A quantitative systematic review of the efficacy of imiquimod monotherapy for lentigo maligna and an analysis of factors that affect tumor clearance

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Background: The reported efficacy of imiquimod for lentigo maligna varies widely, without consensus on tumor or treatment factors that can impact tumor clearance.

Objective: We sought to provide a more precise estimate of clearance rates in patients with lentigo maligna who are treated with imiquimod and to analyze factors that can impact tumor clearance.

Methods: We performed a literature search for biopsy-proven lentigo maligna treated with imiquimod monotherapy, linked treatment and outcome data to individual tumors, calculated histologic and clinical clearance rates with 95% confidence intervals (CIs), and analyzed the impact of tumor and treatment factors on tumor clearance using logistic regression.

Results: Based on 347 tumors from 45 studies, histologic and clinical clearance rates were 76.2% (95% CI, 71.4-81.0%) and 78.3% (95% CI, 73.6-82.9%), respectively. The incidence of clinical recurrence was 2.3% (95% CI, 0.5-4.2%), with a mean follow-up of 34.2 ± 11.8 months. Treatment with >60 total applications, or with >5 applications per week was associated with a higher likelihood of histologic clearance (odds ratio, 8.4 [95% CI, 2.9-24.1] and odds ratio, 6.0 [95% CI, 2.4-14.7], respectively).

Limitations: Our limitations included the accuracy and scope of published data, variable follow-up times, potential patient selection, and publication bias related to case series/cohort designs of previous studies.

Conclusion: Imiquimod offers a 76% histologic and 78% clinical clearance rate for lentigo maligna. Both cumulative dose and treatment intensity affect tumor clearance. (J Am Acad Dermatol 2015;73:205-12.)

Key words: imiquimod; lentigo maligna; melanoma.

Lentigo maligna (LM) is the most commonly diagnosed subtype of melanoma in situ,[1] often arising in sun-damaged skin of the head and neck. Left untreated, LM can develop into LM melanoma, which has the same prognosis as invasive melanoma.[2] Multiple treatment modalities for LM exist. Standard excision with a 5-mm margin results in recurrence rates ranging from 6% to 20%.[3-5] Mohs micrographic surgery allows for better pathologic clearance compared to excision, with a 98.2% cure rate.[5,6] However, factors such as resectability, age, patient preference, and potential disfigurement can preclude surgical resections of LM. Nonsurgical options, such as cryotherapy, radiation, laser, and

Abbreviations used:

CI: confidence interval
LM: lentigo maligna
OR: odds ratio

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Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication May 14, 2015.
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Published online June 15, 2015.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.05.022

curettage, can be effective but may result in higher risks of scarring, long-term recurrence, or secondary skin cancers.[7-10]

Imiquimod is a synthetic imidazoquinoline amine that binds to Toll-like receptors, resulting in the production and release of endogenous cytokines and chemokines for antitumor activity and interleukins for antiangiogenic and proapoptotic signaling.[11,12] This topical immunomodulator is approved by the US Food and Drug Administration for the treatment of actinic keratoses, superficial basal cell carcinomas, and external anogenital warts.[13] Since 2000, imiquimod has also been used off-label to treat LM.

Published data on the efficacy of imiquimod in patients with LM remain limited to case reports and cohort studies. Clearance rates varied from 100% in early case reports and small case series to the 60% to 80% range in later larger cohort studies.[14-17] There is only 1 randomized controlled trial that found no statistically significant difference in histologic clearance rates produced by imiquimod monotherapy and imiquimod and tazorac combination therapy for LM (64% vs 78% [$P < .05$]).[18] Existing studies have a wide variation in reported treatment protocols, the assessment of outcomes, and duration of follow-up, making it challenging to reach a consensus regarding the optimal treatment regimen. Literature reviews analyzed data at the study level rather than the individual tumor level and often aggregated outcomes for primary and recurrent tumors, in situ and microinvasive tumors, and for tumors treated with imiquimod alone or in combination therapy with cryotherapy, laser, or other topical agents.[5,19] Therefore, it has been difficult to identify prognostic factors that influence outcomes of imiquimod treatment in patients with LM.

To address some of these issues, we performed a systematic quantitative review of 45 studies published between 2000 and 2014 on the use of imiquimod monotherapy in biopsy-proven cases of LM, encompassing 347 tumors with 660 patient-years of follow-up. Data were collected and analyzed at the tumor level, allowing for more precise estimates of clinical and histologic clearance rates and better statistical analysis of tumor and treatment factors that can impact treatment response.

CAPSULE SUMMARY

- There is variability in the reported efficacy of imiquimod in the treatment of lentigo maligna.
- Based on our systematic review, the histologic clearance rate is 76.2% (71.4-81.0%). Treatment with more than 60 total applications or more than 5 applications per week increased the likelihood of histologic clearance.
- In planning therapy, clinicians should be aware that cumulative dose and treatment intensity impact histologic clearance.

METHODS

Data collection

PubMed search parameters were restricted to studies published in English between 2000 and 2014 containing the following terms: "Aldara," "imiquimod," "lentigo maligna," and "melanoma in situ." These studies were independently reviewed by Ms Mora and Dr Nguyen. Differences in study interpretation were discussed among all 3 authors to reach a consensus. All included cases were treated with imiquimod 5% cream. Tumors were excluded if (1) the diagnosis of LM was equivocal (ie, there was discordance between two pathology reviews of the biopsy specimen); (2) there was an invasive component within the area of LM on the initial or end of treatment biopsy specimens; or (3) if tumors were treated with a combination of imiquimod and topical retinoids, lasers, or cryotherapy. For case series with data at the individual tumor level, only those tumors treated with combination therapy were excluded—the remaining tumors were included in the analysis. For cohort studies with aggregated data, if part of the cohort was treated with combination treatment, the entire cohort was excluded because we cannot determine which specific tumors received combination therapy and which did not.

For each tumor included in the study, the following data were recorded when available: patient age and sex; tumor type, location, and size; previous treatment; number of imiquimod applications; duration of treatment (in weeks); clinical and histologic clearance and recurrence; and follow-up (in months). "Cohort" studies mainly contained aggregate data, while "case report" and "case series" provided detailed information on each tumor. "Primary" tumors had no previous treatment; "recurrent/previously treated" tumors failed ≥1 previous treatments. Clinical clearance was defined as no residual pigmentation based on visual examination, dermoscopy, or confocal microscopy. Histologic clearance was defined as no evidence of residual LM on biopsy specimens examined at the