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Systematic Review

Imiquimod for Cervical and Vaginal Intraepithelial Neoplasia

A Systematic Review and Meta-analysis

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OBJECTIVE: To evaluate the treatment efficacy and the risk of adverse events of imiquimod for cervical intraepithelial neoplasia (CIN) and vaginal intraepithelial neoplasia (VAIN), compared with placebo or no intervention.

DATA SOURCES: We searched Cochrane, PubMed, ISRCTN registry, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform up to November 23, 2022.

METHODS OF STUDY SELECTION: We included randomized controlled trials and prospective nonrandomized studies with control arms that investigated the efficacy of imiquimod for histologically confirmed CIN or VAIN. The primary outcomes were histologic regression of the disease (primary efficacy outcome) and treatment discontinuation due to side effects (primary safety outcome). We estimated pooled odds ratios (ORs) of imiquimod, compared with placebo or no intervention. We also conducted a meta-analysis of the proportions of patients with adverse events in the imiquimod arms.

TABULATION, INTEGRATION, AND RESULTS: Four studies contributed to the pooled OR for the primary efficacy outcome. An additional four studies were available for meta-analyses of proportions in the imiquimod arm. Imiquimod was associated with increased probability of regression (pooled OR 4.05, 95% CI 2.08–7.89). Pooled OR for CIN in the three studies was 4.27 (95% CI 2.11–8.66); results of one study were available for VAIN (OR, 2.67, 95% CI 0.36–19.71). Pooled probability for primary safety outcome in the imiquimod arm was 0.07 (95% CI 0.03–0.14). The pooled probabilities (95% CI) of secondary outcomes were 0.51 (0.20–0.81) for fever, 0.53 (0.31–0.73) for arthralgia or myalgia, 0.31

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(0.18–0.47) for abdominal pain, 0.28 (0.09–0.61) for abnormal vaginal discharge or genital bleeding, 0.48 (0.16–0.82) for vulvovaginal pain, and 0.02 (0.01–0.06) for vaginal ulceration.

CONCLUSION: Imiquimod was found to be effective for CIN, whereas data on VAIN were limited. Although local and systemic complications are common, treatment discontinuation is infrequent. Thus, imiquimod is potentially an alternative therapy to surgery for CIN.

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Imiquimod is a Toll-like receptor 7 and 8 agonist. Although its exact mechanism of action remains unclear, imiquimod has antiviral and antitumor activities.[1,2] Imiquimod induces the production of several cytokines, including interferon-α, interleukin-6, and interleukin-8, through nuclear factor-kappa β-mediated pathway, and stimulates an immune response.[1,3]

Imiquimod is approved for the treatment of external genital warts, actinic keratosis, and basal cell carcinoma by the U.S. Food and Drug Administration.[1] Imiquimod is also used off-label for the treatment of several neoplasms, including vulvar intraepithelial neoplasia, melanoma in situ, extramammary Paget's disease, and cutaneous metastases of malignant tumors.[1,4] Regarding vulvar intraepithelial neoplasia, treatment with imiquimod is recommended by several clinical guidelines.[5,6]

Cervical intraepithelial neoplasia (CIN) and vaginal intraepithelial neoplasia (VAIN) are precancerous conditions associated with human papillomavirus (HPV) infection.[7,8] The standard therapy for CIN 2–3 is surgical removal of the lesion, but the surgery increases the risk of preterm birth in future pregnancies.[8,9] Previous studies suggest that imiquimod is effective for CIN, when compared with placebo or no intervention,[10,11] and is considered as an alternative therapy for patients who want to avoid surgical treatment.[10,12] For VAIN, several treatment modalities have been used, including surgical treatment, carbon dioxide laser, 5-fluorouracil, and radiation therapy. However, recurrence is common, and a standard treatment for VAIN 2–3 has not been established.[13–16] Imiquimod is one of the potentially effective treatments for VAIN 2–3.[7,17]

Although imiquimod is a possible treatment option for CIN and VAIN, adverse events related to vaginal use of imiquimod have not been well investigated. When imiquimod is applied for CIN and VAIN, systemic adverse events, including fever, arthralgia, myalgia, and abdominal pain, can be frequent[10,11,17–19]; systemic adverse events were observed in nearly 90% of patients in some randomized controlled trials (RCTs).[11,19] Further consideration of imiquimod as a treatment option for CIN and VAIN requires a comprehensive evaluation of its therapeutic effect and risk of adverse events. This systematic review and meta-analysis aimed to evaluate the treatment effects and adverse effects of imiquimod for CIN and VAIN, compared with placebo or no intervention.

SOURCES

A review protocol was developed and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines.[20] The primary outcomes were histologic regression of the disease (primary efficacy outcome), including downgrading from high-grade lesions (CIN 2–3 and VAIN 2–3) to normal findings or low-grade lesions (CIN 1 and VAIN 1), and treatment discontinuation due to side effects (primary safety outcome). Secondary outcomes were as follows: fever, arthralgia or myalgia, abdominal pain, abnormal vaginal discharge or genital bleeding, vulvovaginal pain, vaginal ulceration, adverse effects that persisted for more than 2 weeks after treatment discontinuation, and HPV clearance.

The protocol for this study was registered in PROSPERO before the initiation of the review (CRD42022377982).

We included RCTs and prospective nonrandomized studies with control arms that investigated the efficacy of imiquimod for histologically confirmed CIN or VAIN. Single-arm studies were excluded to maintain the quality of included studies. The results of the non-RCTs were used only for the analysis of adverse events. Studies that did not compare the treatment effects of imiquimod with those of a placebo or no intervention were used only to estimate absolute event rates in the imiquimod arm (for example, studies in which the interventions in the control arm was surgery).

We searched the following electronic databases without language restrictions from inception to November 23, 2022: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, ISRCTN registry, ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform. Additionally, we searched websites (drug@FDA and drug company websites) and the references of articles in the full-text screening and review articles on CIN or VAIN found during screening.

Appendix 1, available online at http://links.lww.com/AOG/D231, shows the full search strategy for each database. Briefly, we used "imiquimod" to search clinical trial registries and combination of "imiquimod" and combined the term with broader MeSH terms for cervical intraepithelial neoplasia and vaginal diseases to search CENTRAL and PubMed.

STUDY SELECTION

Two reviewers independently screened all studies. Any disagreement was resolved through discussion with a third reviewer. Two independent reviewers extracted data by using a predesigned data-extraction form. Any disagreements were resolved by discussion with a third reviewer. The following data were extracted: study characteristics (setting, sample size, interventions); patient characteristics (age, proportion of recurrent diseases, proportion of low-grade diseases [CIN 1, VAIN 1]); characteristics of imiquimod treatment (dosage form, application method, weekly dose, dose reduction protocol, treatment period, preventive measures for local symptoms); and outcomes of interest. Whenever possible, we asked the authors of the included articles about uncertain data. For unpublished studies, we contacted the researchers whenever possible to inquire about their status and results.

The risk of bias was assessed independently by two reviewers. The general risk of bias of RCTs and non-RCTs was evaluated using RoB 2 (version 2 of the Cochrane risk-of-bias tool)[21] and ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions),[22] respectively. Furthermore, we added a post hoc risk of bias assessment of the prevalence of adverse events, which was difficult to evaluate using RoB 2 or ROBINS-I. We evaluated three domains in a recently developed tool[23]: representativeness of the study samples, nonresponse bias, and information bias.

We conducted intention-to-treat analyses of treatment effects. For adverse events, patients who started the allocated treatment were analyzed, because including patients who did not start the allocated treatment can lead to the underestimation of the risk of adverse events. For the primary efficacy outcome (histologic regression of the disease), fever, arthralgia or myalgia, abdominal pain, abnormal vaginal discharge or genital bleeding, and HPV clearance, we calculated odds ratios (ORs) with 95% CIs using a random-effects model (inverse variance model). For primary safety outcome and vaginal ulceration, we conducted meta-analyses of proportions in the imiquimod treatment arms (generalized linear mixed model).[24] For vulvovaginal pain, we calculated ORs with 95% CI using a fixed effects Mantel Haenszel method with no continuity correction, because this outcome was expected to be rare in the control group.[25] We also used the estimated ORs and corresponding uncertainty, together with the point estimate of the pooled event rate in the control arms, to estimate absolute risk difference of events. In a post hoc sensitivity analyses, we excluded non-RCTs from the analyses. We also performed sensitivity analyses using the inverse variance method with arcsine transformation to provide individual study weights because these weights are not available in meta-analyses of proportions using a generalized linear mixed model.[24] To explore possible sources of heterogeneity, we conducted preregistered (ie, prespecified in the protocol) subgroup analyses by type of disease (CIN or VAIN), application method (self-applied or physician-applied), average weekly dose (18.75 mg/week or less of imiquimod or more than 18.75 mg/week of imiquimod), and treatment period (8 weeks or less or more than 8 weeks). The cutoff for the dichotomization was prespecified based on our clinical experience.[17] The difference between subgroups was evaluated using the *P*-value for the test for subgroup differences, and by visually inspecting the point estimates and 95% CIs of subgroups in forest plots. In sensitivity analyses, we meta-analyzed proportions of patients that experienced the primary efficacy outcome, fever, arthralgia or myalgia, abdominal pain, abnormal vaginal discharge or genital bleeding, vulvovaginal pain, and HPV clearance.

We evaluated heterogeneity between the studies using I^2 statistics. We used R 4.2.2 with packages meta, version 6.1–0. We assessed the certainty of the evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.[26]

RESULTS

Figure 1 shows a flowchart of study selection. We identified 846 records using the databases and registries. After removing duplicates, two authors independently screened 622 records with the titles and abstracts and assessed 42 full-text records for eligibility. Among 42 records, we further excluded 28 records: records related to the same study as other records (n=16), wrong topic (n =8), nonprospective studies (n=1),[27] single-arm studies (n=2), and uncertain histologic evaluation before treatment (n=1).[28] For six records, which might meet the inclusion criteria, we were unable to retrieve reports: ongoing studies or manuscripts in preparation (n=3),[29–31] study was not started (n=1),[32] finished study data were not

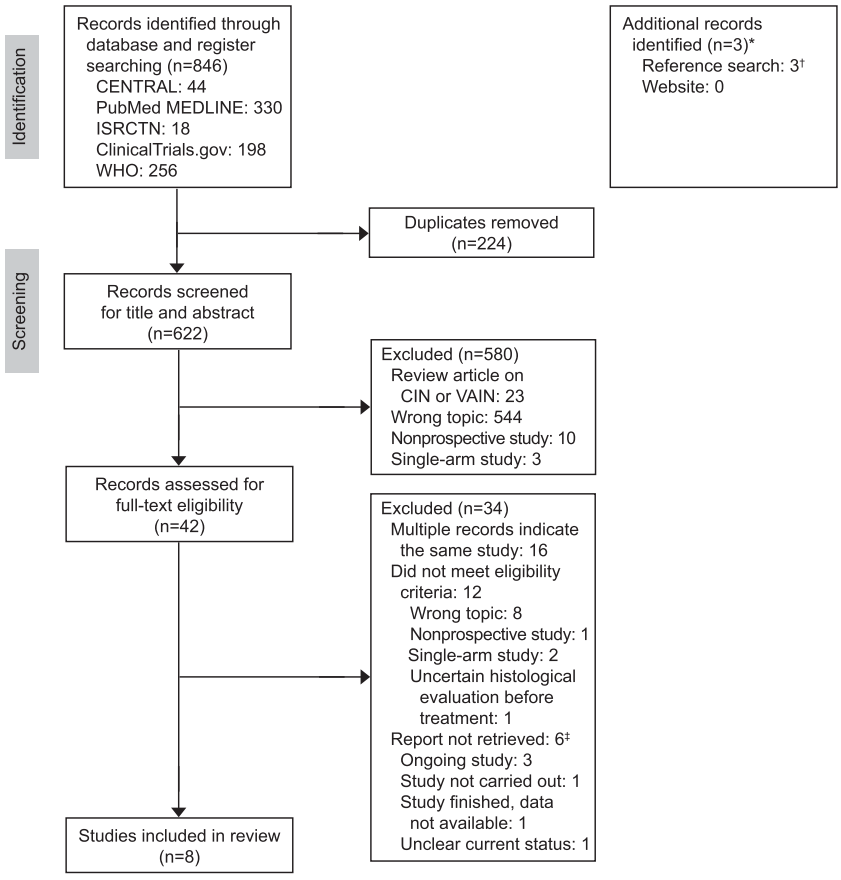

Fig. 1. Study selection. *Additional records excluded for multiple records indicate the same study (n=1), nonprospective study (n=1), and single-arm study (n=1). †Reference lists of 23 review articles identified in the first screening and reference lists of articles that proceeded to the second screening were reviewed. ‡We contacted the investigators in case of records that were not retrieved. ISRCTN, International Standard Randomised Controlled Trial Number; WHO, World Health Organization International Clinical Trials Registry Platform; CIN, cervical intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia.

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available (n=1),[33] and unclear current status (n=1).[34] Finally, we included eight studies.

Table 1 presents the general information of the included studies. Of the eight studies included, six were RCT for CIN,[10,11,18,35–37] one was a non-RCT for CIN,[12] and one was an RCT for VAIN.[19] Two studies[19,35] included patients with recurrent disease. Patients with a previous history of conization were excluded from another study; however, the history of other treatments for CIN was unclear.[37] Seven studies included only patients with CIN 2–3 or VAIN 2–3.[10–12,18,19,36,37] The remaining study partially included patients with CIN 1; this study was excluded from the analysis for treatment effects of imiquimod, because the treatment effect was not investigated after imiquimod treatment and before other interventions were initiated.[35] A placebo or no intervention arm was included in three studies.[11,19,36] In an RCT, Fonseca et al[10] treated patients in the control arm with loop electrosurgical excision procedure; all patients in the imiquimod arm also underwent loop electrosurgical excision procedure after imiquimod treatment. In total, results of four studies were available to compare treatment effects of imiquimod with those of placebo or no-intervention.[10,11,19,36] The remaining four studies were used for the meta-analyses of proportions in the imiquimod arm.[12,18,35,37]

Table 2 provides the details of the imiquimod treatment used in each study. Vaginal suppository was used in three studies,[11,19,37] and 5% imiquimod cream was used in five studies.[10,12,18,35,36] Imiquimod was applied by physicians in two studies using 5% imiquimod cream[10,35] and was self-applied in the remaining studies. Imiquimod was applied a maximum of three times a week in five studies,[11,12,18,36,37] twice weekly in two studies,[19,35] and once weekly in one study.[10] In six studies, *dose reduction* was defined in the protocol as either reduction of a single dose or reduction of frequency.[11,12,18,19,36,37] Vaginal showers by patients or vaginal lavage by physicians were described in five studies.[11,12,18,35,36] The use of imiquimod was continued during menstruation in two studies conducted by the same study group, and vaginal tampons were used to prevent local side effects.[12,36] In three studies, imiquimod treatment was avoided or suspended during menstruation.[11,18,35] The analyzed data in each study are available in Appendix 2, available online at http://links.lww.com/AOG/D232.

Table 1. General Information About the Included Articles

Study	Study Design	Disease	Recurrent Disease (%)	Low-Grade Disease (%)	No. of Arms	Treatment in the Control Arm	Age (y) in the Imiquimod Arm
Grimm et al, 2012 (ITIC)[11]	RCT	CIN	Newly diagnosed only	CIN 2–3 only	2	Placebo	29.2±6.1
Pachman et al, 2012[35],*,†	RCT	CIN	54%‡	CIN 1 (39%)§	2	Excision or laser	30±8.92
Tainio et al, 2016[19]	RCT	VAIN	60%‡,‖	VAIN 2–3 only	3	Observation or laser	49.5 (35–67)¶
Koeneman et al, 2017 (TOPIC)[36]	RCT	CIN	Newly diagnosed only	CIN 2–3 only	3#	Observation# or excision	NA
Cokan et al, 2021[18],*	RCT	CIN	Newly diagnosed only	CIN 2–3 only	2	Excision	28.3±4.2
Fonseca et al, 2021[10],**	RCT	CIN	Newly diagnosed only	CIN 2–3 only	2	Excision**	32±10
Hendriks et al, 2022 (TOPIC3)[12],*	Non-RCT	CIN	Newly diagnosed only	CIN 2–3 only	2	Excision	33.3±9.1
Polterauer et al, 2022 (ITIC2)[37],*	RCT	CIN	Unknown††	CIN 2–3 only	2	Excision	31.4 (27.6–36.4)

ITIC, Imiquimod Therapy in Cervical Intraepithelial Neoplasia; RCT, randomized controlled trial; CIN, cervical intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia; TOPIC, TOPical Imiquimod treatment of high-grade Cervical intraepithelial neoplasia; NA, not available.

Data are mean±SD or median (interquartile range) unless otherwise specified.

* Because treatments in the control arms in these studies were neither placebo nor no intervention, data from these studies were used only for meta-analysis of proportion in the imiquimod arm.

† Because treatment effect was not evaluated after imiquimod treatment before other interventions, only data of adverse events during imiquimod treatment were analyzed.

‡ Proportion of recurrent disease in the imiquimod arm.

§ Proportion of CIN 1 in the imiquimod arm.

‖ Including prior treatment history for CIN, vulvar intraepithelial neoplasia, and cervical cancer. Recurrence of VAIN was 20%.

¶ Median (range).

The observation arm was removed from the study after 9 months.

** Patients in both arms underwent surgery. Because the treatment effects of imiquimod and those of without preceding treatment were compared using the surgical specimen, the results of this study were used for comparison of treatment effects. The mean interval±SD between the diagnosis of CIN 2–3 and surgery was 16.0±6.1 weeks in the control group and 21.0±2.6 weeks in the imiquimod group.

†† Patients with a previous history of conization were excluded, but previous history of other treatments for CIN was unknown.

Among the four RCTs included in the analysis for primary efficacy outcome, two were at low overall risk of bias,[10,11] one had some concern for bias,[19] and one[36] was at high risk of bias (Appendix 3A, available online at http://links.lww.com/AOG/D233). Among the seven RCTs included in the meta-analysis for primary safety outcome, two had low risk of bias,[10,11] one had some concern for bias,[19] and four[18,35–37] had high risk of bias (Appendix 3A, http://links.lww.com/AOG/D233). The risk of bias for the non-RCT included in this analysis was high[12] (Appendix 3B, http://links.lww.com/AOG/D233).

Appendix 3C (http://links.lww.com/AOG/D233) shows the results of the risk of bias assessment in the prevalence of primary safety outcome. The risk of bias for the representativeness of the study samples was low in all studies. Nonresponse bias was low in four studies[10,18,19,35] and was high in the other four studies.[11,12,36,37] Information bias was low, except for a preliminary discontinued RCT.[36]

The pooled OR (95% CI) for the primary efficacy outcome was 4.05 (2.08–7.89) (Fig. 2A, Table 3). Heterogeneity between studies was low (I^2=0%). The absolute risk difference was 0.34 (0.18–0.46). Appendix 4, available online at http://links.lww.com/AOG/D233, presents a funnel plot of this analysis. The pooled response rate (95% CI) in the imiquimod arm (sensitivity analysis) was 0.61 (0.52–0.70) (Fig. 2B and Table 4).

The pooled proportion of primary safety outcome (95% CI) was 0.07 (0.03–0.14) (Fig. 3 and Table 4). Heterogeneity between the studies was moderate (I^2=42%) and was mainly due to the single non-RCT results. This study was conducted at three hospitals. Outcomes occurred in 9% (1/11), 13% (5/38), and 58% (7/12) of the patients in different hospitals.[12]

Table 2. Details of Imiquimod Treatment in the Included Articles

Study	Dosage Form (Dose [mg]) of Imiquimod	Physician-Applied or Self-Applied	Treatment Regimen of Imiquimod (/wk)	Method of Dose Reduction	Shower or Vaginal Lavage	Notes
Grimm et al, 2012 (ITIC)[11]	Vaginal suppository (6.25)	Self	Once (wk 1–2) Twice (wk 3–4) 3 times (wk 5–16)	Reduction of single dose (3.125 mg)	Vaginal shower by patients	Suspend application during the 1st 3 days of menstruation
Pachman et al, 2012[35]	5% imiquimod cream (2.5)	Physician	Twice, total 5 occasions		Vaginal lavage by physicians	Suspended during menses; contraceptive diaphragm was placed as a medical barrier
Tainio et al, 2016[19]	Vaginal suppository (12.5)	Self	Once (wk 1–2) Twice (wk 3–8)	Reduction of single dose (6.25 mg)		
Koeneman et al, 2017 (TOPIC)[36]	5% imiquimod cream (12.5)	Self*	3 times for 16 wk	Reduction of frequency: twice/wk to once/wk	Vaginal shower by patients	
Cokan et al, 2021[18]	5% imiquimod cream (12.5)	Self†	3 times for 16 wk	Reduction of frequency: twice/wk to once/wk	Shower by patients	Avoid using imiquimod for the 1st 3 days of menstruation
Fonseca et al, 2021[10]	5% imiquimod cream (12.5)	Physician	Once for 12 wk			
Hendriks et al, 2022 (TOPIC3)[12]	5% imiquimod cream (6.25)	Self*	3 times 8 wk ×2‡	Reduction of frequency: twice/wk to once/wk	Vaginal shower by patients	Treatment was continued during menstruation; tampon use allowed in case of vaginal discharge to prevent local side effects
Polterauer et al, 2022 (ITIC2)[37]	Vaginal suppository (6.25)	Self	Once (wk 1–2) Twice (wk 3–4) 3 times (wk 5–16)	Reduction of single dose (3.125 mg)		

ITIC, Imiquimod Therapy in Cervical Intraepithelial Neoplasia; TOPIC, TOPical Imiquimod treatment of high-grade Cervical intraepithelial neoplasia.

* A vaginal applicator was used.

† A menstrual cup was used.

‡ Biopsy was conducted after the first 8 weeks of imiquimod treatment. The treatment was stopped in case of complete remission (no cervical intraepithelial neoplasia [CIN]). Treatment was continued for the second 8 weeks in cases of histologic regression to CIN 1 or stable disease.

We did not conduct meta-analyses for the ORs of each adverse event associated with imiquimod (secondary outcomes 1–5) in comparison with placebo or no intervention, because results in both arms were available in only one study.[11] No data were available on abdominal pain, or abnormal vaginal discharge or genital bleeding for calculation of ORs and absolute risk differences. The pooled absolute probabilities of adverse events are described in Table 4, and Appendix 5A–F, available online at http://links.lww.com/AOG/D233, show the corresponding forest plots. Heterogeneity of results was large, except for vulvovaginal ulceration.

In two RCTs, three cases of telogen effluvium were reported.[38,39] Because this symptom was first reported in 2019 and has not been reported in imiquimod treatment for other diseases,[38] the presence of measurement bias cannot be ruled out (Table 4). The pooled OR (95% CI) of HPV clearance was 9.50 (2.98–30.27) (Appendix 5G, http://links.lww.com/AOG/D233) (Table 3). The absolute risk difference was 0.47 (0.19–0.69). The pooled

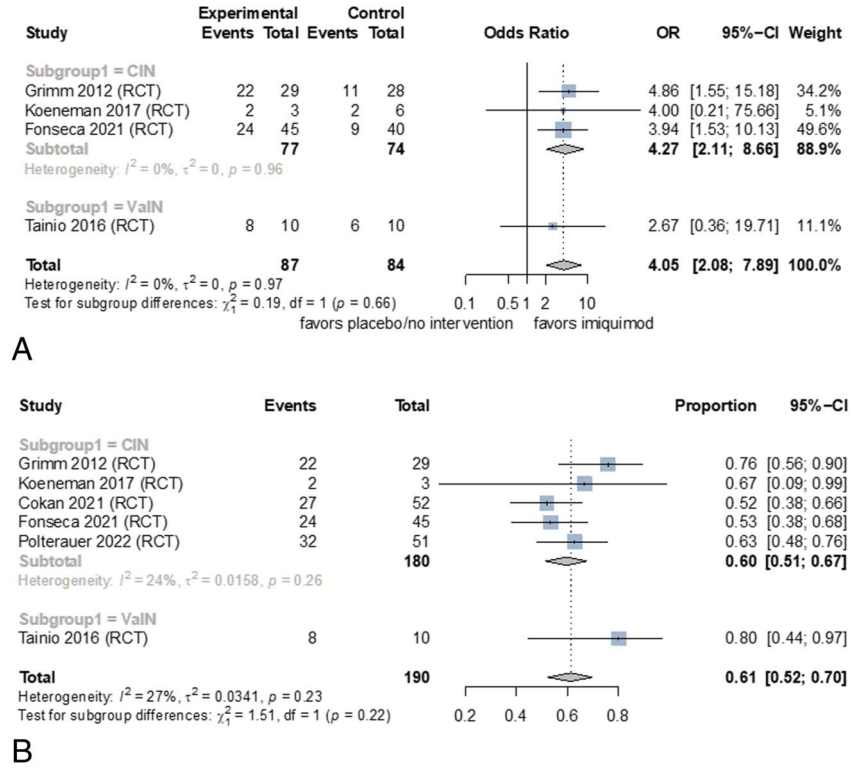

Fig. 2. Forest plots and meta-analysis for histologic regression of the disease (primary efficacy outcome). **A.** Comparison of treatment effects of imiquimod and placebo or no intervention. **B.** Meta-analysis of proportions in the imiquimod arm. CIN, cervical intraepithelial neoplasia; OR, odds ratio; RCT, randomized controlled trial; VAIN, vaginal intraepithelial neoplasia; df, degrees of freedom.

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response rate (95% CI) in the imiquimod arm (sensitivity analysis) was 0.51 (0.35–0.66) (Appendix 5H, http://links.lww.com/AOG/D233) (Table 4).

Appendix 6, available online at http://links.lww.com/AOG/D233, shows results of the post hoc sensitivity analyses excluding the non-RCT. Appendix 7

Table 3. Imiquimod Compared With Placebo or No Intervention

	Outcome	OR (95% CI)	Absolute RD (95% CI)	No. of Participants (No. of Studies)	Certainty of Evidence (GRADE)*
Treatment effect	Histologic regression (primary efficacy outcome)	4.05 (2.08–7.89)	0.34 (0.18–0.46)	171 (4 RCTs[10,11,19,36])	High[†]
	HPV clearance	9.50 (2.98–30.27)	0.47 (0.19–0.69)	71 (2 RCTs[11,19])	Moderate[‡]
Adverse events[§]	Fever	52.20 (6.15–442.83)	0.61 (0.42–0.64)	58 (1 RCT[11])	Moderate[‖]
	Arthralgia or myalgia	27.38 (6.32–118.64)	0.66 (0.32–0.83)	58 (1 RCT[11])	Moderate[‖]
	Vulvovaginal pain	21.64 (4.27–109.62)	0.54 (0.34–0.59)	58 (1 RCT[11])	Moderate[‖]

OR, odds ratio; RD, risk difference; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; HPV, human papilloma virus.

* GRADE Working Group grades of evidence:

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

† We did not downgrade for study quality because the overall risk of bias of two RCTs, which comprise 90% w3 eight in the analysis, was low.

‡ We downgraded a total of one level due to some concerns of risk of bias in the included studies.

§ No data were available for abdominal pain, abnormal vaginal discharge or genital bleeding, and vaginal ulceration.

‖ We downgraded a total of one level due to a possible reporting bias.

Table 4. Proportion of Patients Experiencing Events in the Imiquimod Arm

	Outcome	Observed Range of Probability	Pooled Probability (95% CI)	No. of Participants (No. of Studies)	Comment
Treatment effect	Histologic regression (primary efficacy outcome)	0.52–0.80	0.61 (0.52–0.70)	190 (6 RCTs[10,11,18,19,36,37])	
	HPV clearance	0.37–0.62	0.51 (0.35–0.66)	(3 RCTs[11,19,37])	
Adverse events	Treatment discontinuation due to side effects (primary safety outcome)	0–0.21	0.07 (0.03–0.14)	278 (7 RCTs,[10,11,18,19,35–37] 1 non-RCT[12])	
	Fever	0.11–0.97	0.51 (0.20–0.81)	257 (6 RCTs,[10,11,18,19,35,37] 1 non-RCT[12])	
	Arthralgia or myalgia	0.13–0.81	0.53 (0.31–0.73)	247 (5 RCTs,[10,11,18,35,37] 1 non-RCT[12])	
	Abdominal pain	0.11–0.46	0.31 (0.18–0.47)	135 (4 RCTs[10,18,19,35])	
	Abnormal vaginal discharge or genital bleeding	0.04–0.69	0.28 (0.09–0.61)	217 (4 RCTs,[10,18,35,37] 1 non-RCT[12])	
	Vulvovaginal pain	0.02–0.93	0.48 (0.16–0.82)	230 (5 RCTs,[10,11,18,19,37] 1 non-RCT[12])	
	Vaginal ulceration	0–0.10	0.02 (0.01–0.06)	207 (5 RCTs,[10,11,18,19,35] 1 non-RCT[12])	
	Adverse effects that persisted more than 2 wk after the treatment was discontinued	0–0.067	NA	278 (7 RCTs,[10,11,18,19,35–37] 1 non-RCT[12])	3 cases of telogen effluvium were found; meta-analysis was not conducted considering possible information bias

RCT, randomized controlled trial; HPV, human papillomavirus; NA, not applicable.

(http://links.lww.com/AOG/D233) describes results of the post hoc sensitivity analyses for meta-analysis of proportions using the inverse variance method with arcsine transformation, where the individual study weights are available.

Prespecified subgroup analyses were conducted to explore possible sources of heterogeneity in the results (Appendices 8–11, available online at http://links.lww.com/AOG/D233). The pooled OR for histologic regression of CIN using three studies was 4.27 (95% CI 2.11–8.66); only one small, inconclusive RCT was available for VAIN (OR 2.67, 95% CI 0.36–19.71). Due to the limited number of included studies, subgroup analyses of ORs for HPV clearance were not conducted. In some subgroup analyses, we observed heterogeneity, that is, quite different point estimates among subgroups and substantial lack of overlap in the corresponding CIs. In the subgroup analyses according to the application method, fever (Appendix 9D, http://links.lww.com/AOG/D233), abnormal vaginal discharge or genital bleeding (Appendix 9G, http://links.lww.com/AOG/D233), and vulvovaginal pain (Appendix 9H, http://links.lww.com/AOG/D233) were less frequent in the

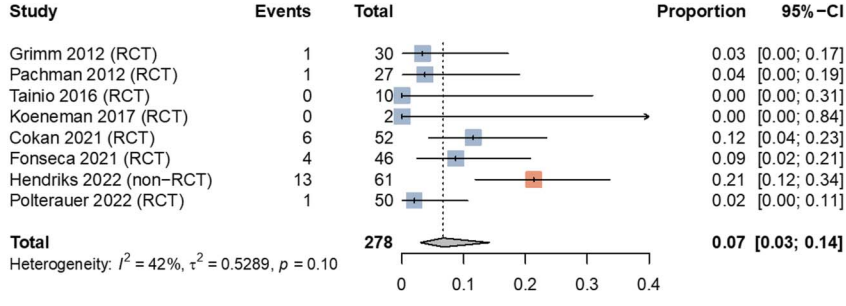

Fig. 3. Forest plots and meta-analysis for treatment discontinuation due to side effects (primary safety outcome). RCT, randomized controlled trial.

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physician-applied group than in the self-applied group. In the subgroup analyses of the treatment period, abdominal pain was less frequent in the 8-weeks-or-less group than in the more-than-8-weeks group (Appendix 11F, http://links.lww.com/AOG/D233). In the remaining subgroup analyses, forest plots did not provide visual indication of heterogeneity between subgroups, CIs between the groups greatly overlapped, or subgroup analyses could not be conducted.

DISCUSSION

The present study showed that the pooled treatment effects of imiquimod, including for CIN and VAIN, were superior to those of placebo or no interventions, both in terms of histologic regression and HPV clearance. However, when examined separately according to disease, whereas the pooled OR for the histologic regression of CIN was 4.27 (95% CI 2.11–8.66), treatment effects of imiquimod for VAIN were estimated with much uncertainty (OR for histologic regression 2.67, 95% CI 0.36–19.71) because there was only one RCT with small sample size. Although minor adverse events were generally frequent, treatment discontinuation occurred in fewer than 10% of the patients, and imiquimod treatment was well tolerated. Our study suggests that imiquimod could be an alternative treatment for patients with CIN who want to avoid surgical treatment in view of the negative effects on future pregnancies. The use of imiquimod for women with CIN who consider future pregnancies is now recommended in the Dutch guidelines.[40] Detailed pretreatment counseling about the possible complications and benefits of imiquimod is important.

Imiquimod treatment for VAIN has recently attracted considerable interest. Observational studies have reported a good treatment response to imiquimod for VAIN.[7,17] A systematic review and meta-analysis including observational studies reported that the pooled complete response to imiquimod for VAIN 2–3 was 76%.[17] A recently published consensus statement on the management of VAIN considered imiquimod as the best topical approach.[41] Although our study cannot conclude that imiquimod is effective for VAIN because of the limited available evidence, it is interesting that the observed heterogeneity of treatment effects of imiquimod in our study was low, suggesting a similar treatment effect on CIN and VAIN, which are both HPV-related premalignancies (Fig. 2).

Understanding possible adverse events of imiquimod and how to deal with them are important to prevent treatment discontinuation. Systemic symptoms could be controlled with nonsteroidal anti-inflammatory drugs or acetaminophen.[4,12,19] Local pain might be decreased by avoiding adhesions of imiquimod to the vulvar skin, and some studies have used tampons to control local pain.[12] In the meta-analysis of the risk for primary safety outcome, heterogeneity was moderate and was due to the non-RCT, which was an outlier. This non-RCT study was conducted in three hospitals, and treatment discontinuation was elevated in one hospital: 1 of 11 (9%), 5 of 38 (13%), and 7 of 12 (58%). The authors argued that the difference in the management of adverse events might have resulted in the difference in treatment discontinuation.[12] Interestingly, the proportions of treatment discontinuation in two hospitals in their study was consistent with those of other studies in our meta-analysis (Fig. 2).

Applying methods of imiquimod to CIN and VAIN has not been standardized (Table 2) and an optimal method of imiquimod administration should be established to balance treatment effects, adverse events, and burden of patient hospital visits. Our subgroup analysis suggested that some adverse events of imiquimod may be lower in the physician-applied method, and in the short treatment duration group. Fonseca et al[10] argued that limited treatment area in their study might have led to the lower frequency of adverse events. Indeed, the treated area has been suggested as a risk factor for systemic responses when imiquimod is used for skin diseases.[1,42] The direction of subgroup analyses results was consistent in that the adverse events were less frequent in the group with less imiquimod use or limited treatment area, suggesting robustness of results. Because the once-weekly application by physicians showed a good treatment response,[10] the treatment effects and adverse events of this method need to be further evaluated in the future studies.

The quality of evidence for comparison was assessed using the GRADE approach. For the primary efficacy outcome, we assessed the certainty of the evidence to be high. We did not downgrade the certainty of the evidence because studies with a low risk of bias accounted for 85% of the weights. For HPV clearance, we downgraded to moderate certainty of evidence due to some concerns of risk of bias in included studies. For fever, arthralgia or myalgia, and vulvovaginal pain, we downgraded to moderate certainty of evidence due to a possible reporting bias.

Among the studies used for the main analysis of primary efficacy outcome, the overall risk of bias was not high,[10,11,19] except for a preliminary discontinued

RCT[36] (Appendix 3A, http://links.lww.com/AOG/D233). Regarding the post hoc risk of bias assessment for the prevalence of adverse events (Appendix 3C, http://links.lww.com/AOG/D233), the risk of bias in the representativeness of the study samples was judged to be low in all studies. This is because, although patients with immunodeficiency, which may affect the immune response including adverse effects, were excluded in most studies, the proportion of these women is limited in most countries.[43] The risk of response bias of the four studies might be thought high because a substantial number of women invited to the study did not participate, resulting in deviation of the sampled population from the studied population. However, candidates for imiquimod treatment in clinical practice will be only those patients who desire imiquimod treatment. Therefore, the studied population might have been closer to the target population than it was to the sampled population, resulting in a lower overall risk of bias. Information bias was low in most studies for primary safety outcome.

This study has several limitations. First, we presented pooled treatment effects, combining CIN and VAIN. This is because CIN and VAIN are both HPV-related intraepithelial premalignant conditions. As shown in Figure 2A, the observed heterogeneity in primary efficacy outcomes between studies was very small, even when we combined studies investigating CIN and VAIN. Therefore, we believe that the pooled treatment effects, combining CIN and VAIN, provide useful information for clinicians. However, it should be noted that the treatment effects of imiquimod for VAIN are inconclusive owing to the limited sample size.

Second, although we described the pooled probabilities of secondary adverse events, the observed heterogeneity was high except for vaginal ulceration. To account for the uncertainty in pooled results, we also show the observed probability ranges (Table 4). Despite this uncertainty, we believe that we have provided the best available evidence on the adverse effects of vaginal use of imiquimod. Third, although some publication bias might have existed, we attempted to obtain unpublished data by contacting the authors of the studies that potentially met our eligibility criteria to minimize the effect of publication bias. Fourth, although most systemic adverse events of imiquimod were transient and disappeared after treatment discontinuation,[44] three cases of telogen effluvium were identified. In all cases, hair loss was reversible and recovered within 2 to 9 months.[38,39] Telogen effluvium was reported in only the above three cases out of more than 500 cases, including observational studies.[38,39] However, the incidence of telogen effluvium should be evaluated further in future studies considering possible information bias resulting in underestimation of incidence. Finally, patients with recurrent CIN or immunodeficiency were not well investigated in the included studies. However, the results of observational studies are promising.[45,46] Imiquimod may also be a good treatment option for patients with recurrent or residual CIN after surgical treatment, because repeated surgery further increases the risk of preterm birth.[9] The results of ongoing studies including these patients are awaited.[30,31]

In conclusion, imiquimod is potentially an alternative therapy to surgery for CIN. Although systemic adverse events are common, treatment discontinuation is not frequently required with appropriate management. For VAIN, imiquimod might be as effective as for CIN; however, this conclusion must be tempered and interpreted with caution because there was only one small, inconclusive RCT that focused on VAIN. Before administering imiquimod treatment in patients with CIN or VAIN, patients and gynecologists should understand the possible adverse events. Further studies are needed to optimize the method of imiquimod administration and mitigate adverse events. We believe that our study provides useful information for clinical decision making regarding the initiation of imiquimod treatment for CIN and VAIN.

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