Received: 14 March 2023 | Revised: 29 May 2023 | Accepted: 4 June 2023

DOI: 10.1002/ijgo.14953

REVIEW ARTICLE

Gynecology

The efficacy of topical imiquimod in high-grade cervical intraepithelial neoplasia: A systematic review and meta-analysis

A. J. M. van de Sande[1] | M. Kengsakul[1,2] | M. M. Koeneman[3] | M. Jozwiak[1] | C. G. Gerestein[4] | A. J. Kruse[3,5] | E. M. G. van Esch[6] | P. J. de Vos van Steenwijk[3,7] | C. L. P. Muntinga[6,7] | W. M. Bramer[8] | H. C. van Doorn[1] | F. J. van Kemenade[9] | H. J. van Beekhuizen[1]

[1]Department of Gynecological Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

[2]Panyananthaphikkhu Chonprathan Medical Center, Department of Obstetrics and Gynecology, Srinakharinwirot University, Nonthaburi, Thailand

[3]Department of Obstetrics and Gynecology, Maastricht University Medical Centre, Maastricht, The Netherlands

[4]Department of Gynecologic Oncology, Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[5]Department of Obstetrics and Gynecology, Isala Clinics, Zwolle, The Netherlands

[6]Department of Obstetrics and Gynecology, Catharina Cancer Institute, Catharina Hospital, Eindhoven, The Netherlands

[7]GROW - School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands

[8]Medical Library, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

[9]Department of Pathology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

Abstract

Objective: A major side effect of cervical excision for high-grade cervical intraepithelial neoplasia (CIN) is premature birth. A non-invasive treatment for reproductive age women is warranted. The aim of the present study was to determine the efficacy of topical imiquimod in the treatment of high-grade CIN, defined as a regression to ≤CIN 1, and to determine the clearance rate of high-risk human papillomavirus (hr-HPV), compared with surgical treatment and placebo.

Methods: Databases were searched for articles from their inception to February 2023. The study protocol number was INPLASY2022110046. Original studies reporting the efficacy of topical imiquimod in CIN 2, CIN 3 or persistent hr-HPV infections were included. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses checklist.

Results: Five studies were included ($n = 463$). Histological regression to ≤CIN 1 was 55% in imiquimod versus 29% in placebo, and 93% in surgical treatment. Imiquimod-treated women had a greater odds of histological regression to ≤CIN 1 than placebo (odds ratio [OR] 4.17, 95% confidence interval [CI] 2.03–8.54). In comparison to imiquimod, surgical treatment had an OR of 14.81(95% CI 6.59–33.27) for histological regression to ≤CIN 1. The hr-HPV clearance rate was 53.4% after imiquimod and 66% after surgical treatment (95% CI 0.62–23.77).

Conclusions: The histological regression rate is highest for surgical treatment followed by imiquimod treatment and placebo.

KEYWORDS

LLETZ, metabolic clearance rate, papillomaviridae, papillomavirus infections, squamous intraepithelial lesions, transformation zone, treatment outcome, uterine cervical neoplasms

This paper had an oral presentation at AOGIN2022 (Asia-Oceania Research of Genital Infection and Neoplasia), Thailand.

Correspondence
M. Kengsakul, Department of Gynecological Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center Rotterdam, P.O. box 2040, 3000 CA Rotterdam, The Netherlands.
Email: m.kengsakul@erasmusmc.nl; malika@g.swu.ac.th

1 | INTRODUCTION

High-grade cervical intraepithelial neoplasia (CIN), also known as high-grade squamous intraepithelial lesion (HSIL), is caused by a persistent infection with high-risk human papillomavirus (hr-HPV), which is primarily transmitted through sexual contact.[1] The majority of HPV infections are cleared by the immune system. However, a number of women whose immune system fails to clear the virus may develop high-grade CIN and subsequently invasive cervical cancer. Approximately 1%–2% of women worldwide suffer from this premalignant stage.[2]

The standard treatment for high-grade CIN involves cervical excision or ablation, such as large loop excision of the transformation zone (LLETZ), cold knife conization and laser conization.[3,4] These surgical procedures were designed to remove the affected area of the transformation zone. In comparison to other methods, a LLETZ procedure appears to provide the most reliable specimens for histology with the least morbidity.[5] Nevertheless, residual disease or recurrence of disease after LLETZ is not uncommon (ranges from 5% to 27%).[3,5] In addition, LLETZ is an invasive procedure with complications and side effects. The most serious side effects are subfertility and premature birth due to cervical insufficiency.[6–8] The risk of premature birth can reach up to 13% in women who have had more than one surgery.[9]

In light of these side effects, there is a need for non-invasive treatment, especially in reproductive-age women. As a topical immune-response modulator, imiquimod binds to Toll-like receptors (TLR) 7 on antigen presenting cells, resulting in a local immune response at the cervix by secreting pro-inflammatory cytokines. In addition to increasing antigen presentation, imiquimod induces an immune response to target HPV-infected cells, resulting in HPV clearance.[10]

The effectiveness of imiquimod in treating vulvar HSIL, which is also caused by hr-HPV, ranges from 35% to 81% after 6–12 months, and is therefore recommended as a first-line treatment.[11]

In a recent study,[12] imiquimod showed a 73% histologic regression in high-grade CIN lesions, after which it was incorporated into the Dutch guidelines for cervical dysplasia treatment as an alternative treatment to avoid LLETZ treatment.[13] A disadvantage of imiquimod treatment is the duration of 16 weeks and the side effects, such as pain and redness of the treated area, tiredness, headache, and flu-like symptoms. In addition to the side effects, the duration of the treatment makes it difficult for women to complete the treatment. Therefore, starting such a treatment should result in a high success rate,[14] but different studies have shown that imiquimod has a lower rate of efficacy than expected by women.

1.1 | Objectives

We performed a systematic review and meta-analysis to summarize the available evidence. In a previous systematic review on imiquimod in CIN, only two studies were included, which concluded that imiquimod was effective in treating low–grade squamous intraepithelial lesion (LSIL), but less effective than surgery.[15] In the present study, a primary objective was to assess the efficacy of topical imiquimod in high-grade CIN lesions compared with LLETZ or placebo. A secondary objective was to determine the clearance rate of human HPV infection after topical imiquimod treatment, compared with LLETZ treatment, as well as to evaluate side effects associated with all treatment modalities.

2 | MATERIALS AND METHODS

2.1 | Information source and search strategy

This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist,[16] the PRISMA –S extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews,[17] and meta-analysis of observational studies (MOOSE) checklist.[18] The search was developed in Embase.com and then translated to other databases by an experienced information specialist (WMB). The search was carried out on February 16, 2023 in the databases Embase.com, Medline ALL via Ovid, and the Cochrane Central Register via Wiley. The search contained the terms imiquimod, cervical dysplasia, and HPV (Table S1). No study registries were searched, but Cochrane Central retrieves the contents of ClinicalTrials.gov and the WHO's International Clinical trials Registry Platform. No authors or subject experts were contacted, and we did not browse unindexed journals in the field. The study protocol was registered in INPLASY (registration no. INPLASY2022110046).

2.2 | Eligibility criteria and study selection

Studies published in the English language with adequate information according to our inclusion criteria and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement were searched.[19] We included retrospective and prospective cohort studies as well as clinical trials that reported the efficacy of topical imiquimod in CIN 2, CIN 3, or persistent hr-HPV infections. Studies that evaluated the efficacy of imiquimod treatment

in intraepithelial lesions or malignancy of other organs, and studies published as conference abstract, narrative review, editorial, letter, or short communication were excluded. The titles and abstracts retrieved from the search strategy were screened for relevance by two authors (AS and HB) independently. Then, they retrieved and reviewed the full texts of the seemingly relevant articles. Any disagreements between AS and HB were resolved through discussion and arbitration by a third author (MK). The reference lists of retrieved articles were searched for possibly missed relevant studies.

2.3 | Data extraction and assessment of risk of bias

The main outcome was the efficacy of topical imiquimod treatment in women with an untreated, histologically proven, CIN 2–3 lesion or women who were persistent hr-HPV-positive. The efficacy of treatment was defined as a histologic regression to CIN 1, complete histologic submission, or negative hr-HPV. The following study characteristics were extracted: name of first author, year of publication, country, study sample size, study design, and treatment protocol. Patients' characteristics were extracted as following: age (years), number of pregnancies, number of sexual partners, history of sexual transmitted disease (yes/no), contraception methods (oral contraception/other hormonal contraception/other), smoking status (yes/no/quit within last 6 months), histology, HPV status (HPV 16/18, HPV 16/18, and other, other hr-HPV, HPV negative or unknown), compliance, and treatment side effects. The methodological quality of the included studies was assessed with the Newcastle-Ottawa Quality Assessment Scale or the risk of bias with the Revised Cochrane risk-of-bias tools for randomized trials. There was one observational study which was assessed by the Newcastle Quality Assessment Scale (www.ncbi.nlm.nih.gov/books/NBK115843/bin/appe-fm3.pdf). This scoring system focuses on selection, comparability, and outcome and each item can be given a number of stars. With these stars the study can be converted to good, fair, or poor quality. All randomized controlled trials were assessed by the revised Cochrane Collaboration's risk-of-bias toll for randomized trials (RoB2),[20] where studies are judged on five different domains. Two independent reviewers (AS and MK) scored each domain of the studies "low risk," "some concern," or "high risk" using the RoB2 tool published in 2019 (https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2). Each study was reviewed on the domains randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result and received on overall score. Discrepancies of both scoring systems were resolved by discussion with a third reviewer (HB).

2.4 | Data synthesis

Results were synthesized by performing random-effects meta-analyses to compute the weighted mean difference (WMD) for continuous variables and the pooled odd ratios (ORs) for binary variables. All pooled estimations are displayed with their 95% confidence intervals (CIs). The mean and standard deviation were calculated based on the method described by Wan et al.[21] if not provided in the study. Existence of heterogeneity among study effect sizes was examined using the I^2 index and the Q-test *P*-value. An I^2 index greater than 75% indicated medium to high heterogeneity. Categorical variables are presented as number (%), and continuous variables as mean ± standard deviation (SD). Statistical significance was defined as a *P*-value <0.05. Publication bias was formally assessed using the Egger test. The analyses were performed using Review Manager (RevMan) version 5.4.1 (the Cochrane Collaboration, 2020).

3 | RESULTS

3.1 | Study selection, study characteristics, and risk of bias of included studies

The primary search strategy yielded 337 citations. After removal of duplications, titles and abstracts of 269 articles were screened. Twenty-four articles were retrieved for a comprehensive review. Finally, five articles involving 463 women with high-grade CIN were included in the analysis (Figure 1). Three studies were randomized controlled trials, one was a randomized trial, and one was a prospective cohort study.

All studies were assessed for risk of bias. Two studies showed good quality, while three showed concerns (Tables S2A,B). Of the three studies, one[22] showed concern regarding differences from intended interventions, and the other two[12,23] showed possible bias in the selection of the reported results. In addition, the trial was prematurely closed because of poor recruitment rate, which may lead to possible patient selection.

The studies spanned from 2007 to 2020. In general, the studies' key inclusion criteria were untreated histologically proven CIN 2–3 with satisfactory colposcopy. Patients with hypersensitivity to imiquimod, cancer, immune deficiency status, pregnancy, or lactation were excluded. Two studies evaluated the effectiveness of topical imiquimod treatment versus placebo/control.[12,22] Three studies compared the effectiveness of topical imiquimod treatment versus LLETZ.[23–25] In three studies, self-applied vaginal suppository was used as an imiquimod applicator.[12,23,25] One study used a self-applied menstrual cup[24] and, in another study, imiquimod was applied weekly by a physician.[22] The outcome measure was assessed by colposcopy-guided biopsy and/or HPV testing. Patients with histological regression to CIN 1 or less, or negative hr-HPV were considered as successfully treated. Details of treatment protocols and follow-up duration are summarized in Table 1.

3.2 | Synthesis of results

Two hundred and thirty-nine of all 463 women (52%) had been treated with topical imiquimod. The mean age was 31 (SD 9.1) years

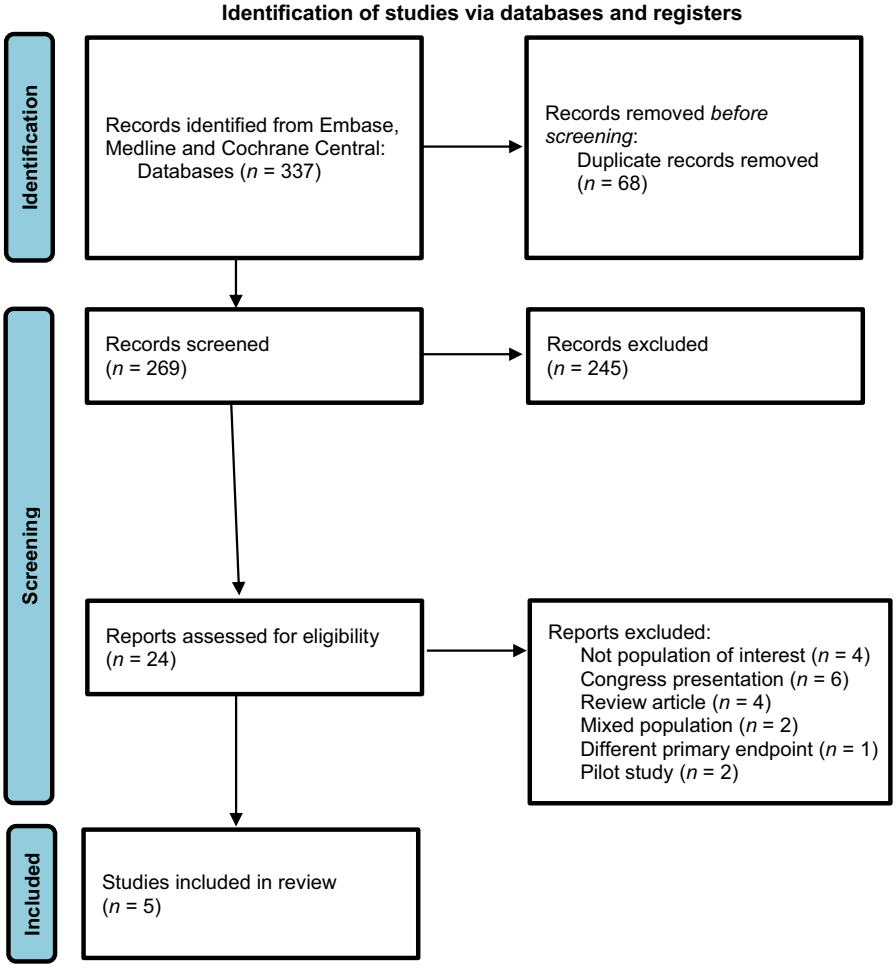

FIGURE 1 PRISMA flow diagram.

versus 32 (SD 10.6) years for the control groups. Four studies reported smoking status; the proportion of daily smokers in the group of women treated with imiquimod was higher than that of the women in control groups (39% vs. 33%). HPV genotype analysis (HPV16, HPV18, and other hr-HPV) had been performed in four studies. This had revealed 87% hr-HPV infections in the imiquimod group and 86% in the control groups at the beginning of the study. The proportions of CIN 2 and CIN 3 status were, respectively, 38% and 62% in the imiquimod group, and 28% and 72% in the control groups. Four studies reported patients' treatment compliance; 82% (158/188) of women in the imiquimod group had completed the protocol without discontinuity. Treatment effectiveness for high-grade CIN was 55% (131/239) for topical imiquimod, 29% (20/69) for placebo, and 93% (106/114) for LLETZ. The clearance rate for HPV was 53% (46/86) in the imiquimod group, versus 66% (60/91) in the group of women treated with LLETZ.

The included articles reported two cases of progression to (micro)invasive disease during imiquimod treatment. One patient was treated with nine applications of imiquimod and subsequently underwent a LLETZ procedure. Treatment was completed with a laparoscopic hysterectomy, where no residual invasive disease was detected. The other patient had a persistent HPV infection and HSIL within the observation period. She received a LLETZ procedure which showed microinvasive adenocarcinoma. No further treatment was required following the resection.

All studies[12,22–25] reported on systemic side effects of imiquimod, mostly according to Common Terminology Criteria for Adverse Events guidelines (grade 0–5). Two studies reported the side effects at any time, which were between 88% and 96%.[22,24] The most common systemic side effect was headache/migraine in 57% (96/168) followed by fatigue in 56% (94/168) and myalgia in 55% (92/168). The most common local side effect was vulvar pain/pruritus in 48% (80/168).

Only one study reported the side effects of placebo,[12] where headache was reported in 21%, fatigue in 35%, myalgia/flu like symptoms in 10% and vulvar pain/pruritus in 38%.

Three studies[23–25] reported on the side effects from a LLETZ procedure, but not all were specified. The most common symptoms were vaginal bleeding (60%), vaginal discharge (57%), and abdominal pain (57%). Almost 6% (6/104) of patients had needed a re-intervention because of postoperative bleeding. There was no report of a subsequent pregnancy in the included studies.

TABLE 1 Overview of clinical studies.

Reference	Study design	Number of patient-groups	Patient age	Lesion grade	HPV+	Dosage imi 5% (application details)	Treatment duration	Follow-up duration	Regression to CIN 1 or less	Progression	HPV clearance (%)
Grimm et al.[12]	RCT	59[a]: imi ($n=30$), PCB ($n=29$)	Mean: imi 31.8	CIN 2,3	59/59 (high risk types)	6.25 mg, 1–3 times/week	16 weeks	20 weeks	IMI 22/30 (73%), PCB 11/28 (39%)	Imi 0/28 (0%), PCB 3/28 (11%)[a]	Imi 18/30 (60%), PCB 4/28 (14%)
			($\sigma=7.3$), PCB 29.2 ($\sigma=6.1$)			Vaginal suppositories by patient					
Fonseca et al.[22]	RT	85: imi ($n=45$), control ($n=40$)	Median: imi 32 (IQR 10), control 36 (IQR 13)	CIN 2,3	65/85	250 mg of 5% imi cream, once a week, applied by doctor	12 weeks	None	Imi 24/45 (53.3%), control 9/40 (22.5%)	Imi 1/45 (2.2%)[a], control 1/40 (2.5%)[a]	NR
Cokan et al.[24]	RCT	104: imi ($n=52$), LLETZ ($n=52$)	Mean: all 28 ($\sigma=4.4$), imi 28.3 ($\sigma=4.2$), LLETZ 27 ($\sigma=4.6$)	HSIL (CIN 2p16+, CIN 3)	NT	Self-applied imi 5% 250 mg in menstrual cup, 3 times/week for a duration of 6–8 h	16 weeks	20 weeks	Imi 27/52 (51.9%), LLETZ 48/52 (92.3%)	NR (no progression to invasive disease)	NR
Hendriks et al.[25]	PS	123: imi ($n=61$), LLETZ ($n=62$)	Mean: imi 33.3 ($\sigma=9.1$), LLETZ 35.2 ($\sigma=7.0$)	CIN 2,3	100/123	Self-applied imi 5% dose of 6.25 mg (half sachet) by vaginal applicator, 3 times/week	8 or 16 weeks	10 or 20 weeks	Imi 26/61 (43%), LLETZ 58/62 (94%)	IMIS 4/61 (6.6%)	Imi 24/35 (69%), LLETZ 33/49 (67%)
Polterauer et al.[23]	RCT	93: imi ($n=51$), LLETZ ($n=42$)	Median: imi 30.1 (IQR 26.7–32.3), LLETZ 31.4 (IQR 27.6–36.4)	CIN 2 (30 years or older), CIN 3 (18 years or older)	86/93	Self-applied vaginal suppositories 6.25 mg imi: in weeks 1–2, once/week; weeks 3–4, 2 times/week; until week 16, 3 times/week	16 weeks	6 months	Imi 32/51 (63%), LLETZ NR	Imi 1/51[a]	Imi 22/51 (43.1), LLETZ 27/42 (64.3%)

Abbreviations: σ, standard deviation; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; imi, imiquimod; LLETZ, large loop excision of the transformation zone; NR, not reported; PCB, placebo; PS, prospective study; RCT, randomized controlled trial.

[a](Micro)invasive disease.

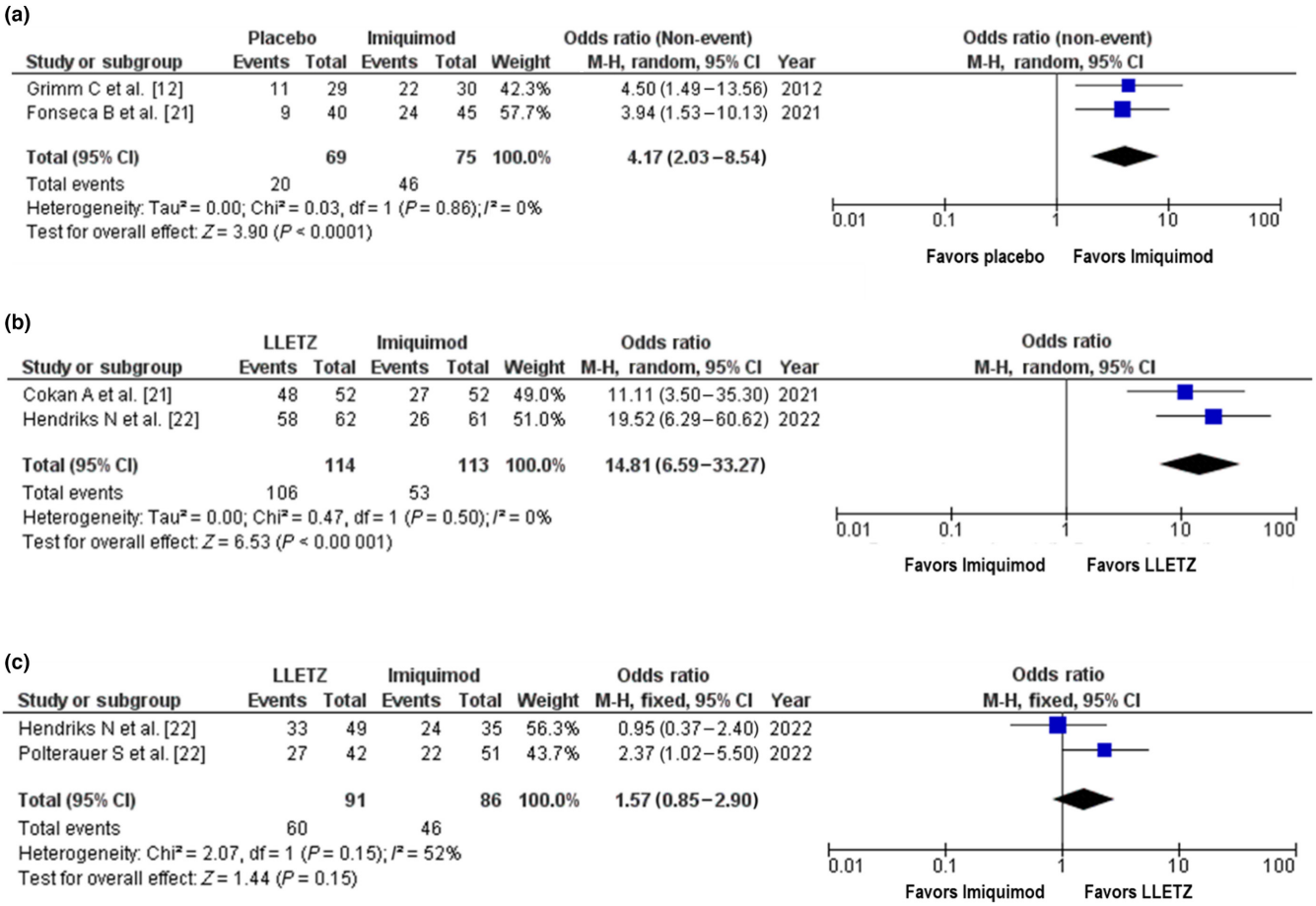

FIGURE 2 (a) Forest plot displaying odds ratios (ORs) of women with high-grade squamous intraepithelial lesion (HSIL) treated with topical imiquimod relative to placebo (histological regression). (b, c) Forest plot displaying ORs of women with HSIL treated with topical imiquimod relative to large loop excision of the transformation zone (LLETZ): histological regression (b); HPV clearance (c).

3.3 | Meta-analysis

Figure 2a illustrates a forest plot displaying ORs of women treated with topical imiquimod versus placebo. Women treated with topical imiquimod had a significantly higher odds of histological regression to CIN 1 or less compared with placebo or control (OR 4.17, 95% CI 2.03–8.54). Two studies compared the effectiveness of topical imiquimod and LLETZ; women treated with LLETZ had a 14.81 higher odds (95% CI 6.59–33.27) of histological regression to CIN 1 or less (Figure 2b). The OR of HPV clearance of women treated with topical imiquimod group did not differ from that of women treated with LLETZ (OR 1.53, 95% CI 0.62–3.77) (Figure 2c). None of the studies had compared HPV clearance between women treated with topical imiquimod and women treated with placebo.

4 | DISCUSSION

The results of this meta-analysis and systematic review suggest that imiquimod is more effective than placebo but less effective than LLETZ in women with high-grade CIN. Imiquimod treatment is probably safe with a 0.8% chance of progression to (micro)invasive disease (2/239 patients). We also found that side effects of imiquimod were common. According to our findings, imiquimod may not be an appropriate treatment for all women with high-grade CIN.

In present study, imiquimod treatment shows a moderate (55%) histological regression rate. Therefore, it is not recommended as a first-line treatment for all high-grade CIN. However, the present study provides evidence for counseling women when considering an alternative treatment for a specific group of patients. Imiquimod was previously explored as an alternative to LLETZ treatment, with a lower efficacy.[12,26,27] In a previous analysis of patients' preferences for LLETZ versus imiquimod, women who chose imiquimod treatment were those who were interested in conceiving or at high risk of premature birth, and therefore also willing to accept a lower success rate.[14]

In addition, imiquimod may be a suitable treatment option for recurrent CIN, in order to prevent repeated LLETZ procedures. In particular, women who wish to become pregnant in the near future may benefit from this treatment. However, to date, there is only one study evaluating the efficacy of imiquimod in this group of women—a retrospective study of only 18 patients, which reported a success rate of 61%.[28] Further research is therefore warranted.

One of the possible options is to carefully select patients for imiquimod therapy. A previous study on the immune microenvironment in patients with CIN and the implication of immunotherapy demonstrated that the pre-existing immune composition may reflect the potential for lesion regression and might be a possible immune biomarker for immunotherapy in high-grade CIN.[29,30] Biomarkers could be useful in selecting patients, counseling patients, and preventing patients with a low likelihood of responding from experiencing unnecessary side effects.

The PRedICT-TOPIC study aims to investigate the potential of immune-related biomarkers on the clinical response of patients with high-grade CIN to imiquimod (Clinical Trials.gov NCT05405270).

Based on the findings of this review, we are unable to propose different treatment effects for CIN 2 versus CIN 3, because the two conditions were essentially not differentiated in most studies. Hence, no subgroup analysis could be performed in the meta-analysis. In addition, the patient should be informed about the possibility of active surveillance. CIN 2 is associated with an overall high spontaneous regression rate of 55%—even higher in young women—and with a low probability of 0.3% of progression to cervical cancer. Thus, conservative treatment of CIN 2 should always be considered, especially in fertile women.[31,32] By contrast, CIN 3 has a spontaneous regression rate of only 28%, so expectant management is not recommended for these patients.

The ideal study design would be to compare LLETZ versus imiquimod versus observation/placebo in women with high-grade CIN. The TOPIC trial attempted this study design, but it was prematurely stopped due to lagging inclusions. The study changed to an open-label design, because of strong patient preference for treatment modalities.[33]

5 | STRENGTHS AND LIMITATIONS

This systematic review and meta-analysis include all available recent studies. Overall, the included studies were small in size and the number of women treated with imiquimod was low. Some studies had prematurely stopped because of a slow inclusion rate or had changed their methods.[12,23,25] This is probably due to uncertain efficacy of imiquimod, treatment duration, and side effects of imiquimod. Also, all studies had a considerable number of dropouts and dosage reductions.[12,24,25] Dosage and duration of imiquimod application differed between studies. Weekly dosages for 12 weeks[22] appear to produce comparable results to longer and higher dosages of imiquimod. Moreover, the success rate was still substantially high (63%)[24] in the group of women who lowered in frequency or stopped their treatment. The question arises whether patients could be relieved from side effects by reducing treatment frequency or duration. In addition, different control groups were used (placebo vs. LLETZ) and outcome measures of the studies differed. One study identified itself as a randomized controlled trial but had no intervention as a control group.[22] The small study size made it impossible to perform subgroup analysis and to differentiate between the effect of imiquimod in, for instance, CIN 2 and CIN 3. Finally, treatment efficacy is limited for patients with small high-grade CIN lesion according to the criteria for each trial. Considering the short follow-up period, the subsequent pregnancy effect was not demonstrated in any study.

In high-grade CIN treatments, LLETZ should remain the gold standard. In the case of selected women who prefer non-invasive treatment, imiquimod may be a useful alternative modality where our data help in making an informed decision about treatment. In comparison with LLETZ, the success rate of imiquimod treatment is moderate. To recommend further implementation of imiquimod, a higher success rate is required; biomarkers for patients' responsiveness are warranted and may help in patient selection and in increasing imiquimod's efficacy.

5.1 | Comparison with the existing literature

In addition to imiquimod, other topical treatments could be an option in the treatment of high-grade dysplasia. For example, 5-fluorouracil and cidofovir have shown promising results.[34] The results seem to be comparable to imiquimod, but need validation in future studies. None of these options seem to be an immediate equal alternative for a LLETZ procedure at this point.

Moreover, there could be a general discussion about the need to explore the different treatment modalities of treatment of high-grade CIN after the introduction of HPV vaccination. However, the global female HPV vaccine coverage still does not exceed 50%, even in high-income countries.[35] Consequently, HPV-related diseases are likely to remain a problem in the future.

6 | CONCLUSION AND IMPLICATIONS

Histological regression rates were highest in patients treated with LLETZ, followed by topical imiquimod and placebo, at 93%, 55%, and 29%, respectively. Both LLETZ and imiquimod have side effects. While most imiquimod side effects occur during treatment, side effects of LLETZ are commonly experienced after treatment, with a long-term effect on subsequent pregnancies. Currently, LLETZ is the gold standard in treating high-grade CIN. In a subgroup of women, imiquimod may be used as an alternative treatment. Future research should focus on improving the efficacy of imiquimod treatment, by better patient selection through possible biomarkers, and on investigating the differences in response between CIN 2 and CIN 3.

AUTHOR CONTRIBUTIONS

A. J. M. van de Sande, M. Kengsakul, A. J. Kruse, H. C. van Doorn, F. J. van Kemenade, and H. J. van Beekhuizen designed the study. A. J. M. van de Sande and H. J. van Beekhuizen collected the data. A. J. M. van de Sande, M. Kengsakul, and H. J. van Beekhuizen analyzed the data. A. J. M. van de Sande, M. Kengsakul, and H. J. van

Beekhuizen drafted the manuscript. All authors actively participated in interpreting the results and revising the paper and all authors approved the final manuscript.

FUNDING INFORMATION

This study was not funded.

CONFLICT OF INTEREST STATEMENT

The authors declare no financial conflict of interests. Some of the authors of this article are co-authors of one of the papers included in the systematic review.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

INPLASY REGISTRATION NUMBER

INPLASY2022110046, DOI number is 10.37766/inplasy2022.11.0046 (https://inplasy.com/?s=2022110046).

ORCID

A. J. M. van de Sande https://orcid.org/0000-0002-7773-2758
M. Kengsakul https://orcid.org/0000-0003-1638-1453
M. M. Koeneman https://orcid.org/0000-0003-4650-9032
M. Jozwiak https://orcid.org/0000-0003-3822-0749
C. G. Gerestein https://orcid.org/0000-0003-0490-2258
A. J. Kruse https://orcid.org/0000-0002-2460-6483
E. M. G. van Esch https://orcid.org/0000-0001-7387-5922
P. J. de Vos van Steenwijk https://orcid.org/0000-0002-9822-9529
C. L. P. Muntinga https://orcid.org/0000-0002-2886-3436
W. M. Bramer https://orcid.org/0000-0003-2681-9180
H. C. van Doorn https://orcid.org/0000-0003-1062-4485
F. J. van Kemenade https://orcid.org/0000-0002-4225-4354
H. J. van Beekhuizen https://orcid.org/0000-0001-8899-7412

REFERENCES

1. Koshiol J, Lindsay L, Pimenta JM, Poole C, Jenkins D, Smith JS. Persistent human papillomavirus infection and cervical neoplasia: a systematic review and meta-analysis. *Am J Epidemiol*. 2008;168:123-137.
2. Santesso N, Mustafa RA, Schunemann HJ, et al. World Health Organization guidelines for treatment of cervical intraepithelial neoplasia 2-3 and screen-and-treat strategies to prevent cervical cancer. *Int J Gynaecol Obstet*. 2016;132:252-258.
3. Guido R, Lonky NM, Diedrich J. Secondary prevention of cervical cancer part 3: evidence-based management of women with cervical intraepithelial neoplasia. *Clin Obstet Gynecol*. 2014;57:302-315.
4. McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol*. 2008;9:425-434.
5. Martin-Hirsch PP, Paraskevaidis E, Bryant A, Dickinson HO. Surgery for cervical intraepithelial neoplasia. *Cochrane Database Syst Rev*. 2013 Dec 4;CD001318.
6. Kyrgiou M, Athanasiou A, Kalliala IEJ, et al. Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease. *Cochrane Database Syst Rev*. 2017;11:CD012847.
7. Spracklen CN, Harland KK, Stegmann BJ, Saftlas AF. Cervical surgery for cervical intraepithelial neoplasia and prolonged time to conception of a live birth: a case-control study. *BJOG-Int J Obstet Gy*. 2013;120:960-965.
8. Crane JM. Pregnancy outcome after loop electrosurgical excision procedure: a systematic review. *Obstet Gynecol*. 2003;102:1058-1062.
9. Kyrgiou M, Athanasiou A, Paraskevaidi M, et al. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. *BMJ*. 2016;354:i3633.
10. Tyring SK, Arany II, Stanley MA, et al. Mechanism of action of imiquimod 5% cream in the treatment of anogenital warts. *Prim Care Update Ob Gyns*. 1998;5:151-152.
11. Voss FO, van Beurden M, Jordanova ES. Topical imiquimod as first-line treatment for vulvar intraepithelial neoplasia. *Lancet*. 2022;399:1755-1757.
12. Grimm C, Polterauer S, Natter C, et al. Treatment of cervical intraepithelial neoplasia with topical imiquimod a randomized controlled trial. *Obstet Gynecol*. 2012;120:152-159.
13. National Institute for Public Health and Environment. *Framework for the execution of the Dutch cervical cancer screening programme*. RIVM; 2021.
14. Koeneman MM, Essers BA, Gerestein CG, et al. Treatment of cervical intraepithelial neoplasia: patients preferences for surgery or immunotherapy with imiquimod. *J Immunother*. 2017;40:148-153.
15. Hecken JM, Rezniczek GA, Tempfer CB. Innovative diagnostic and therapeutic interventions in cervical dysplasia: a systematic review of controlled trials. *Cancers (Basel)*. 2022;14:2670.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
17. Rethlefsen ML, Kirtley S, Waffenschmidt S, et al. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. *Syst Rev*. 2021;10:39.
18. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008-2012.
19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453-1457.
20. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Assessing risk of bias in a randomized trial. *Cochrane Handbook for Systematic Reviews of Interventions*. *Cochrane*; 2019:205-228.
21. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
22. Fonseca BO, Possati-Resende JC, Salcedo MP, et al. Topical imiquimod for the treatment of high-grade squamous intraepithelial lesions of the cervix: a randomized controlled trial. *Obstet Gynecol*. 2021;137:1043-1053.
23. Polterauer S, Reich O, Widschwendter A, et al. Topical imiquimod compared with conization to treat cervical high-grade squamous intraepithelial lesions: multicenter, randomized controlled trial. *Gynecol Oncol*. 2022;165:23-29.
24. Cokan A, Pakiz M, Serdinsek T, et al. Comparison of conservative treatment of cervical intraepithelial lesions with imiquimod with standard excisional technique using LLETZ: a randomized controlled trial. *J Clin Med*. 2021;10:10.

25. Hendriks N, Koeneman MM, van de Sande AJM, et al. Topical imiquimod treatment of high-grade cervical intraepithelial neoplasia (TOPIC-3): a nonrandomized multicenter study. *J Immunother*. 2022;45:180-186.
26. Lin CT, Qiu JT, Wang CJ, et al. Topical imiquimod treatment for human papillomavirus infection in patients with and without cervical/vaginal intraepithelial neoplasia. *Taiwan J Obstet Gyne*. 2012;51:533-538.
27. Pachman DR, Barton DL, Clayton AC, et al. Randomized clinical trial of imiquimod: an adjunct to treating cervical dysplasia. *Am J Obstet Gynecol*. 2012;206:42.e1-42.e7.
28. van de Sande MK AJM, van Baars R, Gerestein CG, Kruse AJ, van Kemenade FJ, van Beekhuizen HJ. Treatment of residual or recurrent CIN with topical imiquimod: a retrospective study. Arch. *Microbiol Immunol*. 2020;4:95-109.
29. Abdulrahman Z, Hendriks N, Kruse AJ, et al. Immune-based biomarker accurately predicts response to imiquimod immunotherapy in cervical high-grade squamous intraepithelial lesions. *J Immunother Cancer*. 2022;10:10.
30. Muntinga CLP, de Vos van Steenwijk PJ, Bekkers RLM, van Esch EMG. Importance of the immune microenvironment in the spontaneous regression of cervical squamous intraepithelial lesions (cSIL) and implications for immunotherapy. *J Clin Med*. 2022;11:11.
31. Tainio K, Athanasiou A, Tikkinen KAO, et al. Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis. *BMJ*. 2018;360:k499.
32. Loopik DL, Bentley HA, Eijgenraam MN, IntHout J, Bekkers RLM, Bentley JR. The natural history of cervical intraepithelial neoplasia grades 1, 2, and 3: a systematic review and meta-analysis. *J Low Genit Tract Dis*. 2021;25:221-231.
33. Koeneman MM, Kruse AJ, Kooreman LF, et al. Preliminary stop of the TOPical imiquimod treatment of high-grade cervical intraepithelial neoplasia (TOPIC) trial. *BMC Cancer*. 2017;17:110.
34. Desravines N, Miele K, Carlson R, Chibwesha C, Rahangdale L. Topical therapies for the treatment of cervical intraepithelial neoplasia (CIN) 2-3: a narrative review. *Gynecol Oncol Rep*. 2020;33:100608.
35. Bruni L, Saura-Lazaro A, Montoliu A, et al. HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010-2019. *Prev Med*. 2021;144:106399.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: van de Sande AJM, Kengsakul M, Koeneman MM, et al. The efficacy of topical imiquimod in high-grade cervical intraepithelial neoplasia: A systematic review and meta-analysis. *Int J Gynecol Obstet*. 2023;00:1-9. doi:10.1002/ijgo.14953