## Imiquimod Treatment of Lentigo Maligna: An Open-Label Study of 34 Primary Lesions in 32 Patients

Lentigo maligna (LM) is an in situ lesion with a 2% to 50% risk of progression to LM melanoma.[1] Currently, surgery or radiotherapy is usually recommended as the primary treatment for LM. In the literature, the recurrence rates reported for radiotherapy range from 0% to 19%, with a mean recurrence rate of approximately 7%; in addition, radiotherapy carries the risk of causing chronic radiodermatitis or radiation-induced malignant neoplasm.[2] A margin-controlled excision using "slow Mohs" (rush permanent sections) and Mohs micrographic surgery has the lowest recurrence rate, perhaps as low as 3%.[3]

**Methods.** Thirty-two patients with 34 histologically confirmed facial LM lesions were enrolled in an open-label trial of imiquimod, 5%, cream (Aldara; 3M Pharma, Rueschlikon, Switzerland). No patient had been treated by other methods previously. The diagnosis was based on clinical examination including dermoscopy and histologic evaluation of a 3-mm punch biopsy specimen. Informed consent was obtained from all patients.

Topical imiquimod, 5%, cream was applied to the pigmented areas of the LM lesions, excluding the surrounding margin, for 2 to 20 weeks. Patients were examined every 3 or 4 weeks. The cream was applied with or without occlusion (Tegaderm; 3M, St Paul, Minnesota) until a weeping erosion of the whole pigmented skin area developed. In 2 cases, inflammation was triggered by 2×2 liquid nitrogen cryotherapy (2 freeze-thaw cycles with a freezing time of 2 seconds each). The patient used a topical antimicrobial solution 2 to 3 times daily. A follow-up examination was performed every 3 months. If complete clinical clearance was not achieved, lesion biopsy specimens were taken again with a 3-mm punch.

**Results.** The clinical details of the patients are listed in the **Table**. Thirty-two patients, 13 men and 19 women (mean age, 75 years) with 34 LM lesions were enrolled in the study. All lesions were on the face, the most com-

**Table. Patient Characteristics**

| Patient No./ Sex/Age, y | Lesion Location | Lesion Size, cm | Duration, wk[a] | Application Frequency, No. | Inflammatory Response | Outcome | Follow-up, mo |
|---|---|---|---|---|---|---|---|
| 1/F/85 | Left cheek | 2.8×1.5 | 4 (2) | 3/wk | Strong | PCC; HC; persisting turgid redness | 22 |
| 2/F/66 | Right cheek | 1.3×1.5 | 13 (8) | 5/wk | Strong | CCC; persisting telangiectasia | 21 |
| 3/F/72 | Left cheek | 1.0×1.0 | 8 (4) | 2/d | Severe | PCC; HC; persisting telangiectasia | 31 |
| 4/F/95 | Left cheek | 0.5×1.8 | 3 (2) | 1/d | Strong | CCC | 16 |
| 5/F/84 | Left neck | 1.5×2.0 | 5 (3) | 1/d | Moderate | CCC | 17 |
| 6/F/68 | Right cheek | 3.5×2.5 | 10 (3) | 1/d; after 3 wk, 2/d for 2 wk plus occlusion | Strong | CCC | 19 |
| 7/F/81 | Right cheek | 2.0×1.5 | 13 (6) | 1/d; after 4 wk, 2/d | Mild | CCC; persisting telangiectasia | 16 |
| 8/F/78 | Left lower eyelid | 0.5×0.5 | 8 (4) | 5/wk plus occlusion | Strong | CCC | 19 |
| 9/F/78 | Left cheek | 4.2×6.2 | 7 (6) | 2/d | Mild | CCC | 22 |
| 10/F/79 | Left temple, left lower eyelid, and right alar wing of nose | 1.5×1.0<br>0.5×0.5<br>1.3×1.2 | 6 (3) | 1/d; after 3 wk, unique 2×2 cryotherapy[b] | Severe | CCC | 18 |
| 11/F/60 | Left cheek | 3.2×1.5 | 2 (1.5) | 2/d | Strong | CCC | 18 |
| 12/F/71 | Left temple | 1.5×1.5 | 7 (5) | 2/d | Strong | PCC; HC | 14 |
| 13/F/61 | Left zygomatic arch | 2.5×1.5 | 7 (4) | 2/d plus occlusion | Strong | PC; HC | 20 |
| 14/F/72 | Right temple | 2.0×1.5 | 12 (10) | 1/d | Severe | CCC | 24 |
| 15/F/64 | Left alar wing of nose | 1.5×1.0 | 20 (16) | 1/d; after 8 wk, unique 2×2 cryotherapy[b] plus occlusion | Strong | CCC | 16 |
| 16/F/76 | Left cheek | 3.0×1.0 | 2 (1) | 2/d | Strong | CCC | 16 |
| 17/F/83 | Tip of nose | 0.5×0.5 | 6 (4) | 2/d | Mild | CCC | 19 |
| 18/F/70 | Left cheek | 3.0×1.0 | 5 (3) | 2/d | Moderate | CCC | 17 |
| 19/F/84 | Right cheek | 4.0×3.0 | 16 (12) | 5/wk; after recurrence, 2/d; after 4 wk, 2/d plus occlusion | Strong | Recurrence at 30 mo | 5 |
| 20/M/93 | Bridge of nose | 1.0×0.5 | 10 (7) | 1/d | Strong | PCC; HC | 17 |
| 21/M/84 | Nose | 2.5×2.5 | 8 (6) | 2/d | Strong | CCC | 18 |
| 22/M/66 | Right earlobe | 0.7×0.5 | 3 (2) | 1/d | Moderate | CCC | 17 |
| 23/M/83 | Left lower eyelid | 0.4×0.4 | 3 (2) | 2/d plus occlusion | Severe | CCC | 17 |
| 24/M/86 | Left earlobe | 1.0×1.0 | 4 (2) | 1/d | Strong | PCC; HC | 19 |
| 25/M/63 | Bridge of nose | 0.8×0.5 | 4 (1) | 2/d | Moderate | CCC | 21 |
| 26/M/79 | Right alar wing of nose | 0.5×0.5 | 7 (6) | 2/d | Strong | CCC | 19 |
| 27/M/50 | Left earlobe | 0.8×0.5 | 7 (5) | 1/d | Strong | CCC | 18 |
| 28/M/68 | Right upper eyelid | 0.5×0.5 | 4 (3) | 2/d plus occlusion | Strong | CCC | 21 |
| 29/M/72 | Right alar wing of nose | 0.5×1.5 | 7 (3) | 1/d | Strong | CCC | 9 |
| 30/M/80 | Left cheek | 2.5×3.5 | 8 (4) | 2/d | Moderate | CCC | 10 |
| 31/M/66 | Right cheek | 2.2×4.0 | 10 (7) | 2/d | Strong | CCC | 12 |
| 32/M/72 | Right cheek | 1.5×1.0 | 5 (3) | 1/d | Strong | CCC | 5 |

Abbreviations: CCC, complete clinical clearance; HC, histologically confirmed; PCC, partial clinical clearance (residual pigmentation).
[a] Duration of treatment (duration to the point of skin reaction).
[b] Liquid nitrogen cryotherapy using 2 freeze-thaw cycles with a freezing time of 2 seconds each.

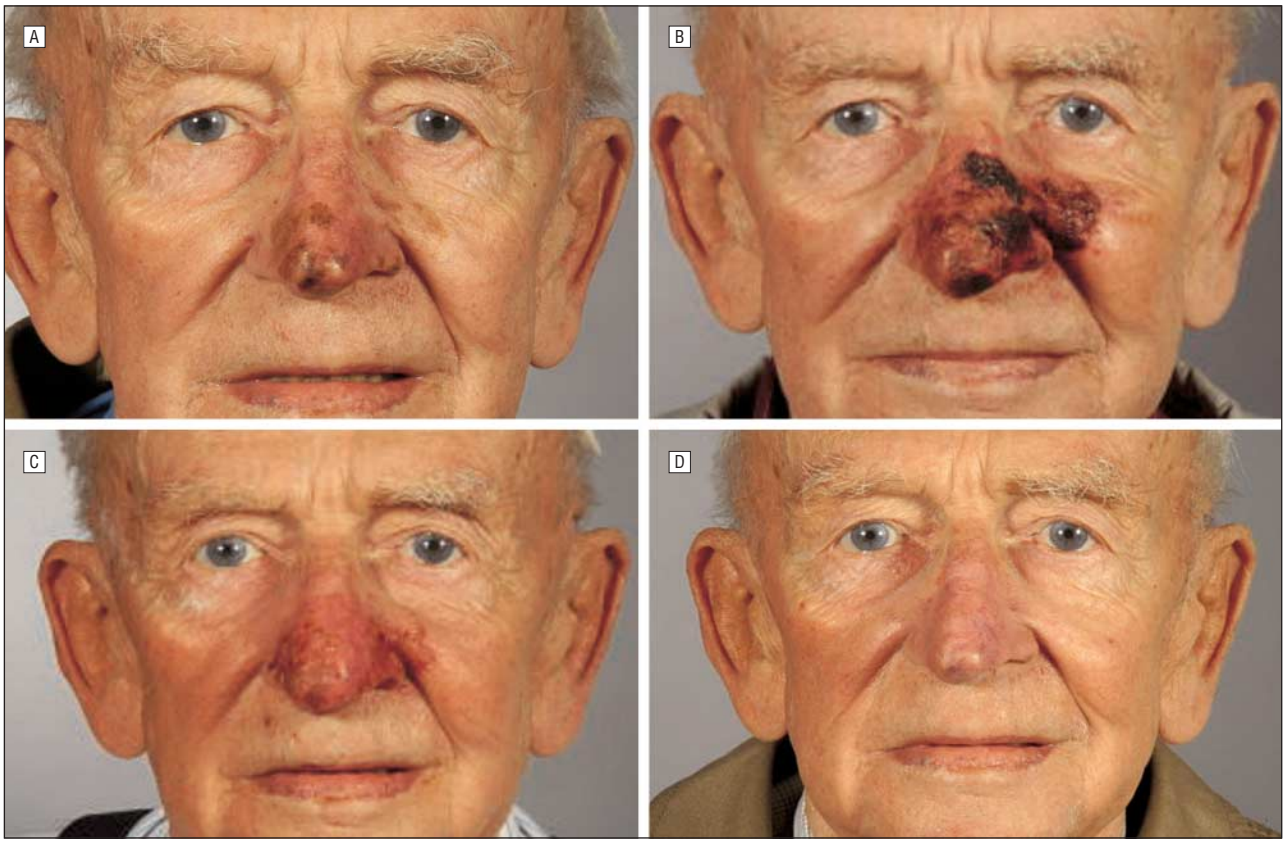


**Figure.** Patient with lentigo maligna treated with imiquimod. A, Before therapy. B, After 20 days of twice-daily imiquimod application. C, Fourteen days after imiquimod treatment was stopped. D, Twelve weeks after imiquimod treatment was stopped.

mon site being the cheeks (14 of 34). All 34 LM lesions completely cleared as assessed clinically (**Figure**). Six lesions showed a reappearance of pigmentation at follow-up. Biopsy specimens were taken of these 6 lesions for histologic and immunohistochemical analysis, the results of which confirmed complete response in all 6 cases; only melanophages and melanin were found within the dermis. No other patient showed recurrences (mean follow-up time, 17.2 months; follow-up range, 5-31 months).

The median time of imiquimod application was 7 weeks (range, 2-20 weeks). In most patients (30 of 34), the cream was applied once or twice daily. The median time to induce an inflammatory response was 4 weeks (range, 1-16 weeks). Clinical evidence of an inflammatory response was seen in all lesions. Six lesions had no clinical evidence of an inflammatory response initially, so the therapy was intensified either by increasing the application frequency of the cream to twice daily or by occlusion or triggering an inflammation with $2 \times 2$ cryotherapy. Three lesions were successfully treated with imiquimod under occlusion from the beginning.

Apart from irritation of the treatment area, no severe local or systemic reactions were seen. In 4 patients, persisting telangiectasia or a turgid redness remained for at least 3 months after therapy. Histologically, a residual cell infiltrate with ectatic vessels was seen in the upper dermis. No patient had clinical evidence of scarring after treatment. One patient developed persistent vitiligo-like white patches on the dorsal surfaces of the hands.

**Comment.** All 34 LM lesions treated with imiquimod completely cleared (for 6 lesions, clearance was histologically confirmed). Only 1 lesion recurred after 30 months, and this was successfully retreated with imiquimod. This patient had immunodeficiency caused by a B-cell lymphoma, which indicates that immunocompetence is important for a complete clearance of LM lesions.

In a review of LM cases,[4] 15 reports were found to describe the successful treatment of LM with imiquimod (11 case reports and 4 open-label studies). Taken together with the data reported herein, the response rates in the open-label studies ranged from 66% to 100%. The mean LM clearance rate was 91% (58 of 64). Clearance was histologically confirmed in 52 lesions.

The factors responsible for a complete clearance of LM lesions are not yet clearly defined. In the case series,[4] 4 of the 6 nonresponders showed no inflammation. In our opinion, the lack of clinical efficacy is most probably due to insufficient inflammatory reaction of the treated skin area. In contrast to reports in the literature, all of our patients showed strong local inflammatory reactions characterized by weeping erosions. The frequency and duration of imiquimod application required to induce this inflammatory reaction differed from patient to patient. Based on our experience, we started the therapy with imiquimod every other day or daily. While a daily application for 2 weeks was sufficient for 1 patient, in some patients, a twice-daily application did not induce a sufficient reaction. We therefore increased the efficacy of the cream by occlusion and/or triggering an inflammation with $2 \times 2$

cryotherapy. The inflammation in our patients always extended beyond the border of cream application, which suggests that cream application peripheral to the lesion may not be necessary.

Of concern, invasive melanoma has occurred in a patient after 1 month of imiquimod treatment[5] as well as progression of longstanding LM lesions to amelanotic LM melanoma following imiquimod therapy.[6] In 1 case an LM lesion almost cleared clinically but did not change histologically,[7] and in another case an LM lesion with a small hyperpigmented area recurred 9 months after the original clearance.[8] Owing to these possibilities, frequent clinical controls and a long follow-up are necessary. A Wood lamp illumination could be helpful to increase clinical sensitivity.[9]

The major advantage of imiquimod therapy is the excellent cosmetic result. Furthermore, to our knowledge, this is the first report of repeated imiquimod application in the treatment LM. The use of topical imiquimod therapy postoperatively might also be discussed to help prevent recurrences after conventional or Mohs micrographic surgery.

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## COMMENTS AND OPINIONS

### Topical Tretinoin, Lung Cancer, and Lung-Related Mortality

Amid continuing controversies over drug safety,[1,2] results of a trial of topical tretinoin—a commonly used medication for acne[3] and skin wrinkles, hyperpigmentation, and roughness[4]—raise serious concerns for the public health. The Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) trial[5,6] was a vehicle-controlled randomized controlled trial (RCT) that studied whether topical tretinoin, 0.1%, cream applied to the face and ears could prevent nonmelanoma skin cancer. As reported in an abstract published in 2005,[6] the study observed 1131 subjects for at least 2 years. After 6 years, and about 6 months prior to the study's scheduled conclusion, a safety monitoring committee stopped the study because of excess mortality among subjects who applied tretinoin (n=82 deaths [14%]) compared with those who applied vehicle (n=53 [9%]) ($P$=.01). Differences in mortality from pulmonary disease (12 vs 4) and non–small cell lung cancer (NSCLC) (11 vs 4) were reported.[5]

A causal link between tretinoin and mortality due to lung cancer or other lung diseases is consistent with previous RCT data. Specifically, the Alpha-Tocopherol, Beta Carotene Cancer Prevention Trial[7] and the Beta-Carotene and Retinol Efficacy Trial[8] both linked vitamin A–related compounds to lung cancer. Ironically, both trials were intended to demonstrate that these compounds could prevent lung cancer. In both studies, however, lung cancer rates in subjects taking vitamin A–related substances were, unexpectedly, significantly higher than in subjects taking placebo, leading to early discontinuation of the vitamin A–related interventions in both trials.

A link between tretinoin and lung-related mortality is biologically plausible, with the putative culprit not tretinoin itself but harmful tretinoin metabolites. This line of association begins with the finding that topically applied tretinoin can be absorbed systemically[9] and therefore can reach lung tissue. Once inside cells, tretinoin can induce its own metabolism; continuous dosing with tretinoin may lead not to higher levels of tretinoin but to higher levels of tretinoin metabolites.[10] It is those tretinoin metabolites that may injure lung tissue, particularly in the presence of cigarette smoke. This was demonstrated in a study that exposed ferrets to beta carotene (a vitamin A precursor) or cigarette smoke or both or neither for 6 months; lungs of all ferrets exposed to beta carotene showed a strong proliferative response and squamous metaplasia that was enhanced by exposure to cigarette smoke.[11] A hypothesis linking lung cancer to adverse effects of tretinoin metabolites is also supported