Treatment of Cervical Intraepithelial Neoplasia

Treatment of Cervical Intraepithelial Neoplasia: Patients Preferences for Surgery or Immunotherapy with Imiquimod

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Summary: Imiquimod has been studied as a noninvasive pharmacological treatment alternative to large loop excision of the transformation zone (LLETZ) for high-grade cervical intraepithelial neoplasia (CIN), to prevent long-term obstetric complications from surgical treatment. This study aims to investigate womens' preferences for treatment of high-grade CIN with imiquimod or LLETZ. A labeled discrete choice experiment was conducted among 100 women with abnormal cervical cytology in 5 hospitals in the Netherlands between March 2014 and December 2015. Participants were asked to choose between imiquimod treatment or standard surgical treatment in 9 separate scenarios, based on the following treatment characteristics: treatment success rate, rate of side effects, risk of premature birth in subsequent pregnancies, and risk of subfertility after treatment. The levels of these characteristics differed for the imiquimod alternatives. Women assigned a positive utility to LLETZ compared with imiquimod. When making a choice for imiquimod, women preferred a higher treatment success rate and a lower risk of premature birth, infertility and side effects. The choice for imiquimod treatment was also influenced by the intention of a future pregnancy. Subgroup analyses revealed that a lower efficacy regarding imiquimod might be more acceptable for women who desired a future pregnancy compared with women who did not desire a future pregnancy. Women with a future pregnancy wish may prefer treatment of high-grade CIN with imiquimod cream over LLETZ, if the risk of subfertility and premature birth is low.

Key Words: cervical intraepithelial neoplasia, treatment, imiquimod, patient preferences

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High-grade cervical intraepithelial neoplasia (CIN) is a relatively common condition and is considered to be the precursor of cervical cancer. It is usually caused by human papillomavirus (HPV)-infection of the uterine cervix.[1] Currently, the gold-standard treatment for high-grade CIN is surgical excision, which is usually performed by large loop excision of the transformation zone (LLETZ). Common side effects of LLETZ are postoperative hemorrhage and vaginal discharge. More importantly, LLETZ is associated with potentially serious long-term side effects. An approximate 2-fold increase in premature birth is seen in pregnancies after a LLETZ procedure.[2,3] Recent evidence also suggests an increase in subfertility after LLETZ. A case-control study showed that women with a history of cervical treatment for CIN are at increased risk of subfertility defined as a time to conception of >12 months.[4]

Imiquimod cream (Aldara) has been studied as a noninvasive pharmacological treatment alternative to reduce pregnancy-related side effects of LLETZ.[5–7] Imiquimod is a toll-like receptor agonist with antiviral and antitumor properties. It is not currently registered for the treatment of high-grade CIN and is not part of treatment guidelines, but it is widely used in HPV-related vulvar intraepithelial neoplasia with good results.[7] The rationale of imiquimod treatment of HPV-induced lesions is to enhance the antiviral immunity of those who are unable to clear HPV naturally.

Treatment efficacy of imiquimod in high-grade CIN has been studied in 1 randomized controlled trial (RCT) and shows promising results: treatment efficacy was reported in 73% of subjects compared with 39% in the placebo group.[5] In comparison, treatment efficacy of LLETZ treatment is higher, with 95% of patients being adequately treated.[8] Vaginal imiquimod can be self-administered by patients, but the treatment is time-consuming and side effects are common. Frequently reported side effects include vaginal pruritus and/or pain, vaginal discharge, and flu-like symptoms.[5,9] Imiquimod, therefore, does not seem to qualify as a replacement for surgical treatment in all women. Nevertheless, subgroups may be identified for which imiquimod treatment does provide a good alternative. Our previous study has shown that gynecologists consider women who desire a future pregnancy and women with recurrent lesions as potential candidates for imiquimod treatment.[10]

The choice for either surgical treatment or pharmacological treatment with imiquimod for high-grade CIN is likely to be preference-sensitive. However, patients' preferences for these treatment modalities are currently unknown. Knowledge of patients' preferences and explanations for their

preference may further aid the identification of subgroups of women for whom imiquimod treatment can be considered a good alternative to LLETZ treatment. The current study investigated patients' preferences for either imiquimod or LLETZ in the treatment of high-grade CIN by means of a discrete choice experiment (DCE).

METHODS

Participants

The study was performed in 5 Dutch hospitals. The target population consisted of women diagnosed with premalignant abnormal cervical cytology (PAP 2/ASCUS to PAP 3b/HSIL), for whom colposcopy was planned and who would thus potentially need treatment for high-grade CIN.

Discrete Choice Experiment

Patient preferences were investigated with a DCE.[11] In a DCE, ≥ 2 interventions are compared based on the attributes of these specific interventions. Attributes represent the characteristics of the intervention, such as treatment efficacy or side effects. The preference for either intervention is then based on the levels of the different attributes: the rate of successful treatment or the rate of side effects. Respondents choose between different hypothetical scenarios described in terms of their attributes and associated levels. Several choice sets are presented that consist of ≥ 2 scenarios in which the levels of the attributes differ. The assumption is that a respondent will choose the scenario that provides the highest utility or benefit.

Attributes and Levels

Selection of the most relevant attributes and their levels was based on literature research followed by a systematic discussion with members of the research team, consisting of a gynecologist (A.J.K.), a resident-gynecologist (M.M.K.), and 2 DCE experts (C.D.D. and B.A.E.). Three reviews and 3 clinical trials reporting on outcome measures of LLETZ treatment and vaginal imiquimod treatment were identified.[3–5,8,9,12] Subsequently, 6 interviews were conducted with women who had undergone colposcopy (with or without diagnostic biopsies or LLETZ treatment) to verify the relevance and relative importance of the selected attributes. The interviews consisted of qualitative, open-ended questions, and discrete interview questions. Ages differed from 30 to 55, and 3 women desired a future pregnancy. The patient interviews did not lead to the identification of additional attributes. The selected attributes and their levels are illustrated in Table 1. Because the evidence on the attributes and levels of imiquimod treatment is limited, we designed a DCE with 2 hypothetical imiquimod options per choice set, in which levels were varied.

Study Procedures

An efficient main-effect design was created, using Ngene software, to select a subset of all possible choice sets (www.choice-metrics.com). An efficient design refers to the precision with which the different model parameters can be estimated.[13] Prior parameter values were based on the importance ranking that was provided in patient interviews. On the basis of the S-estimate (sample size) of the efficient design, 50 patients were sufficient to estimate the significant parameters for a main-effect model. We aimed for the inclusion of 100 patients to be able to explore potential interaction effects.

In total, 9 choice sets were created (Fig. 1). The ordering of the attributes was varied over 4 versions of the questionnaire to control for a potential attribute-ordering effect. To test internal consistency, choice set 5 was repeated at the end of the questionnaire (choice set 10). Internal consistency was evaluated by Cohen κ, in which a $\kappa < 0.20$ denotes poor agreement, 0.21–0.40 fair, 0.41–0.60 moderate, 0.60–0.80 good, and 0.81–1.00 very good agreement.[14]

A pilot study was conducted in 10 women for feasibility, understanding, and to check whether women were willing to trade (switch between the 2 treatment options according to different characteristics). On the basis of oral feedback by these women, minor adjustments were made to the explanatory sections on high-grade CIN, LLETZ, and imiquimod treatment.

After giving informed consent, participants received written information and the DCE questionnaire. The information consisted of a general explanation of the DCE experiment, information about high-grade CIN, and a detailed description of both LLETZ and imiquimod treatment, including illustrations on the LLETZ procedure and the insertion procedure of imiquimod cream and a table with the selected attributes and their levels. The description of LLETZ was based on the existing local information brochure, the description of imiquimod treatment was based on the treatment protocol according to the RCT by Grimm et al.[5] All questionnaires were completed before the planned colposcopy.

Data Analysis

The respondents' choices were analyzed with a multinomial logit regression model in Nlogit version 5. The following model was estimated:

$$\begin{aligned} V(\text{imiquimod}) = {} & \beta_0 + (\beta_1 \times \text{treatment success}) \\ & + (\beta_2 \times \text{premature birth}) + (\beta_3 \times \text{infertility}) \\ & + (\beta_4 \times \text{pain}) + (\beta_5 \times \text{discharge}) + (\beta_6 \times \text{flu}), \end{aligned}$$

$$V(\text{LLETZ treatment}) = \beta_7(\text{fixed constant}),$$

where V represents the relative utility score patients derive from a treatment with imiquimod or LLETZ treatment; β_0 is a constant that, if positive, reflects a preference for the label imiquimod; β_1–β_6 are the coefficients reflecting the effect of a particular attribute level on the utility score; β_7 is the coefficient (ie, alternative specific constant) for the LLETZ treatment with fixed levels. The sign of a coefficient shows whether an attribute has a positive or negative effect on utility. A relative utility score can be calculated by filling in the regression equation with estimated coefficients from the multinomial logit model and levels of the attributes. A higher utility score means that patients prefer one treatment modality over another. To examine whether preferences for the attributes "risk of subfertility," "risk of premature birth in subsequent pregnancy," and the fixed alternative LLETZ treatment are different depending on a desire for a future pregnancy, we included these interaction terms in the model. In addition, a subgroup analysis was performed based on women with or without a future pregnancy wish.

Ethics Approval

The study was evaluated and approved of by the Medical Ethics Committee of the Maastricht University Medical Center (MUMC/METC 13-4-116, January 6,

TABLE 1. Attributes and Levels used in the Discrete Choice Experiment

Attributes	Explanation of Attribute	Level of the Attribute for LLETZ Treatment (%)	Levels of the Attribute for Imiquimod Treatment (%)	References
Chance of successful treatment	Treatment is successful when the entire CIN lesion has resolved after treatment and no additional treatment is necessary	95	55, 75, 95	5,8,12
Risk of premature birth after treatment	Premature birth is the birth of a baby before 37 wk of gestation. Premature babies often have to be admitted to a neonatal ward and experience more health problems	12	6, 12	2,3
Risk of subfertility after treatment	Subfertility is when the time to conception is longer than 12 months	16	8, 16	4
Side effects*				
Vaginal pruritus/pain	Irritation of the vaginal mucosa, which can lead to pruritus or pain	NA	10, 25	5
Abdominal pain	Pain in the lower abdomen	15	NA	12
Vaginal discharge	Bloody or white vaginal discharge	20	10, 30	9,12
Vaginal bleeding	Vaginal bleeding can be both brown and red blood loss	25	NA	12
Flu-like symptoms	Flu-like symptoms include myalgia, headache and fever	NA	10, 25	5,9

*Study subjects were informed that the presented levels indicated the levels of moderate to severe complaints, during the first 2 weeks after LLETZ treatment and during the full period of imiquimod treatment.

CIN indicates cervical intraepithelial neoplasia; LLETZ, large loop excision of the transformation zone; NA, not applicable.

2014). All study procedures were conducted according to the Declaration of Helsinki, 7th revision, 2013.

RESULTS

Respondents and General Results

Respondents were recruited in 5 Dutch hospitals between March 2014 and December 2015. A total of 177 women were consecutively approached for participation in the study, of which 100 gave informed consent and completed the questionnaire (response rate 56.5%). Baseline characteristics of the respondents can be found in Table 2. Three questionnaires had missing data (6 questions in total). Of the 100 women, 82 evaluated the questions as clear or very clear. The internal consistency of the respondents was good, as reflected by a κ value of 0.79 ($P < 0.01$).

DCE Results: Main-Effect Model

The results of the main-effect multinomial logit regression model are shown in Table 3. Women derived a positive utility from choosing the standard LLETZ treatment, as shown by the significant positive coefficient of 4.25. All attributes representing imiquimod treatment were considered important, and women significantly preferred a higher treatment success rate and a lower risk of premature birth, infertility and side effects. A higher utility score for imiquimod treatment compared with LLETZ was only reached when the success rate is 80% with a low risk of subfertility and premature birth in subsequent pregnancies and low levels of side effects [utility score 4.4: V(imiquimod) = $(0.08 \times 80\%$ treatment success) + $(-0.13 \times 6\%$ premature birth) + $(-0.11 \times 8\%$ infertility) + $(-0.03 \times 10\%$ vaginal pain) + $(-0.013 \times 10\%$ vaginal discharge) + $(-0.029 \times 10\%$ flu)]. In the case of a low risk of subfertility and premature birth (as is expected), but a high risk of side effects, treatment efficacy should reach 95% to provide a higher utility score compared with LLETZ treatment.

DCE Results: Interaction Model

The results of the interaction model (2) are presented in Table 3. All 3 interactions were statistically significant, indicating that preferences for the attributes "risk of subfertility," "risk of premature birth in subsequent pregnancy," and the fixed alternative LLETZ treatment are significantly different depending on a woman's plans for a future pregnancy. The LLETZ treatment provides a significantly higher benefit for women without a pregnancy wish compared with women with a pregnancy wish. The model 2, which includes the interactions, significantly improves the model fit compared with model 1 (likelihood ratio test $\chi^2_{251} \geq \chi^2_{7.81}$; $P < 0.05$).

DCE Results: Subgroup Analysis of Women with and without the Desire for a Future Pregnancy

Table 4 presents the results for women with a future pregnancy wish and without a pregnancy wish. Women with a future pregnancy wish show a significant preference for a higher chance of treatment success and a lower risk of subfertility and premature birth. The other attributes do not play a role in their decision for imiquimod treatment. They also assign a positive utility (3.35) to the LLETZ treatment, although this value is significantly lower compared with women who do not desire a future pregnancy (5.76). For women who are planning a future pregnancy, imiquimod must have a treatment success of at least 72% $(0.08 \times 72\%)$ with low levels for subfertility $(-0.19 \times 8\%)$ and premature birth $(-0.15 \times 6\%)$ to result in a higher utility score than that for LLETZ treatment.

Question 1

Attribute	Imiquimod *option 1*	Imiquimod *option 2*		LLETZ
Chance of successful treatment	**55%** *55 of 100 women*	**95%** *95 of 100 women*		**95%** *95 of 100 women*
Risk of premature birth	**12%** *12 of 100 women*	**6%** *6 of 100 women*		**12%** *12 of 100 women*
Risk of subfertility	**8%** *8 of 100 women*	**16%** *16 of 100 women*		**16%** *16 of 100 women*
Risk of side effects:				
Vaginal pruritus or pain	**10%** *10 of 100 women*	**25%** *25 of 100 women*		-
Abdominal pain	-	-		**15%** *15 of 100 women*
Vaginal discharge	**10%** *10 of 100 women*	**30%** *30 of 100 women*		**20%** *20 of 100 women*
Vaginal bleeding	-	-		**25%** *25 of 100 women*
Flu-like symptoms	**10%** *10 of 100 women*	**25%** *25 of 100 women*		-

	Imiquimod *option 1*	Imiquimod *option 2*		LLETZ
Which treatment do you prefer?	□	□		□

FIGURE 1. Example of a choice set. Ten of such choice sets were presented. Study subjects were asked to choose one treatment alternative in each choice set: either imiquimod option 1, imiquimod option 2, or LLETZ. LLETZ indicates large loop excision of the transformation zone.

DISCUSSION

This is the first study reporting on patient preferences in the choice between imiquimod and LLETZ as treatment modalities for high-grade CIN. The results indicate that women derive a positive utility from the standard LLETZ treatment compared with imiquimod treatment. With respect to imiquimod, women prefer a higher treatment success rate and a lower risk of premature birth, infertility and side effects. Subgroup analysis showed that for women who planned a future pregnancy, imiquimod might be a more acceptable treatment modality than for women without a pregnancy wish if the risk of subfertility and premature birth are low.

The study shows that the preference for imiquimod treatment compared with LLETZ treatment is influenced by a future pregnancy wish. This is understandable, considering that the main advantage of imiquimod treatment is a reduction in future subfertility and premature birth. These findings correspond with the results of a recent survey among gynecologists concerning their experience and attitude regarding imiquimod treatment of high-grade CIN.[10] This survey showed that off-label application of imiquimod in high-grade CIN is largely restricted to patients with a future pregnancy wish and/or recurrent lesions in which (repeated) LLETZ treatment may cause long-term morbidity. Our study shows that in women planning a future pregnancy wish, the side effects of vaginal imiquimod treatment may indeed outweigh the risks of surgical treatment, making imiquimod treatment an acceptable treatment alternative for these women.

Treatment efficacy is an important attribute in the decision between LLETZ and imiquimod treatment. The only RCT on imiquimod treatment of high-grade CIN showed a treatment success rate of 73% (defined as histologic regression to CIN 1 or less after 20 weeks from the beginning of treatment). Complete histologic regression was seen in 47% of patients.[5] Assuming a high risk of side effects and a low risk of subfertility and premature birth in clinical practice, our study showed that a treatment efficacy of 95% for imiquimod treatment is desired for a general population of women to derive a higher benefit from imiquimod treatment than from LLETZ treatment. This supports our notion that imiquimod therapy will not develop as a treatment alternative for the general population of women with high-grade CIN. However, we also showed that women who planned a future pregnancy would possibly accept a lower treatment success rate if the risk of subfertility and premature birth was low. In that case, a treatment success rate of 72% would result in women preferring imiquimod over LLETZ treatment. Additional evidence on the long-term treatment efficacy of imiquimod treatment should clarify whether a treatment success rate of at least 72% is actually achievable. Ideally, the individual probability of treatment success should be predictable. A

TABLE 2. Baseline Characteristics of the Respondents

Characteristics	N = 100
Age (mean, range) (y)	38.5, 21–70
Degree of education (absolute)	
Secondary education or intermediate vocational education	62
Advanced vocational school or university	35
Unknown	3
Parity	
Nulliparous	39
Primiparous	23
Multiparous	35
Unknown	3
Age at first birth (mean, range) (y)	27, 18–36
Pregnancy wish in the future	
Yes	34
No	53
Unsure	9
Unknown	4
Previous colposcopy	
Yes	77
No	21
Unknown	2
Previous LLETZ treatment or conization	
Yes	18
No	81
Unknown	1

LLETZ indicates large loop excision of the transformation zone.

combination of patient characteristics and biomarkers reflecting host, viral, and cellular factors may provide a model to make the individual response to imiquimod predictable.[15] Patients with higher chances of treatment success could then be identified and counseled based on the results of this study.

An important strength of this study includes the innovative aspect of the study subject: this is the first study on patient preferences regarding the treatment of CIN. It provides the physician with information on relevant attributes in the choice between imiquimod and LLETZ treatment and on subgroups for who a new treatment modality might be indicated. Another strength is the relatively large patient population, which is twice the size of the calculated sample size. The moderate response rate of 56% can be considered a limitation of this study. Patients received the questionnaire by mail and were asked to complete it before the colposcopy to prevent biased results due to experiences during the colposcopy. Patients who had not completed the questionnaire at the time of the colposcopy could therefore not be included. Nevertheless, the effect of a potential sampling or response bias as a result of low response rates seems limited in other types of surveys.[16] Moreover, the study population is diverse with regard to age and future pregnancy plans, which are characteristics that could be expected to influence their treatment preference. Another potential limitation is the inclusion of the risk of subfertility as a treatment characteristic. A meta-analysis was published after the start of our DCE that concluded that there is no evidence suggesting that treatment for CIN adversely affects fertility.[17] It must be noted, however, that the results of this meta-analysis concerning time to conceive (subfertility) were based on 3 studies, of which 2 were more than 20 years old. The only recent study indicates a higher incidence of subfertility in women after LLETZ treatment.[4] Consequently, it cannot be ruled out that the risk of subfertility is higher after LLETZ treatment.

In conclusion, women generally have a preference for LLETZ treatment of high-grade CIN. A preference for imiquimod treatment is influenced by the desire for a future pregnancy, in which case lower treatment success rates might be more acceptable as long as the risk of premature birth and subfertility are low. Additional evidence is

TABLE 3. Results of the Multinomial Model

	Main-Effect Model (1)		Model with Interactions (2)	
Attributes	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
ASC_imiquimod	0.060	−0.17 to 0.29	0.14	−0.11 to 0.40
Treatment success	0.084***	0.06 to 0.10	0.077***	0.06 to 0.10
Premature birth	−0.126***	−0.19 to −0.06	−0.05	−0.14 to 0.03
Subfertility	−0.109***	−0.15 to −0.06	−0.006	−0.07 to 0.05
Vaginal pruritus and/or pain	−0.031***	−0.05 to −0.01	−0.024**	−0.04 to −0.003
Vaginal discharge	−0.013*	−0.03 to −0.001	−0.009	−0.03 to 0.007
Flu-like symptoms	−0.029**	−0.05 to −0.005	−0.014	−0.04 to 0.011
ASC_LLETZ treatment	4.25***	3.33 to 5.16	6.37***	5.09 to 7.66
Pregnancy wish × subfertility			−0.178***	−0.246 to −0.111
Pregnancy wish × premature birth			−0.103**	−0.193 to −0.013
Pregnancy wish × LLETZ treatment			−0.863***	−1.16 to −0.56
	LL = −738.33		LL = −612.69	
	No. observations = 894†		No. observations = 778‡	
	No. individuals = 100		No. individuals = 87	
Likelihood ratio χ^2 test: model 2 vs. model 1 $\chi^2_{251} \geq \chi^2_{7.81}$; $P < 0.05$				

†100 subjects, 9 questions per subject, 6 questions were not completed: $(100 \times 9) - 6 = 894$ observations

‡In total, 13 subjects were excluded because of uncertainty about future pregnancy wish, 5 questions were not completed: $[900 - (13 \times 9) - 5] = 778$ observations.

ASC indicates alternative specific constant; CI, confidence interval; LL, log likelihood; LLETZ, large loop excision of the transformation zone.

*$P < 0.1$.

**$P < 0.05$.

***$P < 0.01$.

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TABLE 4. Subgroup Analysis

	Women With Desire for Future Pregnancy		Women Without Desire for Future Pregnancy	
Attributes	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
ASC_imiquimod	0.173	−0.21 to 0.56	0.118	−0.23 to 0.46
Treatment success	0.081***	0.05 to 0.11	0.074***	0.048 to 0.09
Premature birth	−0.156***	−0.25 to −0.05	−0.054	−0.16 to 0.03
Subfertility	−0.190***	−0.26 to −0.11	−0.008	−0.08 to 0.06
Vaginal pruritus and/or pain	−0.022	−0.05 to 0.01	−0.027*	−0.055 to −0.0008
Vaginal discharge	−0.004	−0.03 to 0.020	−0.013	−0.035 to 0.008
Flu-like symptoms	−0.006	−0.04 to 0.03	−0.022	−0.058 to 0.013
ASC_LLETZ treatment	3.35***	1.84 to 4.86	5.76***	4.28 to 7.23
	No. observations = 305 No. individuals = 34		No. observations = 473 No. individuals = 53	

ASC indicates alternative specific constant; CI, confidence interval; LLETZ, large loop excision of the transformation zone.
*$P < 0.1$.
**$P < 0.05$.
***$P < 0.01$.

necessary to confirm the safety and applicability of imiquimod treatment of high-grade CIN and should clarify the actual levels of treatment success and side effects.

CONFLICTS OF INTEREST/FINANCIAL DISCLOSURES

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All authors have declared there are no financial conflicts of interest with regard to this work.

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