SHORT REPORT

Long-term sustained lesion clearance from Lmax with imiquimod 3.75%, a new field-directed treatment for actinic keratosis

G. Gupta,[1,*] E. Stockfleth,[2] K. Peris,[3] S. Aractingi,[4,5] A. Alomar,[6] R. Dakovic,[7] T. Dirschka[8,9]

[1]Department of Dermatology, Monklands Hospital, Airdrie, Lanarkshire, UK
[2]Department of Dermatology, Charité – University Medical Centre Berlin, Berlin, Germany
[3]Department of Dermatology, Catholic University of Rome, Rome, Italy
[4]Service de Dermatologie Allergologie, Hôpital Cochin, Paris, France
[5]Université Paris 5 Descartes, Paris, France
[6]Department of Dermatology, Institut Universitari Quiron Dexeus, Barcelona, Spain
[7]Meda Pharma GmbH & Co. KG, Bad Homburg, Germany
[8]Dermatological Practice Centre, Wuppertal, Germany
[9]Faculty of Health, University Witten-Herdecke, Witten, Germany
*Correspondence: G. Gupta. E-mail: Girish.Gupta@lanarkshire.scot.nhs.uk

Abstract

Background In patients with actinic keratosis (AK), subclinical and clinical lesions coexist across large areas of sun-exposed skin. The long-term efficacy of AK treatments depends on their ability to eradicate both types of lesions across the entire field.

Objective To assess the long-term efficacy of imiquimod 3.75% using the reduction in lesions from Lmax (maximum lesion count during treatment), which assesses the ability to clear subclinical and clinical lesions.

Methods Patients with 5–20 AK lesions on the full face or balding scalp from two 14-week, randomized, vehicle-controlled, double-blind studies of imiquimod 3.75% (daily for two 2-week treatment cycles separated by a 2-week treatment-free period) were eligible to enter a 12-month follow-up study if they had no AK lesions at Week 14. Lesion reduction from Lmax was calculated at 6 and 12 months during follow-up.

Results The 42 patients in this long-term study had a median of nine baseline lesions and a median Lmax of 22 lesions. At 6 and 12 months of follow-up, the median absolute reduction in AK lesions from Lmax with imiquimod 3.75% was 21 and 19, respectively. The median percentage reduction in lesions from Lmax to 6 and 12 months was 100% and 97.2%, respectively.

Conclusions The ability of imiquimod 3.75% to eliminate clinical and subclinical lesions across an entire sun-exposed field translates into sustained long-term efficacy. Imiquimod 3.75% may therefore represent a first-choice treatment for patients with AK.

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Conflicts of interest

G. Gupta: Consultant for Meda, LEO and Almirall. E. Stockfleth: Consultant contract with Meda, Almirall, Galderma, Medigene, LEO and Novartis. K. Peris: Reimbursed for conference attendance by Abbvie, MSD and Pfizer; consultant for LEO, Meda, Novartis and Roche. S. Aractingi: Consultant for Meda and Shire. A. Alomar: Consultant for Meda. R. Dakovic: Employee of Meda. T. Dirschka: Reimbursed by Meda Pharma for research, conference attendance and participation in advisory boards.

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Introduction

Actinic keratosis (AK) lesions are the initial clinical manifestation of a disease continuum that may progress from early subclinical disease into invasive squamous cell carcinoma (SCC).[1] The disease usually results from chronic exposure to ultraviolet light over large areas of sun-exposed skin resulting in

the coexistence of clinical and subclinical lesions across the entire cancerous field.[2] The consequence of this pathophysiology is that treatment for AK needs to be able to clear AK lesions (including subclinical lesions) across an entire sun-exposed field. Currently available therapies are only suitable for the treatment of individual lesions or limited areas of a sun-exposed field (e.g. 25 cm^2).[1,2]

To effectively treat AK, a field-directed therapy is required which can detect and clear subclinical as well as clinical lesions on an entire sun-exposed field. Such a treatment should lead to sustained long-term efficacy because the entire field is cleared.

Imiquimod 3.75% is an AK treatment option which has been shown to detect and clear clinical and subclinical lesions across an entire sun-exposed field such as the full face or balding scalp.[3–5] However, so far there is no evidence about whether the eradication of clinical and subclinical lesions by imiquimod 3.75% across an entire sun-exposed field is associated with sustained long-term efficacy. Therefore, this analysis was conducted to follow-up the patients from the pivotal studies of imiquimod 3.75% who had no lesions remaining at the end of the initial studies. The efficacy of imiquimod 3.75% was assessed using the reduction in lesions from Lmax, or the maximum lesion count during treatment. This is a new approach for evaluating the efficacy of field-directed treatments against both clinical lesions and subclinical lesions which become evident during treatment.[5]

Methods

This analysis included patients from two identical 14-week, multicentre, vehicle-controlled, double-blind phase III studies who had 5–20 AK lesions at baseline in an area greater than 25 cm^2 on either their full face or balding scalp who were treated with imiquimod 3.75% (daily during two 2-week treatment cycles separated by a 2-week treatment-free interval); and who had no lesions remaining at the end of these pivotal studies (8 weeks after the last treatment application, i.e. Week 14). These patients then entered a 12-month observational follow-up study. The details of the pivotal and observational studies have been reported previously.[4,6] Written informed consent was obtained from all patients before their participation in the studies. The studies were conducted in accordance with Good Clinical Practice, the Declaration of Helsinki and all relevant local regulations. The study protocols and informed consents were approved by a central institutional review board or at specific institutions as required.

AK lesions were to be counted by the same evaluator at each visit and were considered to be AKs if they presented clinically as rough, crusted, flesh coloured to reddish brown papules or macules, with an adherent scale in a field of sun-exposed skin. Lesions were counted at baseline, at weeks 1, 2, 4, 5, 6, 10 and 14 during the double-blind studies, and at 6 and 12 months after the Week 14 assessment in the long-term extension study (with investigators not having any knowledge of the previous study treatment).

Lmax was defined as the maximum lesion count during the entire treatment period (i.e. from baseline to the last treatment application at Week 6). Median absolute and percentage changes in AK lesion counts from Lmax to 6 and 12 months after the end of the double-blind studies are reported using descriptive statistics.

Results

Forty-two patients from the imiquimod 3.75% groups of the two pivotal studies who had no lesions remaining at the end of these studies entered the 12-month follow-up period. The mean (standard deviation) age of these patients was 65 (11) years, 86% were male, and all were white. At baseline, these patients had a median of 9.0 AK lesions (range: 5.0–20.0).

As shown in Fig. 1, during each of the two treatment cycles, there was an increase in lesion counts as imiquimod 3.75% unmasked previously invisible subclinical lesions. The median Lmax was 22. At the end of the pivotal studies all of the included patients had no AK lesions, and their median lesion count remained at 0 over the following 6 months.

At 6 and 12 months of follow-up (i.e. at 8 and 14 months after treatment had stopped), the median absolute reduction in AK lesions from Lmax with imiquimod 3.75% was 21 and 19, respectively (Fig. 2a). The median percentage reduction in lesions from Lmax to 6 and 12 months of follow-up with imiquimod 3.75% was 100% and 97.2%, respectively (Fig. 2b).

Discussion

The results of this study show that clinical and subclinical AK lesions across an entire sun-exposed field remain clear with sustained long-term efficacy after treatment with imiquimod 3.75%. So far, imiquimod 3.75% is the only AK treatment whose long-term efficacy has been assessed using the Lmax concept and these results are in line with the recommendations from the

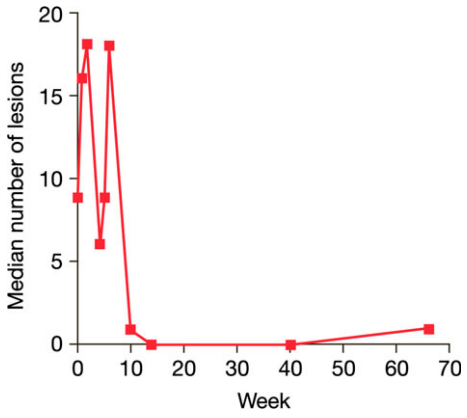

Figure 1 Long-term lesion clearance with imiquimod 3.75%.

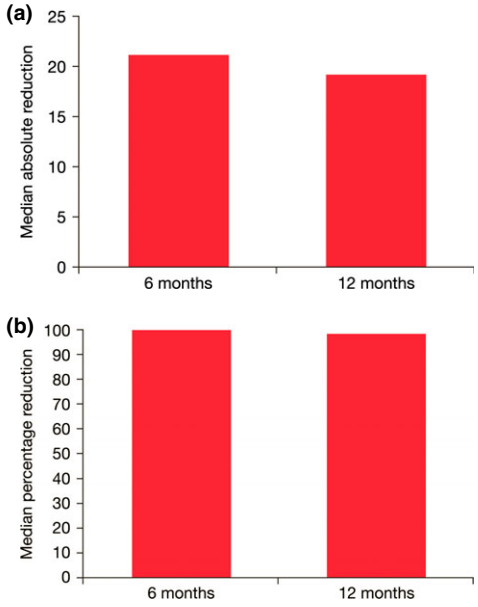

Figure 2 Long-term median absolute (a) and median percentage (b) lesion reduction from Lmax (the maximum lesion count during treatment) with imiquimod 3.75%.

European Skin Academy which emphasize the need to treat all AK lesions.[7] The sustained efficacy over 1 year suggests that imiquimod 3.75% may be able to decrease a patient's risk of subsequently developing invasive SCC.

A recent study showed that two 2-week cycles of imiquimod 3.75% following cryotherapy led to improved efficacy compared with cryotherapy alone.[8] Therefore, in view of the favourable long-term efficacy of imiquimod 3.75%, this therapy could be used as a first-line AK treatment or as a salvage treatment after failure of liquid nitrogen. Further studies are required to address long-term clearance in the salvage setting.

In conclusion, this analysis demonstrates that when AK lesions (i.e. both clinical and subclinical lesions) are detected and cleared across an entire sun-exposed field, this provides sustained long-term efficacy. Imiquimod 3.75% is to date the only AK therapy which has been approved for the treatment of an entire sun-exposed field such as the full face or balding scalp and which has been shown to detect and clear the vast majority of a patient's AK lesions.

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