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REVIEW ARTICLE

Imiquimod for treatment of vulvar and vaginal intraepithelial neoplasia

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Abstract

We searched PubMed, Scopus, Web of Science, LILACS, EMBASE, and Cochrane Library databases to assess the effectiveness and safety of 5% imiquimod cream in the treatment of vulvar and vaginal intraepithelial neoplasia. From the results of the 17 relevant articles identified (1 reported on a randomized controlled trial, 10 reported on case series, and 6 were case reports), 26% to 100% of patients had complete regression, 0% to 60% had partial regression, and 0% to 37% experienced recurrence. The most common adverse events were local burning and soreness, but not severe enough for patients to discontinue treatment. From these reports imiquimod treatment leads to complete response in a considerable percentage of patients, and those who experience partial response will require less extensive excision. Treating vulvar and vaginal intraepithelial neoplasia with 5% imiquimod cream therefore appears to be promising.

1. Introduction

Vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN) are premalignant conditions of the genital tract. Specifically, VIN may affect women of any age; differentiated VIN occurs mostly in postmenopausal women with or without HPV infection; and undifferentiated VIN, which occurs in women during their reproductive years, is associated with human papillomavirus infection (mainly from type 16 virus). Risk factors associated with VIN are HPV infection, HIV infection, other sexually transmitted infections, other lower genital tract neoplasia, and smoking. A major risk factor associated with VAIN is HPV infection in women who received radiation for cervical cancer following hysterectomy, or are immunosuppressed following organ transplantation or because of concurrent HIV infection. Both VIN and VAIN are classified as mild, moderate, or severe (1,

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2, and 3, respectively) according to the level of involvement of the squamous epithelium. Lesion grade is diagnosed on colposcopy and, if necessary, from a biopsy sample [1].

The current therapeutic options for VIN and VAIN are wide local excision, loop diathermy, carbon dioxide laser vaporization, or local use of fluorouracil cream [1]. Whereas the rate of recurrence might be 0% after simple vulvectomy, reported recurrence rates following conservative treatment such as laser ablation or local surgical excision are between 39% and 70% [2,3]. Such high rates are associated with multiple surgical excisions, with all the problems that this practice involves (eg, sexual dysfunction and depression). Given that HPV infection can cause genital warts, VIN, or VAIN (depending on virus type), and given the therapeutic role of imiquimod for external and anal genital warts [4], gynecologists have evaluated whether imiquimod could be beneficial in the treatment of VIN and VAIN lesions and symptoms.

Imiquimod (Aldara; 3M Pharmaceuticals, St. Paul, Minnesota, USA) is a heterocyclic imidazoquinolone amine that acts as an immune response-modifying drug with antiviral and antitumor activity [5,6]. It induces the expression of cytokines such as interferon, interleukin 6, and tumor necrosis factor, and enhances cell-mediated cytolytic antiviral activity in vivo [4]. For these reasons, the therapeutic action of imiquimod probably depends on both local response and the stimulation of the immune response. The drug was approved in 1997 by the US Food and Drug Administration for HPV-induced lesions of the lower genital tract (ie, genital warts). Van Poelgest et al. [7] noted that HPV 16-specific CD4+ T-cell immunity might increase the likelihood of a strong clinical response to imiquimod treatment in women with persistent vulvar intraepithelial neoplasia. Imiquimod is formulated as a 5% cream and each gram contains 50 mg of the compound [8].

The present review synthesizes the available evidence regarding the potential therapeutic role of imiquimod in the conservative treatment of VIN and VAIN. We focused as well on the safety and tolerability of imiquimod when applied to these lesions, and investigated whether the available data could lead to an evidence-based change in clinical practice.

2. Methods

2.1. Data sources

Two reviewers (CI and EP) independently searched PubMed, Scopus, Web of science, LILACS, EMBASE, and Cochrane Library databases via Wiley Interscience for any published or unpublished articles and conference abstracts on the use of imiquimod in the treatment of VIN and VAIN that appeared from 1997 to 2007. The search keywords were *imiquimod*, *intraepithelial neoplasia*, *VIN*, *VAIN*, *vulvar neoplasm*, and *dysplasia*. To achieve complete coverage of the literature and limit reporting bias, we also looked at all the articles cited in the retrieved articles.

2.2. Inclusion and exclusion criteria

Articles in English reporting on women of any age treated with 5% imiquimod cream for confirmed VIN or VAIN lesions were eligible to be included in this review. Excluded were articles dealing with men; girls with cervical neoplasia; squamous cell carcinoma in situ or genital warts; the application of imiquimod to parts of the body other than the vulva or vagina (eg, the face or anus); the use of imiquimod in viral infections and other dermatoses; or combinations of topical treatments (eg, 5-fluorouracil plus imiquimod). The quality or key characteristics of the included studies did not influence their eligibility for inclusion in this systematic review.

2.3. Data extraction

The reviewers extracted the following data from the articles qualifying for inclusion: year of publication, study design, population, 5% dosage of the imiquimod cream, treatment duration, number of enrolled patients, number of participating patients, number of clinically evaluable patients, follow-up duration, response to treatment (complete, partial, or none), adverse events (ulceration, blisters, burning sensation, soreness, erythema, flu-like symptoms, or other), withdrawal of patients owing to severe adverse events, and recurrence. Any discrepancies were discussed and resolved with the consensus of all authors.

2.4. Definitions

The diagnosis of VIN and VAIN was confirmed by biopsy. Patients were considered enrolled in a study when they met the study's inclusion criteria; participating when they agreed to participate in a study to which they were invited; and clinically evaluable when they participated in all phases of the study protocol. Follow-up was the period following treatment when the treated areas were observed by colposcopy and, if necessary, biopsied. Complete response was complete regression of all visible lesions, with a histologic confirmation of VIN 1 or VAIN 1 or a simple HPV infection. Partial response was regression of 50% or more of the lesions or stage skipping (eg, a formerly VIN 3 lesion downgraded to VIN 2). No response to treatment was a regression of less than 50% of the lesions. Adverse events consisted of pain, pruritus, excoriation, and erosions. Recurrence was any lesion progression or relapse noted during follow-up.

3. Results

The process by which we identified the articles used in the study is described in Fig. 1. Initially, the Web search produced 229 articles (66 from PubMed, 78 from Web of Science, 85 from Scopus, and none from LILACS, EMBASE, or Cochrane library). Because overlapping was noted in 71 articles, 158 abstracts were further evaluated. Finally, 17 full-text articles were included in the review. Specifically, 1 article was a randomized, double-blind, placebo-controlled trial [9], 10 articles were observational cohort studies (case series) [10–19], and 6 articles were case reports [20–25]. Overall, 257 patients were enrolled in the various studies, 238 patients actually participated, and 210 formed the clinically evaluable population.

3.1. Controlled trial and case series

The main characteristics reported in the controlled trial and case series included in this review are shown in Table 1. In 7 of these articles [9–11, 13,14,16,17] the patients had VIN 2/3, in 2 articles they had VAIN [12,15], and in 1 article [19] they had either VIN or VAIN. Lesion types were confirmed by biopsy in all but 1 article [15], which included some lesions identified as VAIN 1, 2, or 3 on colposcopic evaluation. The application of 5% imiquimod cream ranged from 1 to 3 times per week, depending on clinical response and the presence of adverse events. Furthermore, 5 articles [12–14,17,19] provided data regarding vulvar or vaginal douches and the removal of imiquimod cream during treatment, while 2 articles [14,15] specified the quantity of imiquimod cream applied to smaller or larger lesions. Treatment duration ranged from 3 weeks [15] to 32 weeks [17], and follow-up ranged from 1 week [15] to more than 30 months [10,12–14,19].

The outcome data of the controlled trial and case series included in this review are shown in Table 2. In all but 1 article [19] the response rates referred either to VIN or VAIN, depending on the type of intraepithelial neoplasia on which the study focused. Thus, the complete response rates for VIN ranged from 25% [14] to 81% [9]; the partial response rate from 0% [18] to 60% [16]; and the nonresponse rate from 0% [13] to 69% [18]. For VAIN the complete response rates ranged form 50% [19] to 86% [12,15]; the partial response rates from 14% [12] to 25% [19]; and the nonresponse rates from 0% [12] to 25% [19].

Six [1,14,15,18,19] of 10 articles reported data on adverse events, and 1 article [11] reported that itching and burning were the most common adverse events but did not specify the number of patients in whom these events occurred. The rates of ulcerations and blisters ranged from 0% [12,14,15,19] to 15% [18]; of burning and soreness from 0% [15] to 85% [17]; of erythema from 0% [12,14,15] to 69% [18]; and of flu-like symptoms from 0% [12,14,15,19] to 15% [18]. In 1 study [13], 7 of 8 patients experienced a reduction in sexual desire and frequency of intercourse. The rates of patients who withdrew from studies owing to severe adverse events ranged from 0% [11–13,15,18] to 42% [14]. The rate of lesion recurrence ranged from 0% [13,14,16] to 37% [19].

3.2. Case reports

The main characteristics and outcome data from the case reports included in this review are shown in Table 3. The patients had VIN in all but 1 case report [21], in which they had high-grade VIN, VAIN, or cervical intraepithelial neoplasia. Patients applied imiquimod cream 3 times per week in most reports [20–23,25], and treatment duration ranged from 8 [21,22,24] to 16 [20,23,25] weeks. In all case reports patients

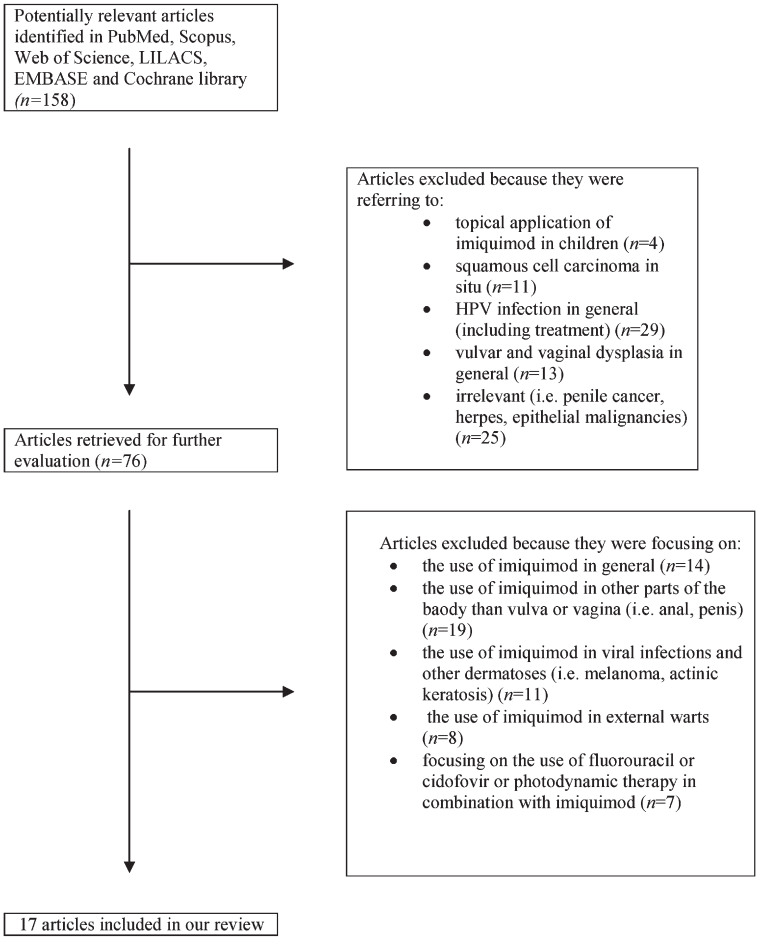

Figure 1 Flow diagram of the reviewed articles.

Table 1 Main characteristics reported in the controlled trial and case series included in this review

First author (year of publication)	Study design	Patient age and lesion grade [a]	Dosage	Treatment duration	Number of patients	Number of participating patients	Number of clinically evaluable patients	Follow-up duration
Mathiesen (2007) [9]	Prospective randomized double-blind, placebo-controlled trial	Median, 46.6 years (range, 21–65 years) VIN 2/3	1/week for 2 weeks, then 2/week for 2 weeks, then 3/week	16 weeks	32	31 (21 imiquimod, 10 placebo)	31	12 months
Le (2007) [10]	Phase 2 prospective study	Median, 54.5 years (range, 33–77 years) VIN 3, unifocal and multifocal	1/week for 2 weeks, then 2/week for 2 weeks, then 3/week	16 weeks	50	39	33	Median, 16 months (range, 2.5–32 months)
Le (2006) [11]	Prospective	Median, 55.2 years (range, 33–77 years) VIN 2/3, unifocal and multifocal	1/week for 2 weeks, then 2/week for 2 weeks, then 3/week	16 weeks	30	23 [b]	17 [b]	NA
Haidopoulo (2005) [12]	Retrospective	Range, 38–61 years VAIN 2/3	3/week	8 weeks	7 [c]	7	7	Mean, 18.4 months (range, 5–31 months)
Marchitelli (2004) [13]	Prospective	<55 years mean, 39.7 years (range 32–51 years) bowenoid and basaloid VIN 2/3	3/week	Up to 16 weeks	8 [d]	8	8	Mean, 22 months [range, 10–30 months on a monthly basis
Wendling (2004) [14]	Prospective	Mean, 41.4 years (range, 27–53 years) VIN, monofocal, and multifocal	3/week	Mean, 5 months (range, 1–7 months)	12 [e]	12	12	Monthly (range, 2–32 months) [e]
Buck (2003) [15]	Prospective	Median, 20 years (range, 18–26 years) VAIN 1/2/3	1–2/week [f]	3 weeks	56 [f]	56	42	1 week to 6 months [f]
Van Seters (2002) [16]	Prospective	Mean, 42.7 years (range, 35–51 years) VIN 2/3, multifocal	1–3/week (depending on clinical response and adverse effects)	6–34 weeks	15 [g]	15	15	NA

Table 1 (*continued*)

First author (year of publication)	Study design	Patient age and lesion grade [a]	Dosage	Treatment duration	Number of patients	Number of participating patients	Number of clinically evaluable patients	Follow-up duration
Jayne (2002) [17]	Retrospective	Mean, 49 years (range, 34–77 years) with VIN 2/3 [h]	3/week	Mean, 3.3 months (range, 1–8 months)	13	13	13	Mean, 5.5 months
Todd (2002) [18]	Prospective	Median, 35 years (range, 25–52 years) VIN 3, multifocal	1–3/week [i]	Up to 16 weeks	15 [i]	15	13	9 months
Diaz-Arrastia (2001) [19]	Retrospective	Median, 47 years (range, 33–60 years) high-grade VAIN, VIN, and CIN [j]	3/week until all lesions cleared	6–16 weeks	8	8	8	Median, 30.5 months

Abbreviations: CIN, cervical intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia.

[a] All diagnoses of VIN or VAIN were biopsy confirmed except in the study by Buck et al., where it was based on either visual inspection or biopsy.

[b] 3/23 patients had VIN 2, 20/23 had VIN 3, 20/23 had unifocal lesions, 9/23 had multifocal lesions, and 23/23 were smokers. 3/17 had VIN 2, 14/17 had VIN 3, 17/17 had unifocal lesions, and 6/17 had multifocal lesions.

[c] 2/7 patients had VAIN 2, 5/7 had VAIN 3, 4/7 were high- and low-risk HPV (+), 2/7 were high-risk HPV (+), 1/7 was low-risk HPV (+), 6/7 had hysterectomy, and 5/7 were smokers.

[d] 5/8 patients were smokers, 2/8 had received previous therapy (1/8 laser and 1/8 surgical excision).

[e] 5/12 had monofocal, and 7/12 had multifocal lesions, 1/7 had multifocal pigments popular, 8/12 had recurrent VIN, 3/12 were infected by HIV and had been receiving highly active antiretroviral therapy for more than 1 year, 9/12 were infected by HPV-16, and 1/12 was infected by HPV-33. 1 patient was lost to follow-up.

[f] 2/week was the treatment for 4/56, while 1/week was for 52/56. In 19/56 patients the diagnosis of VAIN was based on visual inspection, while in 37/56 the diagnosis was based on biopsy. 33/37 patients had VAIN 1, 3/37 had VAIN 2, and 1/37 had VAIN 3. 26/56 patients had external genital warts, 31/56 had CIN (26/31 had CIN 1 and 5/31 had CIN 2), and 13/56 had both external genital warts and CIN. No patient had received previously therapy for VAIN. 26 patients were available for follow-up 6 months after their initial posttreatment examination.

[g] 11/15 patients had been previously treated surgically, 4/15 patients had never been treated, 9/15 had a history of VIN and 2/9 had concomitant anal intraepithelial neoplasia, 1/15 had a history of low-grade non-Hodgkin lymphoma, and 12/15 were smokers (>21 cigarettes per day).

[h] 1/13 patients had VIN 2, 12/13 had VIN 3, 2/13 had primary lesions, and 11/13 had recurrent disease.

[i] 6/13 patients received imiquimod 1/week, 5/13 received 2/week, and 2/13 received 3/week. 12/15 patients had undergone previous surgical excision, 6/15 had received topical steroids, 4/15 had received other treatments, and 14/15 were smokers (>10 cigarettes per day).

[j] 2/8 patients had VAIN, 4/8 had VIN, and 2/8 had CIN, and 5/8 were smokers.

noted a complete regression of their lesions. Two of 4 patients, however, experienced recurrence in 1 report [25], one patient after 2 months and the other after 1 year of follow-up. The recurrences resolved when applications of imiquimod cream were resumed. Only 2 case reports [21,22] included data on adverse events. Whereas one [22] mentioned that no adverse events were related to the use of imiquimod, the other [21] noted that erythema and drug-induced pemphigus developed where imiquimod was applied in 1 patient.

4. Discussion

From the results of this review, applications of 5% imiquimod cream may be considered as an alternative treatment for VIN and VAIN when excision is not the method chosen by the patient and/or surgeon. As the data in this review do not seem to suggest that patients treated with imiquimod experience a higher increase in recurrence rates than patients treated with other topical drugs, imiquimod use can be considered alone, or with the aim of shrinking lesions before performing conservative ablative procedures.

It should be emphasized that the available data regarding the use of imiquimod cream on multifocal lesions of VIN and VAIN are, to some degree, controversial. According to studies by Le et al. [10], Marchitelli et al. [13], Wendling et al. [14], and van Seters et al. [16], the response rates (both complete and partial) for such lesions were 100%, 100%, 58%, and 87%, respectively, whereas in the study by Todd et al. [18] the rate was 31%. In addition, Le et al. [10,11] reported that patient response was the same whether they had unifocal or multifocal

Table 2 Outcome data from the randomized controlled trial and case series included in this review [a]

First author	Response to therapy in clinically evaluable patients [b]		Adverse events in clinically evaluable patients						Withdrawals due to severe adverse events	Recurrences
	Complete response	Partial response	Nonresponse	Ulceration, blisters	Burning, soreness	Erythema	Flu-like symptoms	Other		
Mathiesen [9]	17/21 (81)	2/21 (10)	2/21 (10)	NA	NA	NA	NA	NA	NA	NA
Le [10]	21/33 (64)	9/33 (27)	3/33 (9)	NA	NA	NA	NA	NA	3/39 (8)	5/21 (24)
Le [11]	9/17 (53)	5/17 (29)	3/17 (18)	NA	Not quantified	NA	NA	NA	0/17 (0)	NA
Haidopoulo [12]	6/7 (86)	1/7 (14)	0/7 (0)	0/7 (0)	2/7 (29)	0/7 (0)	0/7 (0)	0/7 (0)	0/7 (0)	2/7 (29) [c]
Marchitelli [13]	6/8 (75)	2/8 (25)	0/8 (0)	NA	6/8 (75)	8/8 (100)	NA	2/8 (25) [d]	0/8 (0)	0/8 (0)
Wendling [14]	3/12 (25) [e]	4/12 (33) [d, e]	5/12 (42)	2/12 (0)	8/12 (67)	0/12 (0)	2/12 (0)	6/12 (50) [f] and 7/12 (58) [g]	3/12 (42)	0/3 (0) [d]
Buck [15]	36/42 (86)	NA	NA	0/42 (0)	0/42 (0)	0/42 (0)	0/42 (0)	2/42 (0) [h]	0/12 (0)	2/26 (8)
Van Seters [16]	4/15 (27)	9/15 (60)	1/15 (7)	NA	NA	NA	NA	NA	2/15 (13)	0/15 (0)
Jayne [17]	8/13 (65)	4/13 (31)	1/13 (8)	NA	NA	NA	NA	NA	NA	NA
Todd [18]	4/13 (31)	0/13 (0)	9/13 (69)	2/13 (15)	11/13 (85)	9/13 (69)	2/13 (15)	0/13 (0)	0/13 (0)	4/13 (31) [i]
Diaz-Arrastia [19]	4/8 (50)	2/8 25)	2/8 (25)	0/8 (0)	1/8 (12)	5/8 (62)	0/8 (0)	5/8 (62) [i]	1/8 (12)	3/8 (37)

Abbreviation: NA, not applicable.

[a] Values are given as number/total number (percentage).

[b] Response to therapy was defined after completion of therapy. Complete response indicates complete disappearance of all visible lesions, with biopsy-confirmed VIN 1 or VAIN 1 or a simple HPV infection; partial response indicates of 50% or greater decrease in lesion areas.

[c] 1/7 patients showed recurrence at 14 months of follow-up and partial vaginectomy was performed; 1/7 patients showed recurrence at 26 months of follow-up and total vaginectomy was performed.

[d] 1/8 patients had erosions and 1/8 had edema. The treatment was interrupted for a week.

[e] No progression to invasive vulvar squamous cell carcinoma was observed.

[f] 1/4 partial responders underwent laser vaporization at the end of treatment, and 2/4 did not experienced progression during follow-up. 6/12 patients experienced itching, 7/12 erosion, and 1/12, who was HIV positive, had hepatitis. Data regarding recurrences were given for the 3 complete responders.

[g] 2/56 experienced excoriation.

[h] 1 patient with recurrence was treated once per week whereas the other 3 were treated 3 times per week.

[i] Pain and pruritus.

lesions. These observations are of major significance because multifocal lesions of VIN and VAIN have traditionally been very difficult to manage and the current treatment of choice, partial or even total vulvectomy or vaginectomy, are procedures of high financial and psychological cost.

A lack of response to imiquimod treatment does not seem to be associated with a higher risk of lesion progression. From the data included in this review, the lesions of nonresponders remained stable through treatment and follow-up. No further progression or transformation to invasive carcinoma was observed in this relatively small number of patients.

Furthermore, imiquimod cream appears to be safe and well tolerated by most patients. The adverse events were local irritation, most commonly with burning and soreness, but systemic adverse events were extremely rare. Unusual adverse events were flu-like symptoms and hepatitis [14], erythema, pain, excoriation, dyspareunia, blisters, and ulceration. These reactions are also noted in some patients treated with imiquimod cream for actinic keratosis and precancerous or cancerous skin lesions [26,27], and are due to an immune response to imiquimod applications. Le et al. [10,11] reported that the need for dose reduction due to local irritation was associated with a higher chance of complete response; it seems that the higher the intensity of local reaction to imiquimod, the higher the probability that VIN and VAIN lesions will be controlled.

Table 3 Main characteristics and outcome data from case reports included in this review

First author (year of publication)	Study design	Patient age and lesion grade [a]	Dosage	Treatment duration	Number of patients	Number of participating patients	Number of clinically evaluable patients	Follow-up duration
McQuillan [20]	2007	A 33-year-old with VIN 2/3 and no evidence of invasive malignancy	3/week	16 weeks	1	NA	1/1 (100)	NA
Campagne [21]	2003	A 27-year-old with high-grade CIN, VIN, and VAIN	3/week [b]	8 weeks	1	8 months	1/1 (100)	0/1 (0)
Diakomanolis [22]	2002	38-, 58-, 61-year-old patients with VIN 2/3	3/week	8 weeks	3	NA	3/3 (100)	NA
Travis [23]	2002	A 27-year-old with VIN 3	3/week for 2 weeks; stopped for 2 weeks; resumed treatment	4 months	1	4 months	1/1 (100)	0/1 (0)
Petrow [24]	2001	A 38-year-old with bowenoid papulosis	Until no visible irritation of the skin, alternate days for 10 days; then once daily for another 10 days	8 weeks	1	18 months	1/1 (100)	0/1 (0)
Davis [25]	2000	32, 35, 61, 54 years old with VIN 3	3/week	Max 16 weeks	4	1 year	4/4 (100)	2/4 (50)

Abbreviations: CIN, cervical intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia.
[a] All diagnoses of VIN or VAIN were biopsy confirmed.
[b] Imiquimod was the treatment for the remaining vulvar lesions after large-loop excision of the transformation zone of the cervix or carbon dioxide laser vaporization, under general anesthesia of all lesions in the vagina, urethra, anal canal, and part of the vulvar lesions.

Many studies reported that adverse events resolved spontaneously. In the study by Marchitelli et al. [13], the decrease in the sexual desire and intercourse frequency resolved 1 month after the end of treatment. In the study by Wendling et al. [14], the flu-like symptoms resolved after 16 h without any treatment, or after 1 h with administration of paracetamol, whereas cytolytic hepatitis, which occurred in an HIV-infected patient, resolved after the end of treatment. In the study by Todd et al. [18], 1 patient experienced severe erythema and required hospitalization, catheterization, and analgesia; and in the case report by Campagne et al. [21], 1 patient was treated with 0.05% clobetasone cream for drug-induced pemphigus. All patients resumed treatment with imiquimod after resolution of the adverse effects. Although the adverse effects were not severe enough to cause treatment discontinuation, they led to poor compliance, reduction in the number of applications, and, in some cases, long interruption periods without any imiquimod applications.

A major limitation of the findings of this review is that imiquimod is a very recent drug. Only 1 randomized controlled trial versus placebo has been carried out, and there are no randomized controlled trials versus wide local excision, loop diathermy, carbon dioxide laser vaporization, or local use of fluorouracil cream in patients with VIN or VAIN lesions. Thus, most articles included in this review are merely observational uncontrolled studies. Another limitation is that the number of overall patients included in this review is too small for a definitive conclusion to be made.

It is also likely that publication bias may have influenced the publications, as reports describing complete or partial responses to this new treatment are more likely to appear in the literature. Furthermore, only Wendling et al. [14] provided data regarding the type of VIN (differentiated or undifferentiated), and only 5 studies [10,12,14,16,18] reported the kind of lesions (unifocal or multifocal), that their patients had. In the study by Buck et al. [15], 4 of 56 patients had high-grade VAIN lesions.

Moreover, the application schedule was not standard in the different studies, and patients had the option to skip or reduce the number of imiquimod applications or even to interrupt treatment because of discomfort. In addition, only 5 articles [12–14,17,19] provided specific data regarding the possible removal of imiquimod (e.g., by washing the treated area) during treatment, while only 2 articles [14,15] specified the quantity of imiquimod cream applied to more or less extended lesions.

The median time to treatment response was reported only by Le et al. [10,11] and van Seters et al. [16], and it was 7 and 9 weeks, respectively. Furthermore, follow-up duration was short (the maximum was 30 months), which is also a serious limitation when evaluating the effectiveness of imiquimod in the management of patients with VIN/VAIN lesions. Finally, only 7 studies [1,10,11,13,17,18,19] reported on funding.

Those by Mathiesen et al. [9], Le et al. [10,11], Todd et al. [18], and Diaz-Arrastia et al. [19] were financed by 3M Pharmaceuticals, the manufacturers of imiquimod, and those by Marchitelli et al. [13], van Seters et al. [16], and Jayne et al. [17] received no funding from a pharmaceutical company.

5. Conclusion

From this review of the current evidence, it can be concluded that the effect of imiquimod treatment for VIN and VAIN lesions is still under investigation. From the available data, it seems that it may be an effective and well-tolerated alternative option in the treatment of these lesions; however to make safe conclusions regarding the effectiveness, recurrence rates, and recurrence free interval duration of this treatment, longer follow-up periods are needed.

For these reasons, before an evidence-based change in clinical practice can be recommended, large randomized controlled trials of imiquimod versus other classic methods of treatment should be designed and carried out for VIN and VAIN lesions.

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