

Treatment of actinic cheilitis with imiquimod 5% and a retractor on the lower lip: clinical and histological outcomes in 5 patients

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Abstract

Imiquimod 5% (Aldara™, 3 M Healthcare Ltd.) is a topically applied immune response modifier used in the treatment of superficial basal cell carcinoma, actinic keratosis, and genital warts. We reviewed the casenotes of 5 patients with histologically confirmed dysplastic lower lips who had been treated with topical imiquimod.

Each patient was provided with a specially designed lower lip retractor to prevent spread of the cream. Treatment was stopped after 6 weeks or if an acute inflammatory reaction developed. The lower lip was biopsied 4 weeks later, and histologically the dysplastic changes had been reversed in all 5 patients. The lip retractor was well-tolerated, and prevented spread of the cream. Imiquimod 5% cream offers an alternative method to manage dysplastic lips. Our lip retractor is a simple and cost-effective method of isolating the lower lip and allowing application of topical agents. The method could equally well be used for agents other than imiquimod.

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Introduction

Actinic cheilitis is common, and can be defined as “a clinical term for an ulcerative, sometimes crust-forming lesion of the mucosa of part of or the entire vermilion border of the lower lip”.¹ Histologically there are basophilic changes in the lamina propria with various degrees of dysplasia or carcinoma in situ.^{1,2} The condition is potentially malignant.^{3,4} It is generally accepted that dysplasia develops progressively from mild to severe, and that more severe

dysplasia has a higher rate of malignant transformation. However, we know of no studies of untreated actinic cheilitis of sufficient size or quality to indicate rates of malignant transformation, and data for other oral sites is also poor.

Treatment is aimed at avoiding malignant transformation and can be surgical or non-surgical. Removal of the affected tissue with mucosal advancement (lip shave) and carbon dioxide laser ablation have both been described. Topical 5-fluorouracil or diclofenac preparations have also been described. More recently, photodynamic therapy has been advocated.⁵ Less severe-looking lesions can be reviewed regularly and treated only if their appearance worsens. There are no studies of sufficient quality to recommend one treatment over another.

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Imiquimod is a topically applied modifier of the immune response. It comes in single application sachets containing the active ingredient of imiquimod 5% in a carrier medium. It is commonly used for the treatment of external genital and perianal warts. There is growing evidence of its efficacy in the treatment of actinic keratosis and superficial basal cell carcinoma.^{6–8} There are reports of its use in both cutaneous lentigo maligna and intra-epithelial melanoma of the oral mucosa.^{9,10}

It exerts its action through toll-like receptor 7, which forms part of the innate immune system.¹¹ Binding of this receptor elicits intracellular signalling, which leads to release of interferon α and other pro-inflammatory cytokines.^{11,12}

The use of imiquimod in the treatment of actinic cheilitis was first published in 2002 and showed clinical improvement in histologically confirmed actinic cheilitis with topical imiquimod 5% three times a week for 4–6 weeks.¹³ There are currently no published studies to our knowledge showing the histological outcomes of treatment.

Our early experience of using imiquimod cream on the lip resulted in poor compliance as the preparation spread intraorally, removing it from the desired site of action and occasionally causing unwanted side effects in the mouth. In response to this each patient was given a custom-made lower lip retractor to isolate the lip and prevent the early removal and unwanted spread of the ointment. The retractor also everted and presented the lip, and smoothed out vermillion creases allowing easier and even application of the imiquimod cream.

Patients and methods

We obtained permission to review the medical notes of 5 consecutive patients who had been treated in our department with histologically confirmed actinic cheilitis using topical imiquimod 5% with a custom-made lower lip retractor. The lip retractor was constructed on a standard dental stone cast from an aliginate impression of the patient's lower teeth or dentures. It was made from a widely available cold-curing



Fig. 1. Lip retractor which, when it is in place, acts to evert and present the lip.

addition silicone commonly used as a soft denture relining material. Each unit cost about £50 to construct and took about 3 h of laboratory time (Fig. 1).

Imiquimod 5% cream (AldaraTM, 3 M Healthcare) is widely available, but treatment of actinic cheilitis is an off-licence application. It has recently been licenced for the treatment of cutaneous superficial basal cell carcinomas and actinic keratosis in the UK.

Each of the 5 patients had the lower lip biopsied before treatment to confirm the diagnosis of actinic cheilitis. Dysplasia was graded as mild, moderate, or severe. Photographs were taken before treatment and each patient had a lip retractor made. Patients were instructed to insert the lip retractor and apply a thin layer of imiquimod 5% to the lower lip once a day on Monday to Friday but not on Saturday and Sunday. The preparation was to stay in place until it had been completely absorbed. Patients could then remove the lip retractor and wash the lip with warm soapy water. The end point was either after 6 weeks of treatment or if there was a local tissue reaction consisting of crusting, erythema, ulceration, and pain. Experience with imiquimod 5% for skin conditions suggests that patients who experience such reactions tend to have had an adequate response and do not benefit from longer treatment. After a healing period of 4 weeks, photographs were taken and the most clinically suspicious area of the lip was biopsied. All biopsy specimens were reviewed by one pathologist.

Results

Outcomes were reviewed in 3 ways: the success of the lip retractor; any clinical change in the appearance of the lips; and histological changes between the biopsy specimens taken before and after treatment.

All lip retractors were fitted easily and none required adjustment. All patients reported that they were simple to fit, remove, and maintain, comfortable to wear, and prevented unwanted removal and spread of the cream.

All patients showed pronounced improvement in the appearance of the lip after treatment. Lips showed less blotch-



Fig. 2. Photograph after treatment showing improvement in the clinical appearance of the lip.

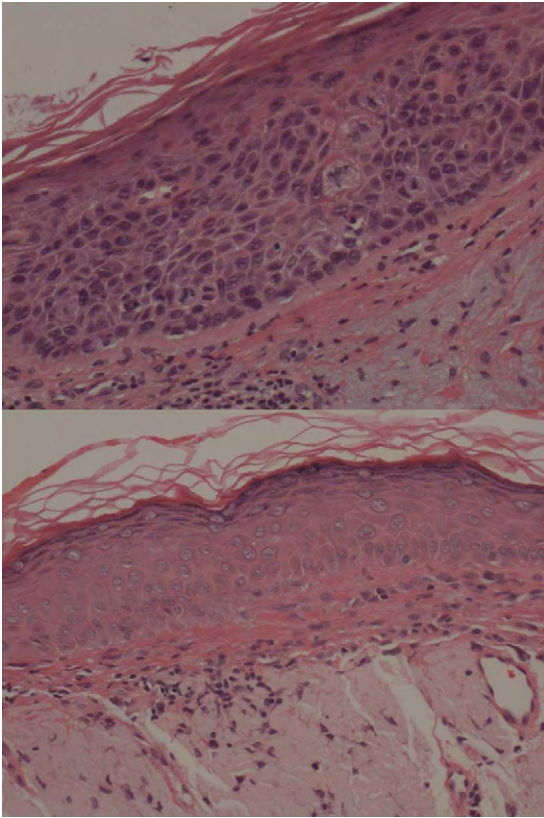


Fig. 3. Histological appearance before (top) and after (below) treatment showing a reduction in the severity of the dysplasia (haematoxylin and eosin, original magnification $\times 40$ (top) and $\times 20$ (below) \times).

ing, erythema, pallor, or ulceration and had a more distinct vermillion (Fig. 2). The degree of dysplasia was downgraded in all patients after treatment (case 1 = severe to mild; cases 2 and 3 = moderate to mild; and cases 4 and 5 = mild to none) (Fig. 3).

The time to tissue reaction varied (range 2–5 weeks). All patients reported that pain and ulceration were the main features and had resolved within 1 week of stopping treatment. All reported that pain was controlled with simple oral analgesics.

Discussion

Local tissue reactions to topical imiquimod treatment are common when treating actinic keratosis and cutaneous basal cell carcinomas. Our experience in the treatment of cutaneous lesions suggests that patients with such reactions tend to show good clinical and histological outcomes despite not completing 6 weeks of treatment. This was reflected in our results.

Our regimen of once-daily application of imiquimod 5 days a week was the approved dose at the time of treatment. Since then, 3 times weekly application has been approved for the treatment of actinic keratosis. Our experience suggests that good histological and clinical results are still obtained.

We now use this regimen as first line treatment for actinic cheilitis in our department. Further study into the optimal dosing regimen is required. Further study of long term outcomes of imiquimod treatment and those of other treatments is required, as evidence is lacking.

Lower grades of dysplasia are generally accepted as having lower rates of malignant transformation, although the published evidence specific to lip dysplasia is lacking. Our results show a reduction in dysplasia from moderate and severe to mild and from mild to no dysplasia in specimens taken after treatment. This raises the possibility that a further course of imiquimod may have additional benefit to patients with residual dysplasia. Repeat treatments are commonly used in the treatment of skin lesions. Further study in this area is required.

Biopsy specimens were taken 4 weeks after the cessation of imiquimod application. In some cases, an inflammatory infiltrate was present, which upgraded the degree of dysplasia. This inflammation may have been the residual effect of imiquimod and a delay in sampling the lesion to 6 weeks may have produced less inflammation and more downgrading of dysplasia.

Our study suggests that imiquimod 5% applied topically, in conjunction with our lip retractor, downgrades the degree of dysplasia in lower lips with actinic cheilitis. Further study is required to find out if this is maintained over time, and its effect on rates of malignant transformation. Further study is also needed to investigate the optimal dosing regimen.

We have also shown that our lip retractor is an effective, cheap, and well-tolerated method of allowing controlled application of topical treatments to the lower lip. This could be useful for agents other than imiquimod.

Conflict of interest

Colin Fleming has received grant support from 3M in past for studies. No other potential conflicts of interest.

References

- van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa: terminology, classification, and present concepts of management. *Oral Oncol* 2009;**45**:317–23.
- Cavalcante AS, Anbinder AL, Carvalho YR. Actinic cheilitis: clinical and histological features. *J Oral Maxillofac Surg* 2008;**66**:498–503.
- Kaugars GE, Pillion T, Svirsky JA, Page DG, Burns JC, Abbey LM. Actinic cheilitis. A review of 152 cases. *Oral Surg Oral Med Oral Path Oral Radiol Edod* 1999;**88**:181–6.
- Zide MF. Actinic keratosis: from the skin to the lip. *J Oral Maxillofac Surg* 2008;**66**:1162–76.
- Rossi R, Assad G, Buggiani G, Lotti T. Photodynamic therapy: treatment of choice for actinic cheilitis? *Dermatol Ther* 2008;**21**:412–5.
- Eigentler TK, Kamin A, Weide BM, Breuninger H, Caroli UM, Mohrle M, et al. A phase III, randomised, open label study to evaluate the safety and efficacy of imiquimod 5% cream applied thrice weekly for 8 and 12 weeks in the treatment of low-risk nodular basal cell carcinoma. *J Am Acad Dermatol* 2007;**57**:616–21.

7. Jorizzo J, Dinehart S, Matheson R, Moore JK, Ling M, Fox MS, et al. Vehicle-controlled, double blind, randomised study of imiquimod 5% cream applied 3 days per week in one or two courses of treatment for actinic keratosis on the head. *J Am Acad Dermatol* 2007;**57**:265–8.
8. Ezughah FI, Affleck AG, Evans A, Ibbotson S, Fleming C. Confirmation of histological clearance of superficial basal cell carcinoma with multiple serial sectioning and Mohs' micrographic surgery following treatment with imiquimod 5% cream. *J Dermatol Treat* 2008;**19**:156–8.
9. Spenny ML, Walford J, Werchniak AE, Beltrani V, Brennick JB, Storm CA, et al. Lentigo maligna (melanoma in situ) treated with imiquimod cream 5%: 12 case reports. *Cutis* 2007;**79**:149–52.
10. Spieth K, Kovacs A, Wolter M, Bug R, Kaufmann R, Gille J. Topical imiquimod: effectiveness in intraepithelial melanoma of oral mucosa. *Lancet Oncol* 2006;**7**:1036–7.
11. Zhu J, Lai K, Brownile R, Babiuk LA, Mutwiri GK. Porcine TLR8 and TLR7 are both activated by a selective TLR7 ligand, imiquimod. *Mol Immunol* 2008;**45**:3238–43.
12. Schiller M, Metz D, Luger TA, Grabbe S, Gunzer M. Immune response modifiers—mode of action. *Exp Dermatol* 2006;**15**:331–41.
13. Smith KJ, Germain M, Yeager J, Skelton H. Topical 5% imiquimod for the therapy of actinic cheilitis. *J Am Acad Dermatol* 2002;**47**:497–501.