REVIEW

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Immunotherapy with imiquimod in cervical, vaginal, and vulvar intraepithelial lesions – a review of the literature

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Summary

Imiquimod is a topical immunomodulatory agent commonly used in treating various skin conditions, including precancerous lesions. This review summarizes current evidence on the efficacy and safety of imiquimod for treating vaginal, cervical, and vulvar intraepithelial neoplasias (VAIN, CIN, and VIN, respectively). These lesions are often associated with human papillomavirus (HPV) infections and can progress to cancer if left untreated.

The review highlights that Imiquimod can stimulate the immune response to clear HPV-infected cells, suggesting it is a promising non-invasive treatment option for these lesions. Studies report varying success rates, with Imiquimod being particularly effective in treating VIN and showing potential in CIN and VAIN management. The treatment's advantages include its non-invasive nature, fewer side effects than traditional treatments (such as surgery), and the potential to preserve normal tissue. However, side effects such as local inflammation and discomfort are common, and treatment response can vary by lesion type and patient factors. The review concludes that Imiquimod therapy is a promising form of treatment, but more studies are needed to determine its optimal use, including treatment duration, dosing, and patient selection criteria.

KEYWORDS: *imiquimod, human papillomavirus infection, non-surgical treatment, genital intraepithelial lesion*

1. INTRODUCTION

Imiquimod is an immune response modulator with antiviral and antitumor effects often used in the management of various clinical manifestations of human papillomavirus infections(1-4).

The genesis of cervical, vaginal, and vulvar intraepithelial lesions in the vast majority of patients is associated with human papillomavirus (HPV)(4,5). The management of genital non-invasive lesions has been the subject of many studies and debates over several decades. The currently preferred treatment modality for high-grade genital intraepithelial lesions is surgical excision(4). Surgical procedures might have significant adverse effects, such as infection, bleeding, scarring, and iatrogenic injury of adjacent anatomical structures, as well as high recurrence rates. Reported recurrence rates following conservative treatment for vulvar and vaginal intraepithelial lesions are between 39% and 70%(3,6,7). The five-year risk of recurrent cervical intraepithelial neoplasia grade 2

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or worse after treatment ranges from 5% to 16%, depending on the histology of the treated lesion and the preceding Pap test results(8). Also, surgical treatment of vaginal intraepithelial lesions is often difficult and not always feasible(3,4), while surgical treatment of cervical intraepithelial lesions can have a negative impact on subsequent pregnancies(3,4,9). Therapy with 5% imiquimod cream has been evaluated as an alternative to surgical excision for the treatment of high-grade genital lesions(10,4).

Imiquimod, a topical immune response modifier, has emerged as a promising therapeutic agent in the management of these lesions due to its ability to modulate the local immune environment and enhance viral clearance. This review summarizes current evidence on the efficacy and safety of imiquimod for treating vaginal, cervical, and vulvar intraepithelial neoplasias (VAIN, CIN, and VIN, respectively).

Imiquimod acts by stimulating the innate immune system via the Toll-like receptor 7 (TLR7) pathway, leading to the production of pro-inflammatory cytokines and the activation of various immune cells, including dendritic cells, macrophages, and T cells. This immunomodulatory effect enhances the host's ability to clear HPV-infected cells and induces regression of intraepithelial lesions.

1.1. Imiquimod in cervical lesions

Several studies have investigated the efficacy of imiquimod in treating cervical intraepithelial lesions, with varying results. A randomized controlled trial by van de Sande et al.(11) compared the efficacy of imiquimod with LLETZ in women with residual or recurrent cervical intraepithelial neoplasia (rrCIN) (Figure 1).

The study found that imiquimod had a significantly lower success rate in achieving normal cytology and clearing hr-HPV compared with LLETZ. Similarly, a trial by Cokan et al.(12) reported that imiquimod treatment was successful in 51.9% of HSIL patients, whereas LLETZ had a success rate of 92.3%. Despite these findings, other studies have highlighted the potential of imiquimod as a non-surgical alternative. Fonseca et al. (13) demonstrated that weekly topical application of imiquimod led to a significant histologic regression of cervical high-grade squamous intraepithelial lesions compared to the control group. Additionally, our case report by Danolić et al.(14) noted a 73% regression rate of premalignant cervical lesions with the use of 5% imiquimod in women who opted to avoid surgery.

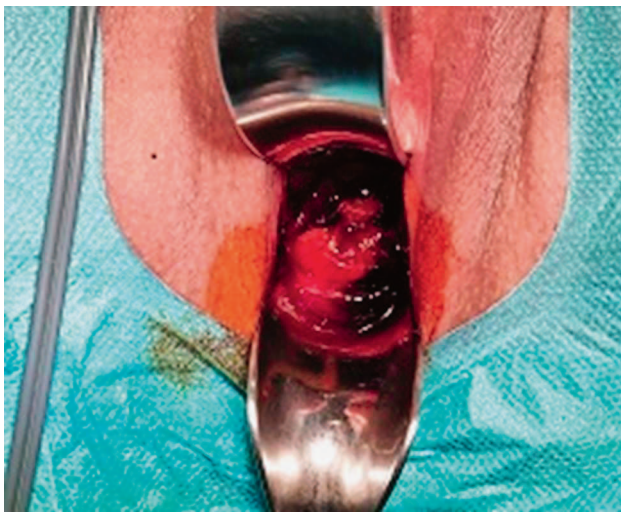

Figure 1. Recurrent cervical HSIL

The variability in patient response to imiquimod treatment has prompted research into predictive biomarkers that could guide patient selection. Esch et al.(15) identified a coordinated local immune response as a key factor associated with a positive response to imiquimod therapy. This finding led to the development of an immunohistochemical biomarker approach that could potentially predict which patients are likely to achieve complete lesion regression with imiquimod treatment. Additionally, the study by Abdulrahman et al.(16) emphasized the role of T-cell and myeloid-cell composition in predicting treatment outcomes, further supporting the use of immune-based biomarkers in clinical decision-making.

Imiquimod is generally well-tolerated, but it is not without adverse effects. Local skin reactions, such as erythema, erosion, and itching, are common and can be managed with symptomatic treatment. However, systemic adverse events, though rare, can occur. A case report by Cokan and Pakiz(12) described delayed telogen effluvium (hair loss) following imiquimod treatment for cervical HSIL, underscoring the need for careful monitoring during treatment.

The choice between surgical intervention and immunotherapy is often influenced by patient preferences, particularly concerning fertility pres-

ervation. Koeneman et al.(17) reported that women with a future pregnancy wish may prefer imiquimod treatment over LLETZ due to the lower risk of subfertility and premature birth associated with non-surgical management. This preference underscores the importance of considering patient-centered outcomes when selecting treatment modalities for cervical intraepithelial lesions.

1.2. Imiquimod in vaginal lesions

Vaginal Intraepithelial Neoplasia (VAIN) is a rare but significant condition that represents a premalignant change in the vaginal epithelium. It is closely associated with human papillomavirus (HPV) infection, particularly high-risk subtypes. VAIN is classified into three grades based on the severity of dysplasia, with VAIN 3 representing the most severe form, which is a precursor to invasive vaginal cancer. Standard treatment options for VAIN have historically included surgical excision, laser ablation, and observation. However, these methods can be invasive, associated with significant morbidity, and often lead to high recurrence rates. In recent years, topical immunotherapy with Imiquimod has emerged as a promising non-invasive treatment alternative.

Several studies have investigated the efficacy of Imiquimod in treating VAIN, with encouraging results. A systematic review and meta-analysis reported a pooled complete response rate of 76% and an overall response rate of 89% in patients treated with Imiquimod for VAIN 2-3. This is particularly notable given the challenges associated with treating high-grade VAIN, which often requires aggressive management(18).

In a randomized controlled trial comparing Imiquimod with laser vaporization and expectant management, Imiquimod was found to be as effective as laser treatment, with higher HPV clearance rates. This study highlights Imiquimod's potential not only to treat dysplasia but also to target the underlying viral etiology, thereby reducing the risk of recurrence.

Case series and observational studies further support the efficacy of Imiquimod. For instance, a study by Policiano et al.(19) documented the successful use of Imiquimod in patients with high-grade VAIN, showing a significant reduction in lesion size and progression-free survival. Another study by Sasagasako et al.(20) described a complete response in a patient with recurrent VAIN 3 after Imiquimod treatment, indicating its potential role in managing recurrent cases.

Compared with other treatment modalities, Imiquimod offers several advantages. It is less invasive than surgical options, reducing the risk of complications such as scarring, stenosis, and sexual dysfunction, which are significant concerns with traditional treatments like laser ablation or excisional surgery. Moreover, Imiquimod can be self-administered, offering convenience and potentially improving patient compliance. However, the treatment is not without side effects. Local skin reactions, including erythema, erosion, and discomfort, are common but generally manageable. Systemic side effects are rare but may include flu-like symptoms due to the drug's immune-activating properties. The typical regimen for Imiquimod involves applying a 5% cream to the affected area once to three times a week for several weeks, depending on the severity of the lesions and patient tolerance. Patient selection is crucial to optimizing outcomes. Imiquimod is particularly well-suited for patients who are not ideal candidates for surgery due to comorbidities, those who wish to preserve vaginal anatomy and function, or in cases of multifocal disease where surgical excision would be challenging. The future of Imiquimod in the treatment of VAIN appears promising, particularly as further research continues to refine its use. Ongoing trials and studies are likely to expand the indications for Imiquimod and establish standardized treatment protocols that can be widely adopted. Additionally, the potential for combining Imiquimod with other therapeutic modalities, such as vaccines or other immunotherapies, offers an exciting avenue for future research.

1.3. Imiquimod in vulvar lesions

Vulvar intraepithelial neoplasia (VIN) represents a significant precursor to vulvar cancer, characterized by dysplastic changes in the vulvar epithelium (Figure 2).

Traditional management of VIN often involves surgical excision, which, although effective, can result in significant morbidity, including scarring and functional impairment. As an alternative, non-surgical options like immunotherapy with imiquimod, a topical immune response modifier, have gained prominence. This review aims to

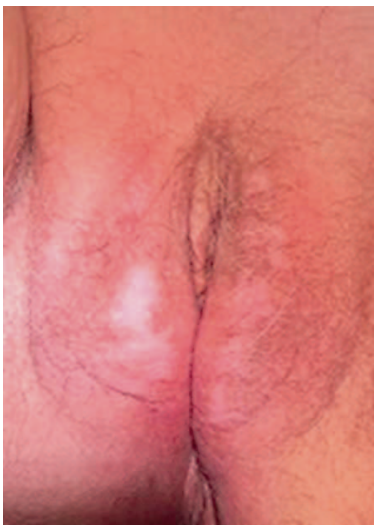

Figure 2. Vulvar HSIL

consolidate the evidence on the efficacy, safety, and outcomes of imiquimod therapy for the management of vulvar intraepithelial lesions.

Several studies have demonstrated the efficacy of imiquimod in treating VIN. For instance, a study conducted in Korea reported that 66.6% of patients with VIN experienced complete or partial responses after treatment with 5% imiquimod cream(21). Similarly, another investigation highlighted that imiquimod treatment resulted in complete remission in 41.18% of patients with vulvar intraepithelial neoplasms, making it a valuable alternative to surgical interventions, especially in younger patients(22).

Long-term follow-up studies suggest that imiquimod not only offers immediate therapeutic benefits but also contributes to sustained disease control. A retrospective study assessed the long-term response to imiquimod in patients with vulvar high-grade squamous intraepithelial lesions (HSIL). It found that the presence of human papillomavirus (HPV) could influence the persistence or recurrence of vulvar HSIL after treatment, underscoring the need for vigilant post-treatment surveillance(23).

The local application of imiquimod is associated with several side effects, primarily localized skin reactions such as erythema, erosion, and edema. These reactions are usually self-limited and resolve after discontinuation of therapy. Systemic side effects are rare, given the drug's minimal systemic absorption when applied topically.

Aesthetic and functional outcomes are often better with imiquimod compared to surgical methods. For example, patients treated with imiquimod for high-grade squamous intraepithelial lesions (HSIL) of the vulva reported good aesthetic outcomes and stable psychosexual health, comparable to those undergoing surgical treatment(24).

Recent research has identified potential biomarkers that could predict the response to imiquimod therapy. A coordinated local immune response involving specific T-cell subsets (e.g., CD8+ T cells) and inflammatory myeloid cells has been linked to complete responses in patients with vulvar HSIL treated with imiquimod(16). Moreover, the development of an immunohistochemical biomarker could help identify patients most likely to benefit from imiquimod treatment, further personalizing therapy(15).

Imiquimod has also been compared with other treatment modalities, such as CO2 laser vaporization. Patients treated with imiquimod had less severe histological recurrence than those treated with CO2 laser, suggesting that imiquimod may be more effective at reducing the severity of recurrent lesions(25).

2. DISCUSSION

Imiquimod, an immune response modifier, has been explored extensively for its potential in treating various intraepithelial lesions, including vaginal, cervical, and vulvar neoplasias. The efficacy of imiquimod in these contexts is influenced by its ability to modulate the local immune microenvironment, enhancing the body's natural defenses against human papillomavirus (HPV)-associated lesions.

While less studied than cervical and vulvar lesions, vaginal intraepithelial neoplasias (VaIN) have also been targeted with imiquimod treatment. The sensitivity of HPV testing in vaginal precancer lesions has been found to be comparable to that for cervical lesions, suggesting that similar therapeutic approaches, including the use of imiquimod, could be effective. However, the specific immune responses and efficacy rates in vaginal lesions require further research to establish robust treatment protocols(26).

Treatment of residual vaginal HSIL after wide local excision, hysterectomy, and proximal partial vaginectomy is difficult and not always

feasible. The goal of treatment is to prevent disease progression to vaginal carcinoma, which occurs in 2-8% of patients(27,28). To this date, there is no standardized treatment protocol for the management of recurrent VaIN. In their study(28), in which seven patients with vaginal intraepithelial lesion (VaIN) 2/3 took part, two patients (28.5%) were managed by vaginectomy, one for persistent and one for recurrent high-grade VaIN, while the other five patients (86%) were found to have either HPV infection or low-grade VaIN after 5% imiquimod therapy. Lin et al.(29) reported a clearance rate of 40% following treatment with 5% imiquimod. Tranoulis et al. 30) conducted a systematic review and meta-analysis of six studies including 94 patients with any grade of VaIN who received 5% imiquimod. They reported a complete clinical response rate of 76.5% and HPV clearance rate of 52.5%, and concluded that the use of 5% imiquimod for the treatment of VaIN is associated with a relatively high response rate. Topical therapy with 5% imiquimod appears to be a promising, non-invasive treatment option(30). The advantage of topical therapy with 5% imiquimod rather than a repeat excision, in patients with recurrent vaginal disease, is in treating the entire vaginal surface with good coverage of vaginal recesses, especially if multifocal vaginal HSIL is present.

In the realm of cervical intraepithelial lesions, imiquimod has been primarily studied in high-grade squamous intraepithelial lesions (HSIL). Recent studies suggest that the effectiveness of imiquimod is closely tied to the lesion's immune microenvironment. For example, a robust and coordinated infiltration of specific immune cells, including T helper cells, M1-like macrophages, and dendritic cells, has been observed in complete responders to imiquimod treatment. In contrast, non-responders tend to have greater infiltration of regulatory T cells, which may suppress the immune response and reduce the effectiveness of the therapy(31).

Furthermore, the identification of immune-based biomarkers, such as the CIBI, has proven valuable in predicting which patients with cervical HSIL will respond favorably to imiquimod treatment. This approach allows for a more personalized treatment plan, potentially reducing unnecessary adverse effects in non-responding patients(31).

The initial approach to the management of patients with cervical stump HSIL must consider treatment-related morbidity. The goal of treatment is to prevent disease progression to invasive disease. Tainio et al.(32) reported in their meta-analysis that most CIN2 lesions (50%) regress spontaneously, so active surveillance rather than immediate surgical intervention is justified. Non-surgical medical therapy with topical imiquimod appears to be more effective than no treatment, inducing disease regression in 73%(4,10,17,33). Current management approach for CIN is based on observation and/or excisional procedures(33). Data on topical imiquimod use in the treatment of cervical dysplasia are limited since most trials were small and had limitations(4,10,33). Grimm et al.(10) in their study estimated the efficacy of a treatment with self-applied vaginal suppositories containing 5% imiquimod in patients with CIN 2/3 and find higher complete histologic remission in the imiquimod group (47%) compared with the placebo group (14%), increased HPV clearance rate in the imiquimod group (60%) compared with the placebo group (14%) and in the group of patients with HPV16 infection complete remission rates of 47% in the imiquimod group compared with 0% in the placebo group. Progression to invasive disease was observed in three of 59 patients, all within the placebo group(10). Evidence regarding the effectiveness of imiquimod for treating residual or recurrent cervical intraepithelial neoplasia (rrCIN) is relatively scarce. A recent retrospective case study by van de Sande et al.(34) involved 18 patients diagnosed with rrCIN who received 5% imiquimod administered intravaginally. The treatment was successful in 11 of the women (61%), including 8 out of 10 women (80%) with high-grade CIN (grades 2 and 3), and was generally well tolerated. Additionally, comparisons with other studies (35) suggest that LLETZ may not be more effective than imiquimod for the treatment of rrCIN. However, further research is necessary to directly compare imiquimod therapy with a secondary LLETZ procedure in patients with rrCIN lesions. Topical medical therapy with 5% imiquimod of CIN lesions, at this point, cannot replace surgical therapy(4,10), but may be considered as an off-label treatment option for a selected group of women who want to avoid further surgery, especially during standard observation after primary biopsy, as shown in our report.

Standard management options for vulvar HSIL range from excision and ablation to topical medical therapy(4,36). The treatment depends on the pathohistological results of the biopsy and prior treatment history. Patients who undergo surgical treatment have 50% chance of recurrence within a few years(37). Patients with recurrent vulvar HSIL are usually treated with ablative or topical therapy to avoid multiple excision procedures and treatment-related morbidity(4). Imiquimod 5% creme is the preferred initial topical treatment for recurrent vulvar HSIL(4,36). Van Seters et al.(36) compared imiquimod with placebo in a randomized controlled trial and found significantly greater histologic regression of VIN in the imiquimod group than in the placebo group, and significantly greater HPV clearance in the imiquimod group than in the placebo group. In a study published in *The Lancet Oncology*, Tristram et al.(38) reported the results of a randomized phase 2 trial investigating the use of topical imiquimod for treating vulvar high-grade squamous intraepithelial lesions (HSIL). Of 91 patients treated with imiquimod, 42 (46%) achieved a complete response. The authors concluded that imiquimod is an effective alternative to surgical intervention and can be considered for patients with vulvar HSIL, provided that hidden invasive disease is ruled out. Also, De Witte et al.(4) in their systematic review of treatment of high-grade VIN included eight prospective studies, four retrospective chart reviews, and two randomized controlled trials, and reported a complete response rate obtained by histology from 5% to 88% and a complete response rate obtained clinically from 16% to 76%. Lawrie et al. (37) in their meta-analysis of three randomized trials including 104 patients, found that topical imiquimod after a 16-week course was more effective than placebo for the treatment of vulvar HSIL, with complete response rates of 58% in the imiquimod group and 0% in the placebo group.

According to the literature review, medical topical therapy with 5% imiquimod seems to be a safe mode of treatment for high-grade genital intraepithelial lesions in selected patients, especially for vaginal and vulvar HSIL. Van Seters et al.(36) suggested that imiquimod could be considered the primary treatment option for vulvar intraepithelial neoplasia. In the future, topical therapies might become the preferred choice for treating patients with vulvar HSIL, while surgical procedures would be reserved for those who do not respond to initial treatment(39). However, no studies have compared the efficacy of imiquimod topical treatment with traditional surgical treatments(37,40). New studies with standardized treatment protocols and longer follow-up are needed to confirm the efficacy of imiquimod and to determine long-term recurrence rates.

3. CONCLUSION

The use of imiquimod as an immunotherapy for intraepithelial lesions of the vagina, cervix, and vulva is a promising approach, particularly when tailored to the immune profile of the lesion. Identifying immune-based biomarkers and understanding the local immune microenvironment are crucial for optimizing treatment outcomes. While imiquimod shows considerable potential, its use should be guided by a thorough understanding of the patient's immune status and the specific characteristics of the lesion, necessitating further research in this domain to refine treatment strategies and improve patient outcomes.

DISCLOSURE STATEMENT

The authors report no conflict of interest.

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Sažetak

Imunoterapija imiquimodom u vaginalnim, cervikalnim i vulvarnim intraepitelnim neoplazijama – pregled literature

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Imikvimod je topikalni imunomodulatorni lijek koji se široko primjenjuje u liječenju različitih dermatoloških stanja, uključujući prekancerozne lezije. Ovaj pregledni rad sintetizira dostupne dokaze o učinkovitosti i sigurnosti imikvimoda u liječenju vaginalnih, cervikalnih i vulvarnih intraepitelnih neoplazija (VAIN, CIN I VIN). Navedene lezije često su povezane s infekcijom humanim papiloma virusom (HPV) te ukoliko se ne liječe, mogu progredirati u invazivni karcinom. Dosadašnja istraživanja upućuju na to da imikvimod potiče lokalni imunološki odgovor, omogućujući eliminaciju HPV-om inficiranih stanica, čime se potvrđuje njegov potencijal kao neinvazivne terapijske opcije za liječenje ovakvih lezija. Objavljene studije navode heterogene stope terapijskog odgovora, pri čemu je imikvimod pokazao najveću učinkovitost u liječenju vulvarne intraepitelne neoplazije (VIN) dok rezultati za cervikalnu (CIN) i vaginalnu (VAIN) također ukazuju na klinički značajan terapijski učinak. Prednosti primjene imikvimoda uključuju neinvazivan pristup, manju učestalost nuspojava u usporedbi s kirurškim metodama te očuvanje anatomskog i funkcionalnog integriteta zahvaćenog tkiva. Međutim, lokalne nuspojave, poput eritema, upale i subjektivne nelagode, česte su tijekom terapije, a odgovor na liječenje može varirati ovisno o vrsti lezije i individualnim obilježjima bolesnica. Zaključno trerapija imikvimodom predstavlja obećavajući modalitet liječenja intraepitalnih lezijagenitalnog trakta. Ipak potrebna su dodatna prospektivna i randomizirana istraživanjakako bi se utvrdili optimalni terapijski protokoli, uključujući trajanje liječenja, doziranje i kriterije selekcije bolesnica.

KLJUČNE RIJEČI: *imiquimod, infekcija humanim papiloma virusom, nekirurško liječenje, genitalne intraepitelne neoplazije*