Efficacy of Imiquimod Cream, 5%, for Lentigo Maligna After Complete Excision

A Study of 43 Patients

Lena Ly, MBBS; John William Kelly, MBBS, FAcD, MD; Rodney O’Keefe, MBBS, FRCPA; Tina Sutton, BSc, BMBS; John P. Dowling, MBBS, FRCPA; Sarah Swain, MBBS, FRCPA; Marguerite Byrne, MBBS; NathanCurr, MBBS; Rory Wolfe, BSc, PhD; Alex Chamberlain, MBBS, FAcD; Martin Haskett, MBBS, FAcD

Objective: To determine the efficacy of imiquimod cream, 5%, in the treatment of lentigo maligna (LM).

Design: Open-label before-and-after interventional study.

Setting: A multidisciplinary melanoma clinic at a major tertiary hospital.

Patients: Forty-three patients with biopsy-proven LM of greater than 5 mm in diameter completed this study.

Interventions: Imiquimod cream, 5%, was applied to the lesion 5 days a week for 12 weeks. The original lesion was excised with a 5-mm margin.

Main Outcome Measures: The primary outcome was histopathologic evidence of LM in the excision specimen assessed independently by 2 of 3 dermatopathologists. Visible inflammation during treatment and macroscopic clearance were recorded.

Results: When 5 of the 43 patients with discordant histopathologic assessment of the excision specimen were excluded, 20 of 38 patients (53% [95% confidence interval, 36%-69%]) demonstrated histopathologic clearance of LM after imiquimod treatment. Visible inflammation was significantly associated with histopathologic clearance (P = .04), but the positive predictive value was low (62%). Macroscopic clearance showed some association with histopathologic clearance (P = .11). Dermatopathologist concordance for all 43 specimens was substantial (κ = 0.77; 95% confidence interval, 0.57-0.96).

Conclusions: Imiquimod cream, 5%, has limited efficacy in the treatment of LM when determined by histopathologic assessment of the entire treated area. The clinical signs of visible inflammation during treatment and apparent lesion clearance cannot be relied on to assess efficacy.

Trial Registration: anzctr.org.au Identifier: ACTRN12610000066088

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R ESEARCHERS AND DERMATOLOGISTS have shown considerable interest in imiquimod cream, 5% (Aldara; Graceway Pharmaceuticals, LLC, St Paul, Minnesota), in the treatment of lentigo maligna (LM), with 12 case series reporting variable response rates ranging from 67% through 100%.1-12 The methods used in these series are highly variable, and some do not acknowledge the limitations regarding macroscopic or histopathologic assessment of LM and its margins. Significant interobserver variation between pathologists when delineating the edge of LM as distinct from adjacent changes of melanocytic hyperplasia in sun-damaged skin has been reported.13-15 Inherent difficulties in histopathologic assessment of the excision specimen were excluded, 20 of 38 patients (53% [95% confidence interval, 36%-69%]) demonstrated histopathologic clearance of LM after imiquimod treatment. Visible inflammation was significantly associated with histopathologic clearance (P = .04), but the positive predictive value was low (62%). Macroscopic clearance showed some association with histopathologic clearance (P = .11). Dermatopathologist concordance for all 43 specimens was substantial (κ = 0.77; 95% confidence interval, 0.57-0.96).

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Author Affiliation: Victorian Melanoma Service (Drs Ly, Kelly, Sutton, Dowling, Swain, Byrne, Curr, Chamberlain, and Haskett) and Department of Anatomical Pathology (Drs Dowling and Swain), Alfred Health, and Departments of Medicine (Dr Kelly) and Epidemiology and Preventive Medicine, Monash University (Dr Wolfe), Melbourne; Dermpath Pty Ltd, East Ivanhoe (Dr O’Keefe); Skin and Cancer Foundation, Carlton (Dr Sutton); Anatomical Pathology, Peter MacCallum Institute, East Melbourne (Dr Swain); and Department of Anaesthetics, Fremantle Hospital and Health Service, Fremantle (Dr Curr), Australia.
lesions were marked with a surgical marking pen (Acculine Engineering, Inc, Waterbury, Connecticut) and photographed (Nikon 4500 COOLPIX S9 camera; Nikon Corporation, Tokyo, Japan).

**Treatment Protocol**

Patients were instructed to apply imiquimod cream, 5%, to cover the lesion and 1 cm beyond its margin, massaging the cream in until invisible, once daily, Monday through Friday, for 12 weeks. They were instructed to apply nothing else to the area for the next 8 hours. The 12-week period was chosen to equate with the longest periods of imiquimod treatment used for management of basal cell carcinoma and to limit the period for which patients had to tolerate inflammation. Patients were instructed to take rest periods whenever the patient or treating dermatologist judged there was excessive inflammation, defined as marked discomfort, weeping or crusting of the lesion, or epidermal erosion. Patients were instructed to recommence application of the cream when this inflammation subsided. All patients undergoing evaluation completed a total treatment period of 12 weeks including rest periods.

**Wide Local Excision**

Wide local excision was planned to occur within 4 weeks of completion of imiquimod treatment and was performed after complete resolution of macroscopic inflammation. A standard 5-mm margin was added to the pretreatment lesion markings as determined by the tattoo or pretreatment photographs.

**MAIN OUTCOME MEASURES**

The same dermatologist (M.H.) assessed and recorded the severity of inflammation at least monthly, and after 12 weeks of treatment, he assessed the treatment site visually using loupe magnification, dermoscopy, and the Wood lamp. The presence of residual pigmentation was recorded. The entire wide local excision specimen was serially sectioned and histopathologically assessed with hematoxylin-eosin stains by 2 of 3 dermatopathologists (J.P.D., S.S., and R.O.). Residual LM was defined by the presence of a proliferation of atypical melanocytes arranged as single cells or nests along the basal epidermis or eccrine ducts. We assessed the interpathologist concordance rate.

**STATISTICAL ANALYSIS**

We used commercially available software (Stata, release 11; StataCorp LP, College Station, Texas) to conduct all analyses. An exact binomial confidence interval (CI) was calculated for histopathologic efficacy. We used $\chi^2$ tests to assess the statistical significance (defined as $P < .05$) of associations of macroscopic clearance and inflammation with histopathologic clearance. We also calculated the sensitivity and specificity of macroscopic clearance and inflammation as a marker for identifying histopathologic clearance. We used the methods of Landis and Koch\textsuperscript{19} to interpret $k$ statistics for interpathologist agreement and we calculated normal-theory CIs for $k$ values from 1000 bootstrap resamples of the data.

**RESULTS**

Forty-eight patients were enrolled and 5 withdrew, leaving 43 who completed the study. The withdrawals occurred due to intolerable local inflammation ($n=3$), re-
In this study, imiquimod cream, 5%, was shown to have efficacy, with clearance of LM identified in 20 of 38 patients (53% [95% CI, 36%-69%]). Efficacy was assessed after imiquimod application for 12 weeks by 2 dermatopathologists independently examining the specimen provided by excision of the entire lesion and a 5-mm margin beyond it. An association between macroscopic clearance (removal of pigment) and histopathologic clearance was shown (P = .11; PPV, 65%) but this low value similarly limits its use as a clinical marker of therapeutic response. A visible inflammatory response usually occurs (sensitivity, 90%) with a successful outcome, but it cannot be depended on as an indicator of successful treatment (specificity, 39%; P = .04; PPV, 62%). Although discordance was noted in histopathologic assessments of 5 of 43 excision specimens, substantial agreement occurred between the 3 expert dermatopathologists (κ = 0.77; 95% CI, 0.57-0.96).

The best assessment method for therapeutic trials for LM is the recurrence rate found in long-term follow-up. Because standard wide-excision surgery offers as high as 90% efficacy and permits the assessment of the entire treated lesional area, it is the next best assessment method. An efficacy rate of 50% based on 10 patients followed up for a mean of 33 months (range, 11-56 months) has been recently reported. Two previous studies based on histopathologic assessment of the complete surgical excision specimen reported histopathologic clearance rates of 67% (4 of 6) and 75% (30 of 40) (Table 2). Their efficacy rates and our rate of 53% (20 of 38) are noted to be lower than those of other studies, which used partial biopsy findings or macroscopic clearance to assess efficacy. Such assessment methods may overestimate treatment efficacy by missing persistent disease.

No standardized application protocol exists, to our knowledge, and our results are limited to a treatment regimen of 5 days per week for 12 weeks, which is similar to that of 9 other studies that used treatment duration of 12 weeks but with variable application fre-
and in sun-damaged skin.42 Although it has been argued that there is a risk of missing minor residual changes if reliance is placed on hematoxylin-eosin stains only without additional immunohistochemical stains, the use of melan-A has been shown to contribute to errors in the diagnosis of melanocytic lesions in sun-damaged skin tumors.43,44 Therefore, immunostaining was not relied on for diagnosis of LM in this study. Partial biopsy of lesions compounds these difficulties. Patients with pretreatment discordant histopathologic findings were not entered into this study, and discordant histopathologic findings occurred only in 5 posttreatment specimens (discarded from analysis), so the overall concordance was high.

Imiquimod cream, 5%, used 5 days a week for 12 weeks as monotherapy, has lower efficacy in treating LM than surgical excision but may be comparable with that of other nonsurgical options for treatment of LM, including radiotherapy, cryotherapy, and carbon dioxide laser, with reported 5-year recurrence rates of 13.2%, 34.3%, and 42.2%, respectively.45 Although a visible inflammatory response usually is associated with treatment success, the inflammatory response and apparent macroscopic clearance were not reliable means of assessing therapeutic success. Imiquimod could be used as an adjunct field treatment before or after surgical excision to decrease recurrence rates and also may have a role in the management of LM when surgery is contraindicated. Close follow-up of patients with LM treated with this modality only is strongly recommended.

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Correspondence: Lena Ly, MBBS, Victorian Melanoma Service, Level 1, Alfred Center, Alfred Health, Commercial Road, Melbourne, Victoria, Australia 3004 (lenaly21@yahoo.com.au).

Author Contributions: Dr Haskett had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kelly, Sutton, Byrne, Curr, and Haskett. Acquisition of data: Ly, Kelly, O’Keefe, Sutton, Byrne, Curr, Chamberlain, and Haskett. Analysis and interpretation of data: Ly, Kelly, Dowling, Swain, Wolfe, Chamberlain, and Haskett. Drafting of the manuscript: Ly, Kelly, Swain, Wolfe, Chamberlain, and Haskett. Critical revision of the manuscript for important intellectual content: Ly, Kelly, O’Keefe, Sutton, Dowling, Swain, Byrne, Curr, Wolfe, Chamberlain, and Haskett. Statistical analysis: Wolfe. Obtained funding: Sutton and Haskett. Administrative, technical, and material support: Ly, Kelly, Sutton, Byrne, Curr, and Haskett. Study supervision: Kelly, Chamberlain, and Haskett.

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Table 1. Inflammation and Clearance in 38 Patients Treated With Imiquimod Cream, 5%

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Histopathologic Clearance, No. of Patients</th>
<th>Predictive Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Visible inflammation</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Macroscopic clearance</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>

Abbreviations: neg, negative; pos, positive.

Table 2. Summary of Case Series Using Staged Wide Local Excision to Assess Imiquimod Treatment Efficacy

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Male to Female Ratio/ Age Range, y</th>
<th>Location</th>
<th>Imiquimod Cream, 5%, Regimen</th>
<th>Clearance, No. (%)</th>
<th>Time to Surgical Excision, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>38 /1.26/27-90</td>
<td>Mostly face</td>
<td>5 d/wk for 12 wk</td>
<td>20/38 (53)</td>
<td>20/38 (53)</td>
<td>4</td>
</tr>
<tr>
<td>Cotter et al, 2008</td>
<td>40 /1.11/49-92</td>
<td>Mostly face</td>
<td>5 d/wk for 12 wk &amp; 4</td>
<td>33/40 (83)</td>
<td>30/40 (75)</td>
<td>8</td>
</tr>
<tr>
<td>Fleming et al, 2004</td>
<td>6 /Unknown/42-79</td>
<td>Mostly face</td>
<td>Daily application for 6 wk</td>
<td>5/6 (83)</td>
<td>4/6 (67)</td>
<td>2</td>
</tr>
</tbody>
</table>

*Ten patients also applied tazarotene, 0.01%.
REFERENCES


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