

## CLINICAL REPORT

# Twelve-week Treatment of Lentigo Maligna with Imiquimod Results in a High and Sustained Clearance Rate

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**Topical imiquimod cream is increasingly applied in the treatment of lentigo maligna (LM), in particular for large lesions where surgery may lead to disfiguring scars. Published studies suggest that more frequent and prolonged treatment with topical imiquimod is associated with higher efficacy. In this study we prospectively treated 27 patients suffering from LM on the face with imiquimod 5% cream using an intensive treatment regimen consisting of daily applications for 12 weeks inducing skin inflammation for at least 10 weeks. Twenty-four patients completed the treatment as recommended, 23 were available for follow-up (mean 39 months). Clinical and histopathological clearance was observed in 20 patients after a mean of 14 weeks of treatment. Notably, histopathological examination of a skin biopsy showed clearance of the LM in all 24 patients, including those who still showed some hyperpigmentation at 4 weeks off treatment. A clinical recurrence occurred in only 1 of the 23 patients available at follow-up. These findings suggest that the efficacy of imiquimod can be improved by implementing a more intensive treatment regimen. Randomized controlled trials are needed to confirm our results and establish the role of topical imiquimod in the treatment of LM. Key words: lentigo maligna; imiquimod; clearance, cosmetic.**

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Lentigo maligna (LM) is a slowly evolving type of melanoma *in situ* mainly occurring in chronic sun-damaged skin of the face. The estimated lifetime risk of progression of LM to invasive lentigo maligna melanoma (LMM) is 5% (1). Currently, surgical excision is the treatment of choice for LM (2). However, local recurrences are expected in about 30% after 5.5 years if surgical margins of 5 mm are used. Progression of such local recurrences to LMM is rare and not usually the cause of death (3). Surgical margins of 9 mm are recommended by some (4). Alternatively, staged excision, usually requiring 1–1.5 cm margins for histological clearance, which leads to lower recurrence rates, may be undertaken (5–7). Disadvantages

of surgical treatment are disfiguring scars and functional impairment in particular in larger, facial lesions. Radiotherapy has also been used in the treatment of LM, but is associated with an estimated recurrence rate of 5% after a mean of 5 years. Functional impairment, secondary malignancies, and radiodermatitis are potential adverse effects (8–10).

The risk of local recurrences after cryosurgery are much higher, ranging from 7 to 34%, and scarring may be severe (11, 12).

Treatment of LM with topical imiquimod was first described in 2000 (13). Imiquimod, a toll-like receptor 7 agonist, modulates immune responses and also directly inhibits melanocyte proliferation (14). The obvious advantage of imiquimod treatment in LM lies in the excellent cosmetic result. Therefore, treatment with topical imiquimod is increasingly used for larger LM lesions on the face, where scars after surgery are particularly undesirable, or in patients who decline surgical management. However, the reported treatment efficacy of topical imiquimod for LM is very variable. Response rates in a few hundred reported patients range between 50% and 100% for the off-label use of imiquimod in LM (15–21). These published studies used different treatment regimens, in particular with respect to frequency of application and treatment duration and are therefore difficult to compare (Table I). However, from an analysis of the published data we suggest that treatment of LM with imiquimod is possibly more effective after longer treatment duration and higher frequency of application; this is also supported by our clinical experience. Furthermore, induction of a local inflammatory response seems an important determinant of efficacy.

We therefore designed a prospective study to treat patients with imiquimod cream with an intensive treatment regimen inducing local skin inflammation for a prolonged period of time.

## PATIENTS AND METHODS

All patients consulting the department of Dermatology at the VU Universiteit Medical Center for LM were given the option of treatment with either surgery, radiotherapy or topical imiquimod. Twenty-seven patients (21 women, mean age 71 years [range: 44–87], 6 men, mean age 69 years [52–85]; previous excision or cryotherapy in 20/27) decided for topical imiquimod and were treated between Nov 2007 and 2012 for histopathologi-

Table I. Studies of imiquimod 5% cream for lentigo maligna

Applications/week (Ref)	Duration of treatment, weeks, n	Inflammation	Responders/included patients n	Response %	Follow-up, months post Rx Mean
7/7 (15)	5–13	No comment	6/6	100	10
7/7 (16)	5–13	No comment	22/28	80	12
5/7 (17)	12	Associated with histological clearance ( $p=0.04$ )	20/38 (5 excluded)	53	1, then excision
5/7 (18)	12	30/40 <sup>a</sup>	33/40 clinically	83	2, then excision
			30/40 histologically	75	
3/7 for 4 weeks, if no erythema: 7/7 (19)		31/37 responders; 2/11 non-responders	37/48	77	49
7/7 (Present study)	14 [12–23]	24/24	20/24 clinically	83	1
			24/24 histologically	100	
			<u>At follow-up</u>		
			22/23 clinically		
			20/21 clinically & histologically <sup>b</sup>	95	39

<sup>a</sup>In 10/40 no erythema after 4 weeks; after addition of tazarotene 0.1% gel erythema in all. <sup>b</sup>Excluding one 44-year-old woman who had undergone excision of the lesion after imiquimod treatment because there was remaining hyperpigmentation, in retrospect excision was unnecessary; 2 not available for a biopsy but only clinical follow-up.

cally proven LM. Patients were instructed to apply imiquimod 5% cream (Aldara®, Medapharma) once daily with a 1–2 cm margin around the pigmented lesion for at least 12 weeks. A local inflammatory reaction (erythema/crusts), usually appearing within 2 weeks, was required to be clinically visible for at least 10 weeks. Depending on the local reaction the treatment was adjusted (minimum 3 times per week, maximum 3 times per day). Approximately 4 weeks and 1 year after cessation of treatment patients were reviewed for clinical evaluation, with a biopsy taken from the original site of the LM for histopathological examination. The study design was reviewed and consented by the ethics committee of the VUmc.

## RESULTS

Of the 27 patients, 24 (19 women, 5 men) completed the treatment as recommended (see Table I). Complete clinical clearance (no remaining hyperpigmentation) at 4 weeks post treatment was achieved in 20/24 patients after a mean of 14.2 weeks (median 12 [12–23]) treat-

ment. Interestingly, histopathological investigation of skin biopsies at 4 weeks after treatment showed regression of LM in all 24 patients who completed treatment according to protocol. A second biopsy taken 12 months after treatment showed persistent regression in 20/21 patients available for biopsy. A clinical recurrence occurred at 12 months after treatment with imiquimod in one patient, whose LM had been incompletely excised before imiquimod treatment. At 39 months clinical follow-up (median 38 [21–70]) no recurrence has occurred in 22/23 patients (excluding the one patient who had undergone complete excision: lost to follow-up) (Fig. 1).

Three patients did not complete the treatment; two patients discontinued treatment after 4 and 6 weeks because of intolerable local inflammation. One 84-year-old patient did not respond with inflammation after 8 weeks twice daily imiquimod; we assume the patient was not compliant with treatment. The LM had not changed at 12 weeks follow-up.

Adverse effects were flu-like systemic reactions ( $n=2$ ), postinflammatory erythema ( $n=4$ )/hyperpigmentation ( $n=2$ ), oedema ( $n=2$ ) and dysaesthesia/sensitive skin ( $n=2$ ) (6 females, 1 male). Apart from persistent erythema/oedema on the cheek in 2 females, the cosmetic results were excellent and there was no functional impairment.

## DISCUSSION

Using an intensive treatment regimen, consisting of initially daily imiquimod applications leading to visible skin inflammation for at least 10 weeks, histological clearance was achieved in all treated patients. This confirms our hypothesis that intense treatment results in a high clearance rate. Ninety-two percent (22/24) of patients (excluding the one patient with a recurrence and one with excision after imiquimod) who completed the treatment protocol had sustained remission after a 39-months mean follow-up. Patient compliance is crucial as the inflamma-

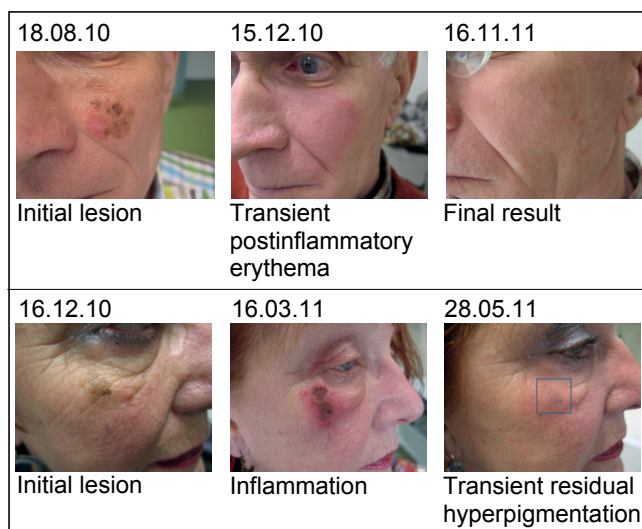


Fig. 1. Effect of topical imiquimod in lentigo maligna. Permission is given to publish this figures by the patients.

tion is not always easy to tolerate. Only one recurrence occurred in a woman whose LM had been incompletely excised prior to imiquimod treatment.

Residual hyperpigmentation after treatment with imiquimod does not necessarily indicate persistence of LM. A skin biopsy, for example 3 months after imiquimod treatment, will show if any further treatment is needed.

In the case of clinical remission we recommend a biopsy 3 months and/or one year after treatment to confirm remission of LM histologically. A biopsy 4 weeks after cessation of treatment seems unnecessary and possibly misleading, as sometimes the effect of the treatment is not complete and the response to treatment cannot be judged at that stage. There is a very small subset of patients that seems unresponsive to imiquimod treatment.

Several concerns with respect to imiquimod treatment of LM remain. Firstly, there is the potential risk of LMM being misclassified as LM. It is estimated that approximately 16% of surgically treated cases diagnosed as LM upon biopsy, represent invasive LMM after pathological examination of the completely excised lesion (22, 23). Surgical treatment is preferred over application of a topical agent in such cases (24). Secondly, LM may recur following treatment with imiquimod without clinically visible hyperpigmentation. This pitfall can be managed with post-treatment biopsies and histopathological examination.

Large, randomized, long-term studies of topical imiquimod for the treatment of LM are needed. The results of our study strongly suggest that more intensive treatment regimens are associated with higher treatment efficacy. Randomized controlled trials comparing surgery with the presented intensive imiquimod treatment for LM should follow.

In conclusion, treatment of LM with excision or radiotherapy leads to high success rates and are therefore first and second choices of treatment, respectively. However, both excision and radiotherapy have their own disadvantages, they may e.g. cause disfiguring scars and are not suitable for every patient. Treatment with topical imiquimod is an alternative for patients with LM who object to excision or radiotherapy or are not suitable for other reasons. We have demonstrated the feasibility of an intensive treatment regimen with imiquimod leading to high and sustained remission rates with excellent cosmetic results.

*The authors declare no conflicts of interest.*

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