Physicians' Awareness, Attitudes, and Experiences Regarding Imiquimod Treatment of Vaginal and Cervical Intraepithelial Neoplasia

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Objective: The aim of the study was to assess awareness, attitudes, and current clinical experiences of gynecologists regarding imiquimod as a potential treatment modality for vaginal intraepithelial neoplasia (VAIN) and cervical intraepithelial neoplasia (CIN).

Materials and Methods: A 37-item questionnaire consisting of both multiple choice and open questions was sent to all Dutch gynecologists who regularly perform colposcopies in all 87 Dutch hospitals, in December 2014. The outcomes were assessed using descriptive statistics.

Results: Gynecologists from 52 hospitals (60%) completed the questionnaire. Of the 77 respondents, 79% and 58% were aware of imiquimod for treating VAIN and CIN, respectively. Twelve and 5 respondents had used imiquimod to treat VAIN and CIN, respectively; most treatments were for intractable VAIN lesions and recurrent lesions and to avoid surgical treatment for CIN in patients with a future pregnancy wish. Most respondents reported successful treatment outcomes but frequent adverse effects. Most (96%) stated that they would consider using imiquimod to treat high-grade CIN in selected patients, but only upon additional evidence and inclusion into treatment guidelines.

Conclusions: The awareness of imiquimod as a potential treatment for VAIN and CIN was limited, possibly because of the paucity of evidence regarding vaginal imiquimod efficacy, the lack of inclusion into guidelines, and the high frequency of adverse effects. Imiquimod was applied off-label in a limited number of selected patients, with good treatment results. The respondents generally had a positive attitude toward treating VAIN and CIN with imiquimod. Additional evidence on treatment efficacy and inclusion in treatment guidelines is necessary before application in clinical practice.

Key Words: attitude, cervical intraepithelial neoplasia, imiquimod, professional practice, vaginal intraepithelial neoplasia

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Imiquimod is a toll-like receptor antagonist that has antiviral and antitumor properties. Imiquimod cream is currently registered for the topical treatment of certain types of basal cell carcinoma, actinic keratosis, and genital warts. It is also an effective treatment modality for human papillomavirus (HPV)-induced vulvar intraepithelial neoplasia (VIN).[1] Indeed, imiquimod therapy is being applied in VIN to reduce potentially mutilating effects of surgical therapy and is recommended in current treatment guidelines.[2,3]

Imiquimod has also been studied as a treatment modality for HPV-induced vaginal intraepithelial neoplasia (VAIN) and cervical intraepithelial neoplasia (CIN), to reduce the adverse effects and challenges associated with the standard treatment modalities for these conditions. At present, advised treatment modalities for high-grade CIN include ablation or excision of the transformation zone or hysterectomy in selected patients with recurrent or persistent high-grade CIN.[4] When treatment is indicated, this is usually performed by large loop excision of the transformation zone (LLETZ), which is associated with moderately severe short-term adverse effects, including prolonged bleeding and vaginal discharge. An important long-term adverse effect of LLETZ treatment is a 2-fold increase in the risk of premature birth in subsequent pregnancies.[5,6] For this reason, management by observation is recommended for young women with either CIN 2 or CIN 3 and adequate colposcopy.[4] The preferred treatment modalities for VAIN are surgical excision and laser ablation. However, VAIN treatment can be challenging, because the lesions can be large and scattered. As a result, the rates of residual and recurrent VAIN after primary treatment are high.[7,8]

Treatment effectiveness of imiquimod in VAIN and CIN has been examined in several studies.[9–13] Although the patient populations and outcome measures in these studies were heterogeneous, the results were generally promising. One of these studies was a randomized controlled trial (RCT); it showed that in 22 (73%) of 30 patients with high-grade CIN, imiquimod treatment caused histopathologic regression to CIN 1 or less. However, adverse effects of vaginal application of imiquimod were common.[11]

Imiquimod is currently not approved for the use for the treatment of VAIN and CIN and is not part of treatment guidelines. Additional studies on treatment efficacy and clinical applicability are currently conducted, but awareness and attitudes of physicians regarding imiquimod treatment VAIN and CIN are unknown. In both research and clinical implementation of a new treatment modality, awareness and attitudes of physicians toward the treatment modality may be important factors for success. In addition, knowledge on current off-label clinical experiences may provide valuable additional information on the clinical applicability of imiquimod in VAIN and CIN and perceived treatment indications.

This study aimed to assess awareness, attitudes, and current clinical experience of gynecologists with regard to imiquimod treatment of VAIN and CIN.

MATERIALS AND METHODS

The study design and questionnaire were developed according to Checklist for Reporting Results of Internet E-Surveys guidelines.[14] A completed Checklist for Reporting Results of Internet E-Surveys guideline has been attached as a supplement (Supplemental Digital Content 1, http://links.lww.com/LGT/A21). Because this study is a survey among physicians, ethical approval was not necessary.

Population

The electronic survey was sent to all gynecologists in the Netherlands who regularly perform colposcopies and treat VAIN and CIN lesions. Because a specific mailing list was not available, all hospitals in the Netherlands in which colposcopies are conducted (n = 87) were contacted by telephone to identify these gynecologists. Of the 87 hospitals, 8 were university hospitals, 37 were large semispecialized teaching hospitals, and 42 were general nonteaching hospitals. In total, 176 gynecologists were identified and contacted by an e-mail containing an invitation message and a link to the survey. The first invitation was sent in November 2014. Reminders were sent after 3 and 6 weeks to only those gynecologists who had not responded (as tracked by the survey program). The survey was closed after 9 weeks.

Questionnaire

An anonymous electronic questionnaire was constructed by the authors and administered as an electronic, online survey available through SurveyMonkey.com (SurveyMonkey 2014, Portland, OR) (see Supplemental Digital Content 2, http://links.lww.com/LGT/A22). The questionnaire was composed by an expert panel of 4 gynecology oncologists with experience in colposcopy and treatment of VAIN and CIN. The questionnaire was tested by 5 colleagues; this led to several changes to the questionnaire. The questionnaire consisted of 37 items relating to current colposcopy practice, awareness of imiquimod as an immunotherapy for genital warts and VIN lesions, and as an experimental treatment modality of VAIN and CIN lesions, whether the gynecologist had used imiquimod to treat VAIN and CIN and what the outcomes were (only when relevant), and opinions about imiquimod use for high-grade CIN lesions. The questions concerning current colposcopy practice were included to determine whether the physicians were aware of the risk of premature birth after LLETZ and their clinical practice with regard to this potential adverse effect. Most questions were multiple choice, and it was possible to make a comment. The survey system automatically stored all responses in a database. E-mail addresses of all respondents were stored by the survey system for the purpose of sending reminder messages to nonresponders. Respondents could only complete the questionnaire once.

Statistics

The descriptive statistics were generated by using SPSS (IBM Corp., released 2012, IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY).

RESULTS

Gynecologists from 52 hospitals (60%) responded to the questionnaire. The questionnaire was started by 79 participants and was completed by 77 participants (44%). The 2 incomplete questionnaires were completely blank and were therefore excluded from the analysis. The professional function, type of hospital, and number of colposcopies that each gynecologist conducted or supervised yearly are displayed in Table 1. All respondents were aware that imiquimod could be used to treat genital warts and thus were familiar with the drug.

Current Colposcopy Practice

A large subset of the respondents had tailored their colposcopy practice to the individual patient: 32 respondents (42%) perform diagnostic biopsies in patients who wish to become pregnant and applied a see-and-treat policy in patients without a future pregnancy wish. Thirty respondents (39%) never applied a see-and treat policy, whereas 10 respondents (13%) always applied a see-and-treat policy. Most respondents (n = 52, 68%) considered the risk of premature birth after LLETZ to be unchanged or only marginally increased. The other respondents estimated the relative risk at approximately 2.7 (range, 2–6). Of all the respondents, 53 (69%) did always discuss this risk with patients and 15 (19%) did never discuss this risk.

Awareness of Imiquimod as Immunotherapy for VIN, VAIN, and CIN

The vast majority of respondents (n = 70, 91%) were aware that imiquimod could be used to treat VIN. Sixty-one (79%) of the respondents were aware of the application of imiquimod for VAIN, in literature or clinical practice. Forty-five (58%) of the respondents were aware of the application of imiquimod for CIN, in literature or clinical practice. Respondents who performed more than 100 colposcopies yearly and (fellow) gynecologic oncologists or semispecialized gynecologic oncologists associated with a higher level of awareness in all cases. Results are displayed in Table 2.

Off-Label Application of Imiquimod in VAIN and CIN

Twelve (16%) and 5 (7%) respondents had used imiquimod to treat VAIN and CIN lesions, respectively (see Table 2). Clinical application of imiquimod was more frequent in respondents who performed more than 100 colposcopies yearly and (fellowship-trained) gynecology oncologists or semispecialized gynecology oncologists, compared with the total respondent population. Frequency of application and lesion characteristics are displayed in Table 3. Most respondents applied it less than 5 times in VAIN and less than 10 times in CIN. Imiquimod was applied in both low- and high-grade lesions and in both primary and recurrent lesions.

TABLE 1. Professional Function, Type of Hospital, and Number of Colposcopies Performed by the Respondents

1. What is your professional function?	n (%)
Gynecologic oncologist or fellow gynecologic oncologist	13 (17)
Gynecologist with semispecialization in gynecologic oncology	41 (53)
Gynecologist with other (semi)specialization	23 (30)
2. In what hospital type are you currently employed?	
University hospital or specialized oncological center	12 (16)
Semispecialized teaching hospitals	42 (55)
Nonteaching hospital	23 (30)
3. How many colposcopies do you conduct or supervise yearly?	
<30	6 (8)
30–100	40 (52)
>100	31 (40)

TABLE 2. Awareness and Off-Label Use of Imiquimod as an Immunotherapy for VIN, VAIN, and CIN by Respondents Divided According to Colposcopy Experience and Professional Function

	Total Respondent Population (N = 77)	Respondents Who Conduct >100 Colposcopies Yearly (n = 31)	(Fellow) Gynecologic Oncologists and Semispecialized Gynecologic Oncologists (n = 54)
Aware of imiquimod in VIN	70 (91)	30 (97)	52 (96)
Aware of imiquimod in VAIN	61 (79)	29 (94)	46 (85)
Aware of imiquimod in CIN	45 (58)	23 (74)	35 (65)
Applied imiquimod in VAIN	12 (16)	9 (29)	11 (35)
Applied imiquimod in CIN	5 (7)	5 (16)	5 (9)

VIN indicates vulvar intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia; CIN, cervical intraepithelial neoplasia.

The most common reasons for choosing imiquimod to treat VAIN were recurrence after laser and/or excisional therapy (n = 5) and the estimation that laser or excisional therapy would be too difficult or impossible (n = 4). The reasons for choosing imiquimod to treat CIN were recurrence after LLETZ (n = 3), large CIN lesions that demanded a large LLETZ in patients with a future pregnancy wish (n = 1), and refusal by the patient to undergo LLETZ (n = 1).

In both VAIN and CIN, imiquimod was applied via vaginal capsules, vaginal suppositories, vaginal tampons, or vaginal applicators. The respondents used a fairly consistent treatment dose and protocol, which generally consisted of 2 to 3 applications per week for 12 to 16 weeks. The exception was 1 respondent who applied imiquimod 5 times per week for 6 weeks to treat VAIN. All respondents used one 6.25 mg sachet per application.

Treatment effectiveness was mostly evaluated by colposcopy, with diagnostic biopsies on indication. Four respondents combined colposcopy with cervical cytology after imiquimod treatment of VAIN. One respondent performed cervical cytology only after imiquimod treatment of CIN.

The treatment outcome was reported by 11 of the 12 respondents for VAIN and by all 5 respondents for CIN (see Table 3). Nine respondents (75%) experienced treatment success in VAIN and all 5 respondents experienced treatment success in CIN; invasive therapy was no longer needed. Only 1 author reported disease progression, in VAIN. All authors would apply the therapy again. Because this study did not aim to systematically document treatment outcomes, overall treatment effectiveness cannot be derived from the results.

Adverse effects of imiquimod treatment of VAIN and CIN were common: all but one of the respondents reported that the treatment had adverse effects. The adverse effects consisted of vaginal and vulvar pain, vulvar erythema, vulvar erosion and/or ulceration, vaginal discharge, flu-like symptoms, arthralgia, and fatigue. The adverse effects were subjectively graded by the respondents and were generally considered to be mild to moderate; only 1 respondent documented severe adverse effects. Nevertheless, 5 respondents stated that at least one of their patients had stopped treatment because of the adverse effects (three for VAIN patients and two for CIN patients).

Taking into consideration the effectiveness and adverse effects of imiquimod treatment, all respondents stated that they would use imiquimod again in patients with VAIN and CIN.

Future Application of Imiquimod

All participants were informed in the questionnaire of the results of a recent RCT on the efficacy of imiquimod in high-grade CIN.[11] On the condition that the study results were validated in a larger patient population, 74 respondents (96%) stated that they would consider applying imiquimod in high-grade CIN. Thirteen respondents also commented on this question. Several respondents stressed that it is important that additional high-quality evidence of treatment efficacy becomes available; they also emphasized the need for additional research on the long-term effects, recurrence rates, and cost-effectiveness of imiquimod therapy for VAIN and CIN. Two respondents stated that imiquimod treatment

TABLE 3. Off-Label Application of Imiquimod in VAIN and CIN by the Respondents: Frequency, Lesion Characteristics, and Treatment Success

	VAIN (n = 12), n (%)	CIN (n = 5), n (%)
How often have you applied imiquimod for this indication?		
1–5 times	10 (83)	3 (60)
6–10 times	1 (8)	2 (40)
>10 times	1 (8)	0 (0)
What was (were) the lesion grade(s)?		
Low-grade lesion(s) (VAIN/CIN 1)	2 (16)	1 (20)
High-grade lesion(s) (VAIN/CIN 2–3)	7 (58)	3 (60)
Both	3 (25)	1 (20)
Was it a primary or recurrent lesion?		
Primary lesion(s)	4 (33)	1 (20)
Recurrent lesion(s)	4 (33)	3 (60)
Both	4 (33)	1 (20)
Was treatment of the lesion(s) with imiquimod successful? (multiple options possible)[a]		
Yes, lesion regression or complete remission, invasive therapy no longer needed	9 (75)	5 (100)
No, persistent lesion	3 (25)	1 (20)
No, progressive lesion	1 (8)	0 (0)
Would you recommend treatment of VAIN/CIN with imiquimod, and would you apply it again?		
Yes	12 (100)	5 (100)
No	0 (0)	0 (0)

[a]Percentages add up to >100% because some respondents treated more than 1 patient and reported on both disease regression and persistence or progression.

VAIN indicates vaginal intraepithelial neoplasia; CIN, cervical intraepithelial neoplasia.

would have to be incorporated in national guidelines on treatment of VAIN and CIN before they would apply it. One author commented that he/she would consider applying imiquimod in CIN 2 but not in CIN 3. Several respondents were concerned about the clinical applicability of imiquimod in CIN; they questioned whether the treatment would be tolerable for patients because of the common adverse effects, relatively long treatment duration, and practicalities such as the mode of application. One respondent stated that patient perspectives regarding imiquimod treatment for gynecological conditions should be researched further. Most respondents (n = 72, 94%) stated that they would consider participating in a RCT on the treatment efficacy of imiquimod in high-grade CIN.

DISCUSSION

The current study shows that there is limited awareness among gynecologists in the Netherlands regarding investigational treatment of VAIN and CIN with imiquimod; this was especially true for CIN. A small number of the respondents had used imiquimod as an off-label treatment for VAIN and CIN. The main reasons for their off-label application of imiquimod were recurrence of VAIN and CIN lesions, VAIN lesions that could not otherwise be optimally treated, and to avoid surgical treatment in patients with CIN who had a future pregnancy wish. The respondents reported good treatment efficacy but also stated that the adverse effects of imiquimod therapy were common. Nevertheless, all gynecologists who had treated patients with imiquimod stated that they would use this treatment modality again in the future. The attitude of gynecologists regarding imiquimod as a potential treatment of high-grade CIN is generally positive: a vast majority of participating gynecologists are willing to apply imiquimod for high-grade CIN but recommend additional trials and subsequent inclusion of this therapy in CIN guidelines.

The limited awareness and clinical application of imiquimod in VAIN and CIN may be explained by the relative paucity of evidence regarding the efficacy of imiquimod treatment in VAIN and CIN and the fact that imiquimod treatment is not currently part of treatment guidelines. There are only 3 studies on the efficacy of imiquimod treatment in VAIN and two of these focused on only or mainly low-grade lesions.[9,13] The remaining study focused only on patients with high-grade lesions, but the patient population was small; disease regression was observed in 6 of the 7 patients.[10] There are also only 3 studies on the efficacy of imiquimod in CIN. One of these was an RCT that showed 22 (73%) of 30 patients with high-grade CIN exhibited disease regression after treatment.[11] The 2 other studies focused on different outcome measures or had a heterogeneous patient population.[12,13] Large-scale RCTs that confirm treatment efficacy and assess disease recurrence over the long term are lacking. Additional evidence may lead to inclusion of imiquimod in treatment guidelines, leading to increased awareness and clinical application. Indeed, several respondents stressed the need for additional evidence regarding treatment efficacy, adverse effects, and long-term outcomes and stated that they would only use imiquimod to treat VAIN and CIN when it was incorporated in the treatment guidelines.

An important limitation to the clinical application of imiquimod may be the high rate of adverse effects of vaginal imiquimod therapy. All trials on vaginal imiquimod treatment and the current study show high rates of adverse effects. These consist mainly of vaginal discharge, flu-like symptoms, and vulvar pain or pruritus, which were reported in up to 32%, 93%, and 93%, respectively, in previous trials on vaginal imiquimod for CIN lesions.[11,12] Vulvar erosion or ulceration was seen in up to 33% of patients treated with vaginal imiquimod. Flu-like symptoms and vulvar pain or pruritus are not common adverse effects of LLETZ treatment, which is more common associated with prolonged vaginal bleeding and vaginal discharge. An observational study in 185 patients who underwent LLETZ treatment showed that 40% of women experienced moderate to severe discharge and 50% experienced moderate to severe bleeding. Bleeding persisted for more than 2 weeks in approximately 40% of women.[15] Intervention for postoperative hemorrhage is rare: 7 cases (1.3%) were reported in a retrospective cohort study among 557 patients.[16] Indeed, several respondents in the current study who had not used vaginal imiquimod expressed their concern about its potential adverse effects. When choosing imiquimod therapy for VAIN or CIN, the adverse effects of standard treatment modalities should outweigh the adverse effects of imiquimod therapy, making imiquimod an acceptable treatment alternative. As such, imiquimod treatment may have to be limited to those patients who cannot be optimally treated by standard treatment modalities or in whom surgery is to be avoided. The latter group will consist mainly of younger patients with high-grade CIN and a future pregnancy wish. To reduce overtreatment, observation according to the American Society for Colposcopy and Cervical Pathology guideline should be considered first.[4] Imiquimod could be an alternative if treatment is preferred or upon disease persistence. This conclusion was clearly shared by the respondents in the current study who had used imiquimod to treat VAIN or CIN; they only used this treatment for VAIN lesions that could not be optimally treated by laser ablation or surgery, recurrent VAIN or CIN lesions, and patients with CIN lesions who had a future pregnancy wish and who would be at risk of premature birth if they underwent LLETZ treatment. Interestingly, the majority of our respondents underestimated the risk of premature birth in subsequent pregnancies. Moreover, a significant number stated that they do not discuss this risk with patients before LLETZ treatment. More widespread awareness of this risk could increase the clinical application of imiquimod after confirmation of its treatment modality and inclusion in treatment guidelines.

Treatment experiences in Dutch clinical practice were generally good. Off-label clinical application of imiquimod in VAIN and CIN was performed by a limited number of the respondents, of whom the majority experienced successful treatment outcomes. Interestingly, our study also showed that there was a high rate of treatment discontinuation due to adverse effects. Quality of life studies or patient preference studies concerning vaginal imiquimod therapy are currently not available but seem necessary to determine the clinical applicability of imiquimod therapy. Nevertheless, despite the high rate of adverse effects, the respondents of the current study generally considered imiquimod treatment of VAIN and CIN to be successful.

The current study is the first to provide insights regarding the awareness, off-label application, and attitudes of gynecologists with regard to imiquimod treatment of VAIN and CIN. The study has several limitations. First, although the questionnaire was tested before application, formal validation has not been performed. A pilot test was considered to be infeasible considering the small target population. However, we do not believe that the lack of validation influenced the response rate, because only 2 respondents did not finish the questionnaire, and those who did not respond at all could not have seen the questionnaire. Second, participation in the survey was voluntary. As a result, respondents who have a special interest or opinion with regard to the subject may have been more likely to participate, thus resulting in selection bias. The last limitation may be the moderate response rate of the study However, this response rate is comparable with the response rates of other surveys on the knowledge and attitudes of physicians with regard to several medical issues.[17–19] Moreover,

the absolute number of the respondents is substantial. In addition, the survey encompassed the majority of the hospitals (60%) that were contacted. Thus, the results of this survey seem to be generally reliable and valuable.

CONCLUSIONS

The responding gynecologists had limited awareness of imiquimod as an experimental treatment modality for VAIN and CIN. Far fewer actually used this treatment in clinical practice. This is possibly due to the limited evidence of imiquimod efficacy for these diseases, the fact that imiquimod treatment has not yet been incorporated in treatment guidelines, and the common adverse effects of the therapy. As a result, off-label application of imiquimod is currently limited to selected patients. For these patients, the benefits of imiquimod therapy outweighed its adverse effects. The treatment results in these patients were generally good. To facilitate more widespread implementation of imiquimod in clinical practice, more evidence regarding effectiveness, clinical applicability, and long-term outcomes is needed, followed by incorporation of imiquimod as a treatment modality in treatment guidelines. Treatment efficacy, clinical applicability, and long-term outcomes will be addressed by the authors in a RCT: TOPIC trial (TOPical treatment with Imiquimod of high-grade CIN, ClinicalTrial.gov identifier: NCT02329171).[20] This trial aims confirm and assess the efficacy of vaginal imiquimod treatment for CIN and to provide additional evidence on the rate of disease recurrence and the quality of life of the patients during and after this treatment.

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