Ann Dermatol Vol. 27, No. 1, 2015 http://dx.doi.org/10.5021/ad.2015.27.1.66

ORIGINAL ARTICLE

Efficacy of 5% Imiquimod Cream on Vulvar Intraepithelial Neoplasia in Korea: Pilot Study

Jeong-Min Kim[1], Hyun-Joo Lee[1], Su-Han Kim[2], Hoon-Soo Kim[1,3], Hyun-Chang Ko[1,3], Byung-Soo Kim[1,3], Moon-Bum Kim[1,3], Margaret Song[1,3]

[1]*Department of Dermatology, Pusan National University School of Medicine,* [2]*Goun Laser and Cosmetic Clinic,* [3]*Biomedical Research Institute, Pusan National University Hospital, Busan, Korea*

Background: Various therapeutic options, including surgery, electrocautery, cryotherapy, 5-fluorouracil treatment, laser therapy, radiotherapy, photodynamic therapy, and interferon-α/γ injection, have been employed to treat vulvar intraepithelial neoplasia (VIN) with varying degrees of success. To truly cure VIN, human papillomavirus elimination is considered important. **Objective:** To investigate the efficacy of 5% imiquimod cream used to treat VIN in Korean patients **Methods:** We performed a prospective, uncontrolled, observational study. Nine patients with histologically confirmed VIN applied 5% imiquimod cream to their vulvar lesions three to five times a week until a clinical response was apparent. All lesions were photo-documented, and therapeutic efficacy was assessed in terms of local adverse effects lesion number, size, and hyperpigmentation. **Results:** The mean treatment duration was 30.2 months, and the median follow-up period after therapy completion was 30 months. Of the nine patients recruited, six (66.6%) experienced complete responses (CR) or partial responses (PR). Hyperpigmented patches in the VIN lesions were evident in five subjects (55.6%), and all experienced either CR or PR. Only three patients (33.3%) suffered from local adverse effects, which were relieved after temporary suspension of therapy, and better outcomes were attained ultimately. **Conclusion:** The imiquimod cream was more efficacious when used to treat VIN of the hyperpigmented type compared with lesions lacking pigmentation. The unifocal nature of a lesion and the development of local adverse effects are useful factors when imiquimod cream is prescribed. However, although the cream is convenient and effective, regional resistance may develop, and close follow-up is essential because VIN may become malignant. **(Ann Dermatol 27(1) 66～70, 2015)**

-Keywords-
Hyperpigmentation, Imiquimod, Vulvar intraepithelial neoplasia

INTRODUCTION

Most patients with vulvar intraepithelial neoplasia (VIN) tend to visit gynecologists, given the anatomical location of the condition. Consequently, only a few dermatological studies on VIN have appeared. Histopathologically, VIN is the term used by the International Society for the Study of Vulvovaginal Disease to describe squamous cell carcinoma in situ with moderate to severe dysplasia of the vulva[1]. However, this classification does not discuss the clinical manifestations. Of all patients with VIN, approximately 10%～15% have grossly hyperpigmented lesions[2].

Various therapeutic options, including surgery, electrocautery, cryotherapy, 5-fluorouracil treatment, laser therapy, radiotherapy, photodynamic therapy, and local/systemic interferon-α/γ injection, have been employed to treat VIN with varying degrees of success[3]. The anatomical location of the condition encourages physicians to consider non-surgical treatment methods, including imiquimod cream.

Our principal aim was to assess the clinical response of

Received June 25, 2014, Revised October 13, 2014, Accepted for publication November 19, 2014

Corresponding author: Margaret Song, Department of Dermatology, Pusan National University Hospital, 179 Guduk-ro, Seo-gu, Busan 602-739, Korea. Tel: 82-51-240-7338, Fax: 82-51-245-9467, E-mail: smargie@hanmail.net

VIN to topical imiquimod and to describe factors predictive of good outcomes in Korean patients using topical imiquimod.

MATERIALS AND METHODS

Study population

Nine patients diagnosed with VIN were referred to the Department of Dermatology in Pusan National University Hospital between 2003 and 2010. They were treated with 5% imiquimod cream. Patient age, smoking history, medical history, lesional size and distribution, and the presence or absence of lesional hyperpigmentation were recorded. Exclusion criteria were pregnancy, immunodeficiency, any treatment for VIN given within the previous month, and hypersensitivity to the cream.

Methods

Before treatment, we evaluated the clinical characteristics of VIN. Patients were instructed to self-apply imiquimod cream to the vulvar lesion, including normal skin within 1 cm of the lesion, using cotton swabs once daily (late in the evening) three to five times a week. If local side effects such as burning or soreness developed, a reduction in the number of applications was permitted. Patients were instructed to record each application. We evaluated the correlations between clinical response and lesional size, the presence of pigmentation within the lesion, and individual adverse effects. The study endpoint was dermatological in nature, defined as the time when the lesion became clear clinically. Four weeks later, biopsy samples were taken from two patients who developed clinical complete response (CR). Responses were evaluated clinically every month, and we reviewed all series of photographs after study completion. A clinical response was defined as a reduction in total lesion size and was graded as either CR, partial response (PR, 50%～99% reduction in lesion size), minimal response (MR, 25%～50% reduction in lesion size), or no response (NR, ≤25% reduction in lesion size).

RESULTS

The nine consecutive patients ranged in age from 22 to 68 years (mean, 51 years). VIN was diagnosed at a mean of 30.2 months before enrollment (range, 6 months to 10 years). Clinically, one patient (patient 9) had a history of radiation therapy for the treatment of cervical cancer. Three patients (33.3%) had multifocal lesions, one of which involved >50% of the vulvar mucosa. The remaining six patients (66.6%) presented with unifocal lesions.

Table 1. Characteristics and clinical response with 5% imiquimod cream

No.	Age (y)	Duration (mo)	Past history	Presence of hyperpigmentation	Histopathologic type	Lesions	HPV	Tx frequency (/wk)	Tx period (wk)	Adverse effects	Clinical response
1	68	12	–	+	Basaloid	Unifocal	ND	3	16	+	CR
2	41	12	–	+	Differentiated	Unifocal	ND	3	10	+	CR
3	51	120	–	+	Differentiated	Unifocal	ND	3	16	–	CR
4	44	24	–	–	Basaloid	Unifocal	ND	3	32	+	CR
5	61	60	Leiomyoma	+	Basaloid	Unifocal	ND	3	12	–	PR
6	22	6	Nephrotic syndrome	+	Basaloid	Multifocal	ND	5	16	–	PR
7	60	12	CRF, KT, HTN	–	Basaloid	Multifocal	+ (Type 53)	5	25	–	MR
8	49	12	–	–	Basaloid	Unifocal	ND	3	18	–	MR
9	66	14	Cervical cancer (post RTx)	–	Warty	Multifocal	+ (Type 16)	5	31	–	NR

HPV: human papilloma virus, Tx: treatment, ND: not done, CRF: chronic renal failure, KT: kidney transplantation, HTN: hypertension, RTx: radiation therapy. CR: complete response (100% improvement in lesion), PR: partial response (50%～99% reduction in lesion size), MR: minimal response (25%～50% reduction in lesion size), NR: no response (or <25% reduction in lesion size).

The lesions were predominantly pink-to-grayish papules or plaques, and five patients (55.6%) exhibited lesional hyperpigmentation. Four patients had lesions <3 cm in diameter (44.4%), and the other five (55.6%) had lesions >3 cm in diameter.

The most common histological type was basaloid (6/9, 66.7%), followed by differentiated (2/9, 22.2%) and warty (1/9, 11.1%). Two patients with multifocal lesions were subjected to human papilloma virus (HPV) testing; HPV-53 was present in patient 7 and HPV-16 was present in patient 9.

Use of imiquimod cream ultimately yielded four CR (44.4%), two PR (22.2%), two MR (22.2%), and one NR (11.1%) (Table 1). Application frequency, histological subtype, and treatment response did not affect the outcome significantly.

Of the six patients with unifocal lesions, four (66.7%) experienced CR (Fig. 1). None of the three patients with multifocal lesions experienced CR. Similarly, all patients with lesions <3 cm in diameter experienced better therapeutic responses than those with larger lesions. Additionally, pigmented lesions responded better than lesions lacking pigmentation. In one patient in whom the lesion regressed incompletely, the residual lesion actually deteriorated. The patient had a history of radiotherapy for the treatment of intraepithelial cervical neoplasia and, after applying imiquimod for 3 months, was found to have an enlarged, invasive squamous cell carcinoma of the cervix. Despite application of radiotherapy for 5 months, the patient died.

Of all patients, three (33.3%) experienced only local adverse effects, including itching and burning sensations, which resolved after the number of imiquimod applications was reduced. No patient experienced systemic adverse effects during treatment.

DISCUSSION

The treatment of VIN remains challenging for dermatologists and surgeons. Surgery remains the treatment mainstay, but vulvar disfigurement and loss of sexual function

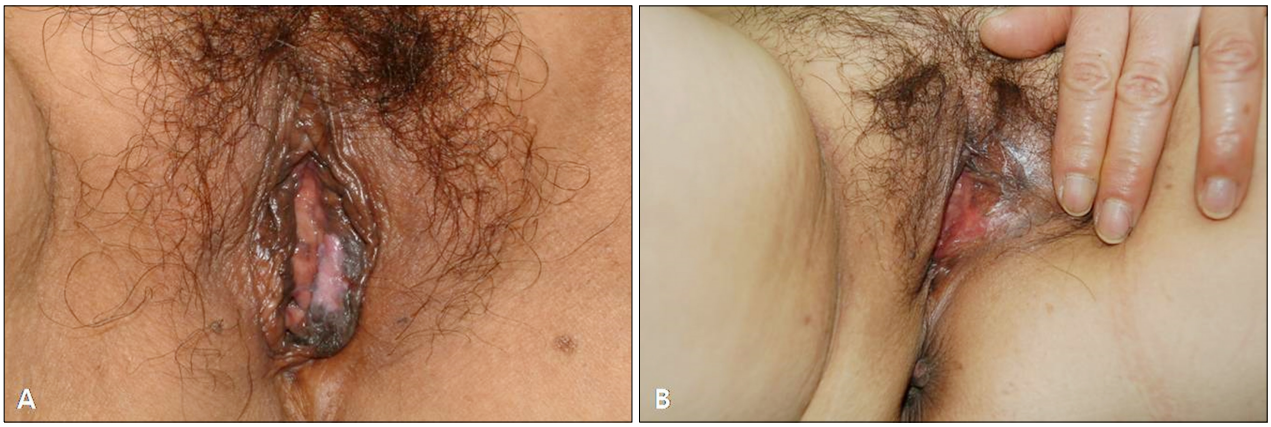

Fig. 1. Localized black-colored pigmented patch on the right vulva (A) showed complete resolution after using 5% imiquimod cream for 8 weeks (B).

Table 2. Imiquimod for the treatment of vulvar intraepithelial neoplasia: review of the literature

Source	No. of patients	No. of responses			No. of recurrence	Mean follow-up (mo)
		CR	PR	Failure&LFU		
Wendling et al.[13] (2004)	12	3	4	5	0	14
Marchitelli et al.[14] (2004)	8	6	2	0	0	22
Le et al.[15] (2007)	33	21	9	3	5	16
Mathiesen et al.[16] (2007)	21	17	2	2	NM	NM
van Seters et al.[7] (2008)	26	9	10	7	0	12
Terlou et al.[9] (2011)	26	10	10	5	1	84
Westermann et al.[10] (2013)	62	47	14	1	17	21
Frega et al.[17] (2013)	32	13	10	9	2	60
Our study (2014)	9	4	2	3	0	24

CR: complete response, PR: partial response, LFU: loss of follow-up, NM: not mentioned.

must be considered. Laser therapy can preserve the anatomical structure, but the recurrence rate is high because of persistent residual HPV infection[4,5]. To ensure therapeutic efficacy, HPV elimination is considered important. Imiquimod is a heterocyclic imidazoquinoline amide that modifies the immune response by acting on the toll-like receptor (TLR)-7 and TLR-8 cascades[6]. The drug also has a direct pro-apoptotic effect on tumor cells and antiviral activity against HPV[7-9]. Several studies have found that imiquimod was the treatment of choice for VIN (Table 2)[10-17]. However, these studies had certain limitations: the treatment periods varied, the follow-up periods were short, and the recurrence rates were unclear. It is unknown whether imiquimod can be used safely and effectively to treat all VIN types, and few useful predictive factors have been suggested. Terlou et al.[9] found a 76% reduction in lesion size in a double-blind randomized trial associated with clinical improvement, but all patients were European (no Asians were included).

The response rate in the present study was 66.7%, which was slightly higher than that found in Western studies. Our subjects did not differ greatly in histopathological subtype, but the frequency of gross lesional hyperpigmentation may have been rather high. Previous reports indicated that 10%～15% of lesions were hyperpigmented, but the present study suggests that hyperpigmentation may be more frequent in Asians[2,12]. However, little is known about the relationship between hyperpigmentation of VIN lesions and the clinical response to imiquimod cream. Of patients with non-hyperpigmented lesions, only one (1/4, 25%) achieved CR. Of patients exhibiting hyperpigmentation, all achieved either CR (3/5, 60%) or PR (2/5, 40%). Therefore, we tentatively suggest that VIN lesion pigmentation may be considered predictive of a good outcome after treatment with imiquimod cream.

All patients who suffered adverse effects experienced CR, whereas only one patient lacking such effects developed CR. We agree with Alessi et al.[12] that the absence of a local reaction to imiquimod is a risk factor for poor response to treatment. The cited authors reported that outcomes were poorer when local reactions were absent.

The recurrence rate after non-surgical treatment of cutaneous neoplasms is concerning. High recurrence rates have been reported after treatments that seek to preserve the vulva; such rates were 40% after laser vaporization, 42% after excision, and 45% after photodynamic therapy[12]. After treatment with imiquimod cream, an earlier reported recurrence rate was 15.6% after 25.6 months. Our current study had a longer follow-up period; the disease-free median follow-up time was 30.2 months. This long-term observation period was a strong feature of our study. However, one limitation was our relatively small sample size. In addition, patient 8 died 3 months after the trial started, following metastasis of intraepithelial cervical cancer. This implies that the malignancy potential must be excluded before imiquimod treatment, because topical imiquimod enhances local skin immune responses, and VIN can potentially progress to invasive vulvar carcinoma. Therefore, if a subject has a history of another malignancy, we recommend evaluation not only of that malignancy but also any possible VIN malignancy.

Both effective and convenient, topical imiquimod may be useful for treating the common forms of VIN. Our present results afford further evidence that topical imiquimod may treat VIN effectively by stimulating the immune system. Further studies with closer observation are required before imiquimod use can become routine.

In conclusion, 5% imiquimod cream showed promise in the treatment of VIN in Korean patients with unifocal, small, or hyperpigmented lesions. Topical imiquimod treatment is convenient, self-administered, and less invasive than surgery. Therefore, we consider topical imiquimod to be the treatment of choice for VIN, but we recommend that the follow-up period be as long as possible and that a poor response to imiquimod be recognized as a sign of low treatment efficacy.

REFERENCES

1. Preti M, Van Seters M, Sideri M, Van Beurden M. Squamous vulvar intraepithelial neoplasia. Clin Obstet Gynecol 2005; 48:845-861.
2. Ronger-Savle S, Julien V, Duru G, Raudrant D, Dalle S, Thomas L. Features of pigmented vulval lesions on dermoscopy. Br J Dermatol 2011;164:54-61.
3. Léonard B, Kridelka F, Delbecque K, Goffin F, Demoulin S, Doyen J, et al. A clinical and pathological overview of vulvar condyloma acuminatum, intraepithelial neoplasia, and squamous cell carcinoma. Biomed Res Int 2014;2014: 480573.
4. Reyes MC, Cooper K. An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. J Clin Pathol 2014;67:290-294.
5. Choi JH, Jue MS, Kim EJ, Joh OJ, Song KY, Park HJ. Extramammary paget disease: minimal surgical therapy. Ann Dermatol 2013;25:213-217.
6. Richter ON, Petrow W, Wardelmann E, Dorn C, Kupka M, Ulrich U. Bowenoid papulosis of the vulva-immunotherapeutical approach with topical imiquimod. Arch Gynecol Obstet 2003;268:333-336.
7. van Seters M, van Beurden M, ten Kate FJ, Beckmann I, Ewing PC, Eijkemans MJ, et al. Treatment of vulvar intraepithelial neoplasia with topical imiquimod. N Engl J Med 2008;358:1465-1473.
8. Terlou A, van Seters M, Kleinjan A, Heijmans-Antonissen C,

Santegoets LA, Beckmann I, et al. Imiquimod-induced clearance of HPV is associated with normalization of immune cell counts in usual type vulvar intraepithelial neoplasia. Int J Cancer 2010;127:2831-2840.
9. Terlou A, van Seters M, Ewing PC, Aaronson NK, Gundy CM, Heijmans-Antonissen C, et al. Treatment of vulvar intraepithelial neoplasia with topical imiquimod: seven years median follow-up of a randomized clinical trial. Gynecol Oncol 2011;121:157-162.
10. Westermann C, Fischer A, Clad A. Treatment of vulvar intraepithelial neoplasia with topical 5% imiquimod cream. Int J Gynaecol Obstet 2013;120:266-270.
11. Hillemanns P, Untch M, Dannecker C, Baumgartner R, Stepp H, Diebold J, et al. Photodynamic therapy of vulvar intraepithelial neoplasia using 5-aminolevulinic acid. Int J Cancer 2000;85:649-653.
12. Alessi SS, Sanches JA, Oliveira WR, Messina MC, Pimentel ER, Festa Neto C. Treatment of cutaneous tumors with topical 5% imiquimod cream. Clinics (Sao Paulo) 2009;64: 961-966.
13. Wendling J, Saiag P, Berville-Levy S, Bourgault-Villada I, Clerici T, Moyal-Barracco M. Treatment of undifferentiated vulvar intraepithelial neoplasia with 5% imiquimod cream: a prospective study of 12 cases. Arch Dermatol 2004;140: 1220-1224.
14. Marchitelli C, Secco G, Perrotta M, Lugones L, Pesce R, Testa R. Treatment of bowenoid and basaloid vulvar intraepithelial neoplasia 2/3 with imiquimod 5% cream. J Reprod Med 2004;49:876-882.
15. Le T, Menard C, Hicks-Boucher W, Hopkins L, Weberpals J, Fung-Kee-Fung M. Final results of a phase 2 study using continuous 5% Imiquimod cream application in the primary treatment of high-grade vulva intraepithelial neoplasia. Gynecol Oncol 2007;106:579-584.
16. Mathiesen O, Buus SK, Cramers M. Topical imiquimod can reverse vulvar intraepithelial neoplasia: a randomised, double-blinded study. Gynecol Oncol 2007;107:219-222.
17. Frega A, Sesti F, Sopracordevole F, Biamonti A, Scirpa P, Milazzo GN, et al. Imiquimod 5% cream versus cold knife excision for treatment of VIN 2/3: a five-year follow-up. Eur Rev Med Pharmacol Sci 2013;17:936-940.