regression to CIN 1 or less 4 weeks after the end of treatment, ie, week 20. Secondary outcomes were complete histologic remission, HPV clearance, and treatment tolerability.

Side effects and adverse events were documented according to Common Terminology Criteria for Adverse Events guidelines 3.0 using a patient's diary and a case report form.[14] At each study visit, patients were asked to report type and severity of local side effects on a visual analog scale ranging from 0 (no symptoms) to 10 (severe symptoms) and systemic side effects according to Common Terminology Criteria for Adverse Events guidelines ranging from grade 0 (no symptoms) to grade 5 (death). Participants were handed out prescriptions for an anti-inflammatory drug (paracetamol) and instructed about the correct dosage of this drug in case of systemic drug-related side effects.[15] In case of persistent local side effects, vaginal suppository application was discontinued for 1 week. In case of persistent systemic or local side effects, Common Terminology Criteria for Adverse Events grade 2 or higher, patients were switched to 0.5 vaginal suppositories (containing 3.125 mg imi-

quimod in the active group and placebo in the control group) while continuing the treatment protocol as described. In case of a positive pregnancy test, participants were excluded from the study and appropriately counseled.

Assuming a two-sided 5% significance level and a power of 80%, a sample size of 24 patients per group was calculated to detect a 35% absolute increase in CIN 2–3 regression (imiquimod compared with placebo; regression by imiquimod based on a 10% CIN 2–3 regression rate with placebo).[16] This sample size was calculated by a χ^2 test without continuity correction and based on a per-protocol calculation. Assuming a drop-out rate of 20%, a total sample size of 59 patients was calculated. To recruit this number of patients, an 18-month inclusion period was anticipated.

The randomization sequence was created using PMX CTM software with a 1:1 allocation and a block size of 30. Allocation concealment was performed by the study pharmacy (Marien Apotheke, Vienna, Austria), where board-certified pharmacologists produced vaginal suppositories containing imiquimod and placebo of identical appearance. Flasks containing vaginal suppositories were consecutively numbered with increasing identification numbers according to the randomization schedule. Participants were consecutively allocated an identification number and received the corresponding flasks. Two flasks were prepared for each participant, labeled with participants' initials, identification number, and either "1.0" or "0.5" according to the vaginal suppository dosage. Good Manufacturing Practice and drug labeling guidelines were applied.

Statistical analyses of primary and secondary end points were performed according to the intention-to-treat principle. The intention-to-treat population comprised all randomized patients, only excluding patients who withdrew before treatment initiation. Patients, who did not complete treatment, were regarded as nonresponders with respect to regression, remission, and HPV clearance. For a comparison of treatment response rates between the two groups, we used the χ^2 test and computed the difference in response rates with a 95% confidence interval. According to the study protocol, an additional per-protocol analysis was performed but is not reported, because the results are virtually identical.

Two additional statistical analyses were performed. The first additional analysis was performed to estimate the influence of patient's HPV type on treatment efficacy of imiquimod. Therefore, patients in the imiquimod and placebo groups were categorized into HPV-16 infection compared with non–HPV-16 infection (ie, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, and 82) and outcome was compared by Fisher's exact test. Human papillomavirus-16 was chosen, because it is the clinically most relevant high-risk HPV type given its high prevalence and aggressive clinical behavior. The second additional analysis aimed to investigate whether dose reduction negatively affected treatment response, because nine (32%) patients in the imiquimod group switched to 0.5 vaginal suppositories as a result of side effects. Therefore, patients in the imiquimod group were categorized into those with dose reduction and those without dose reduction and their outcome was compared by Fisher's exact test.

The present study was partially funded by the Fellinger Cancer Research Fund. MEDA Pharmaceuticals provided the study medication and an unrestricted research grant to the Department of Obstetrics and Gynecology, Medical University of Vienna. This money was partially used to cover costs for production of the study medication and analysis of HPV samples. MEDA Pharmaceuticals was not involved in study design, data collection, data interpretation, or analysis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

In total, 59 patients with CIN 2–3 and high-risk HPV infection were included in this study (Fig. 1, Consolidated Standards for the Reporting of Trials diagram). Baseline characteristics are provided in Table 1. As a result of an intrauterine pregnancy detected after study initiation, two participants were excluded from the study, one allocated to the imiquimod group and one allocated to the placebo group. Both pregnancies occurred despite oral contraception. In the patient allocated to the imiquimod treatment, no teratogenic effects were observed during pregnancy. The child is healthy 6 months after birth. One participant in the imiquimod group stopped treatment after 4 weeks because of systemic grade 1 side effects (fatigue and nausea). One study participant withdrew informed consent without giving further reasons after study inclusion but before application of the first vaginal suppository (Fig. 1).

After 16 weeks of treatment, histologic regression to CIN 1 or less (primary end point) was observed in 73% in the imiquimod group compared with 39% in the placebo group (P=.009). This would result in a number needed to treat of 2.9 (1.7–10.0) to achieve histologic regression. Histologic regression and remission rates are provided in Table 2. Human papillo-

Table 1. Patient Characteristics at Study Entry

Characteristic	Placebo	Imiquimod	*P*
Total n	29	30	
Patient's age (y)	31.8±7.3	29.2±6.1	.14*
No. of pregnancies	1.3±1.7	0.9±1.2	.24*
No. of sexual partners			.88†
1–5	16 (55)	16 (53)	
6–10	9 (31)	8 (27)	
More than 10	4 (14)	6 (20)	
History of STD			>.99†
No	27 (93)	27 (90)	
Yes	2 (7)	3 (10)	
Contraception method			.21†
Condom	9 (31)	13 (43)	
Oral contraceptive	17 (59)	16 (53)	
IUD	0 (0)	1 (3)	
Tubal sterilization	3 (10)	0 (0)	
Smoking			.60†
No	10 (34)	13 (43)	
Yes	19 (66)	17 (57)	
Histology			.20†
CIN 2	13 (45)	19 (63)	
CIN 3	16 (55)	11 (37)	
High-risk HPV type			.51†
High risk-positive‡	29 (100)	30 (100)	
16§	18 (64)	17 (63)	
18§	2 (7)	0 (0)	
Other high-risk HPV type§	8 (29)	10 (37)	
High-risk HPV type not available§	1 (3)	3 (10)	
Cytology			.14†
Normal	0 (0)	1 (3)	
ASC-US	0 (0)	4 (13)	
LSIL	13 (45)	13 (43)	
HSIL	16 (55)	12 (40)	

STD, sexually transmitted disease; IUD, intrauterine device; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade intraepithelial lesions.
Data are mean±standard deviation or n (%) unless otherwise specified.
* Statistical analysis by *t* test; values given as mean (standard deviation).
† Statistical analysis by Fisher's exact test.
‡ According to HPV-Digene Hybrid Capture test.
§ According to HPV-PapilloCheck test.

mavirus clearance rates after treatment were 60% and 14% in the imiquimod and placebo group, respectively (*P*<.001) (Table 2).

As a result of persistent CIN 2–3 at the final study visit, 20 patients were treated with conization. Three women were found to have presence of cervical cancer, all allocated to the placebo group. Because final pathology revealed complete resection of microinvasive cervical carcinoma International Federation of Gynecology and Obstetrics 1A1 without lymphovascular space invasion, patients did not require further treatment. All patients were free of disease at follow-up 6 months after surgery.

Table 2. Histologic Response After Treatment

Characteristic	Placebo (n=28)	Imiquimod (n=30)	*P*, Difference in Response Rate (95% CI)*
Regression†	11 (39)	22 (73)	.009, 34% (8–57%)
Remission‡	4 (14)	14 (47)	.008, 32% (7–55%)
HPV clearance	4 (14)	18 (60)	<.001, 46% (22–67%)

CI, confidence interval; HPV, human papillomavirus.
Data are n (%) unless otherwise specified.
* Statistical analysis by χ^2 test, results given as *P* value and difference in response rate between imiquimod and placebo groups (95% CI).
† Regression is defined as histologically verified regression to cervical intraepithelial neoplasia grade 1 or complete remission.
‡ Remission is defined as complete histologic remission.

Results of HPV type analysis, in which patients with HPV-16 infection are compared with patients with all other high-risk HPV infections, are provided in Table 3. Whereas there was no significant difference between the imiquimod and placebo groups in patients with non–HPV-16 lesions, regression, remission, and HPV clearance rates in HPV-16 lesions were significantly higher in the imiquimod group (Table 3).

The influence of dose modification on treatment outcomes within the imiquimod group was also evaluated. It revealed that dose reduction did not affect treatment outcome negatively because regression (67% and 84%, respectively; *P*=.35), remission (22% and 63%, respectively; *P*=.10), and HPV clearance (63% and 67%, respectively; *P*>.99) rates did not differ between patients with and without dose modification.

The mean medication score was 40.4 (4.7) in the placebo group and 35.8 (9.4) in the imiquimod group (*P*=.03), indicating that patients in the imiquimod group more often switched to 0.5 vaginal suppository or discontinued therapy. Local and systemic side effects are listed in Table 4. As a result of persistent systemic or local side effects, nine patients (30%) within the imiquimod group switched to 0.5 imiquimod vaginal suppositories and one patient (3%) prematurely stopped the treatment. Two patients (7%) within the placebo group switched to 0.5 placebo vaginal suppositories.

DISCUSSION

This trial demonstrates the efficacy of topical imiquimod in the treatment of CIN 2–3. In the imiquimod group, regression to CIN 1 or less was achieved in 73% and complete histologic remission in 47% of patients. Histologic regression and remission

Table 3. Histologic Results After Treatment According to Human Papillomavirus-16 Status at Inclusion Visit

Characteristic	Non–HPV-16			HPV-16		
	Placebo (n=10)	Imiquimod (n=10)	P*	Placebo (n=17)	Imiquimod (n=17)	P†
Regression‡	5 (50)	6 (60)	>.99	5 (29)	14 (82)	.005
Remission‡	3 (30)	4 (40)	>.99	0 (0)	8 (47)	.003
HPV clearance	2 (20)	6 (60)	.17	1 (6)	10 (59)	.002

HPV, human papillomavirus.
Data are n (%) unless otherwise specified.
* Remission is defined as complete histologic remission.
† Statistical analysis by Fisher's exact test comparing non-HPV-16 groups (placebo compared with imiquimod) and HPV-16 groups (placebo compared with imiquimod).
‡ Regression is defined as histologically verified regression to cervical intraepithelial neoplasia grade 1 or complete remission.

rates were significantly higher in the imiquimod group compared with the placebo group. Our findings are novel and clinically relevant, because no conservative treatment has been established for patients with CIN 2–3 so far. Thus, topical imiquimod is a promising agent for the treatment of CIN 2–3 with a number needed to treat of 2.9 (1.7–10.0) patients to achieve histologic regression.

Our findings are of particular interest when compared with a very recent randomized controlled trial, which has investigated the benefit of preoperative imiquimod on persistence rates of CIN after conization.[17] This study did not observe a difference in recurrence rates between the two arms (conization only: 14.3%, conization and imiquimod: 14.3%). Although the trial design is very interesting, this study has several severe limitations. First, the study aimed to include 152 patients but was stopped after 56 patients as a result of slow recruitment. Second, imiquimod was only applied five times before surgery. This is an uncommon and short treatment regime. Third, the treatment included excisional and destructive treatments, for which no stratification was performed. Therefore, the results of this trial are not comparable to the imiquimod regimen tested at our trial.

Three patients of the 59 patients (5% [1–14%]), all allocated to the placebo group, were found to have microinvasive cervical cancer after treatment. Diagnosis of these cases was not established by colposcopically guided biopsies during the treatment period, but by conization after the end of the treatment period. Therefore, it remains unclear whether these cases reflect true progression to invasive disease or presence of occult cancer. Given the relatively short treatment period and previously reported occult cancer rates of 0.5–7%, these cases more likely reflect the presence of occult cancer underdiagnosed by colposcopically guided biopsy.[18–20]

We observed a moderately high rate of CIN regression and remission in the placebo group. This is in accordance with previous studies reporting spontaneous CIN remission rates of up to 38%, 63%, and 68% within 1, 2, and 3 years, respectively, especially in young women with CIN 2.[2,21] On the other hand, these remission rates were observed after 1, 2, and 3 years, which is longer than our study period of 20 weeks. Moreover, we have also included women with CIN 3, a lesion less likely to spontaneously regress. We obtained study-related cervical biopsies at the time of study inclusion and after 8 weeks. Thus, one might argue that the host's potential to clear the cervical lesion might has been positively influenced by local immune stimulation and mechanical removal of parts of the CIN. This reflects a potential shortcoming of the present study. Nevertheless, regression and remission rates were still significantly higher in the imiquimod arm compared with the placebo arm.

As previously reported, imiquimod shows a high antiviral activity in the treatment of HPV and HPV-related diseases by increasing the number of immune cells in the epithelium.[12] Our data confirm that imiquimod is efficacious in clearing cervical HPV infection. High-risk HPV clearance rates were significantly higher in the imiquimod group (60%) compared with the placebo group (14%). Moreover, HPV type analysis demonstrated that imiquimod was equally efficacious in HPV-16 (47% remission) as in non–HPV-16 lesions (40% remission). In contrast, in the placebo group, no spontaneous remission (0% remission) was observed in HPV-16 lesions compared with non–HPV-16 lesions (30% remission). This seems particularly interesting, because HPV-16 lesions are known to be more aggressive and to have higher persistence and progression rates to cervical cancer compared with other HPV high-risk types.[22,23] Of note, HPV

Table 4. Side Effects According to Study Group

Side Effect	Placebo (n=29)	Imiquimod (n=30)	*P*
Reported by the patient			
Vulvar pain or pruritus			
No	18 (62)	2 (7)	<.001*
Yes	11 (38)	28 (93)	>.99†
Grade 2	0 (0)	2 (7)	
Headache			
No	23 (79)	5 (17)	<.001*
Yes	6 (21)	25 (83)	>.99†
Grade 2	0 (0)	1 (3)	
Myalgia			
No	26 (90)	7 (23)	<.001*
Yes	3 (10)	23 (77)	.22†
Grade 2	1 (3)	1 (3)	
Flu-like symptoms (including fatigue and fever)			
No	19 (66)	1 (3)	<.001*
Yes	10 (34)	29 (97)	.64†
Grade 2	2 (7)	4 (13)	
Reported by the investigator			
Erythema			
No	22 (76)	6 (20)	<.001‡
Mild to moderate	7 (24)	13 (43)	
Severe	0 (0)	11 (37)	
Erosion			
No	29 (100)	19 (63)	<.001‡
Mild to moderate	0 (0)	10 (33)	
Severe	0 (0)	1 (3)	
Edema			
No	26 (90)	14 (47)	.001‡
Mild to moderate	3 (10)	12 (40)	
Severe	0 (0)	4 (13)	
Ulceration			
No	29 (100)	28 (93)	.49‡
Mild to moderate	0 (0)	2 (7)	
Severe	0 (0)	0 (0)	

Data are n (%) unless otherwise specified.

* Statistical analysis by Fisher's exact test; variables are calculated no compared with yes.

† Statistical analysis by Fisher's exact test; variables are calculated Criteria for Adverse Events grade 1 compared with Criteria for Adverse Events grade 2.

‡ Statistical analysis by Fisher's exact test; variables are calculated no compared with mild-to-moderate compared with severe.

type analyses have to be interpreted cautiously because they represent subgroup analyses.

Topical vaginal treatment with imiquimod suppositories was well tolerated in our study. Mild pruritus and vulvar pain were the most commonly seen local side effects in the imiquimod group. This is in accordance with previous studies, in which mild local side effects were reported in up to 92% of patients during vulvar application of imiquimod.[12] Of note, none of the participants discontinued therapy as a result of local side effects. In contrast, mild systemic reactions such as flu-like symptoms and fatigue were observed in 97% and 34% of patients of the imiquimod and placebo groups, respectively. Only one patient discontinued imiquimod treatment because of persistent flu-like symptoms and fatigue 4 weeks after treatment start. It has to be noted that this patient refused to take the anti-inflammatory rescue medication, to switch to 0.5 vaginal suppositories, or both. The relatively high rate of flu-like symptoms in the placebo group might partially be attributed to coexisting viral infections during the common cold season. However, we did not specifically test study participants for the presence of the common flu.

When interpreting the findings of our study, it has to be kept in mind that the participants represent a selected group of patients with satisfactory colposcopy, fully visible transformation zone, and a positive high-risk HPV status at the time of inclusion. Furthermore, for safety concerns, only newly diagnosed, untreated patients were included in the study to minimize the potential risk for progression to microinvasive cervical cancer. Therefore, the results of our study are not applicable to the general population of women with cervical dysplasia.

Self-application of vaginal suppositories and the satisfying imiquimod tolerability make the treatment described in this study convenient and feasible in an outpatient setting. In contrast, previously described conservative treatments were reported to have limitations related to the application mode, requiring physician-applied therapy and tolerability.[17,24,25]

The need for a medical treatment alternative to surgical therapy of CIN 2–3 is high as a result of the high disease burden of cervical dysplasia and the long-term sequelae of cervical conization, namely preterm birth.[7,8] Topical, patient-applied, vaginal imiquimod therapy was demonstrated in our study to be an efficacious, feasible, and well-tolerated treatment option for patients with CIN 2–3. As a result of these promising preliminary data, a large randomized controlled noninferiority phase III trial comparing imiquimod with conization is planned (clinicaltrials: NCT01283763).

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