International Journal of Dermatology

Report

Imiquimod 3.75% for field-directed therapy of actinic keratosis: results of a prospective case-series study in Greece

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Funding: This study was funded by Meda, a Mylan Company. Medical writing assistance in the preparation of this manuscript was provided by David Harrison (Medscript Ltd) and Jane Murphy (CircleScience, an Ashfield Company, part of UDG Healthcare plc).

Conflict of interest: AB, VT, AP, VC, and CA: no conflict of interest to declare. AJS: Received research support and honoraria for participation in scientific events from MEDA, LeoPharma, Roche, Novartis, Abbvie and Merck.

[Corrections]: The copyright line for this article was changed on April 30, 2019, after original online publication.

doi: 10.1111/ijd.14397

Abstract

Background Imiquimod 3.75% is a field-directed treatment for actinic keratosis that can detect and treat clinical and subclinical lesions across an entire sun-exposed field. The detection of subclinical lesions is evidenced by an increase in lesions to the maximum lesion count during treatment (L_{max}). We report clinical outcomes for the first 15 patients treated with imiquimod 3.75% in daily clinical practice in Greece.

Methods Fifteen patients with actinic keratosis lesions were treated with imiquimod 3.75% in an outpatient setting in two 2-week treatment cycles separated by a 2-week treatment-free interval. Actinic keratosis lesions were counted before treatment, at the end of the first treatment cycle (Week 2; L_{max}), and 2 weeks after the second treatment cycle (Week 8). Local skin reactions (LSR) were also evaluated at Weeks 2 and 8.

Results The median baseline actinic keratosis lesion count was 25, which increased to a median L_{max} of 29 at Week 2 and decreased to a median of 5 at Week 8. The median percentage and absolute reduction in actinic keratosis lesions from L_{max} to Week 8 were 87% and 23%, respectively. Most of the LSR were mild-to-moderate in intensity at Week 2 and had resolved by Week 8.

Conclusion Imiquimod 3.75% effectively detected and cleared both the clinical and subclinical actinic keratosis lesions across the entire sun-exposed field in this cohort of Greek patients. Treatment was well tolerated.

Introduction

Actinic keratosis (AK) is an increasingly prevalent dermatological condition, which requires treatment due to the potential of the lesions to transform into invasive squamous cell carcinoma (SCC).[1,2] The key risk factors for the development of AK lesions include: male gender, older age, sun-sensitive complexion, high lifetime sun exposure, and prolonged immunosuppression.[3] Current estimates indicate that between 0.025 and 16% of AK lesions progress into SCC per year.[4] The transformation of AK lesions into invasive SCC is believed to occur both via direct transformation of early AK lesions and disease progression along a stepwise pathway.[5] AK lesions themselves are surrounded by subclinical or invisible lesions across the entire affected area, resulting in field cancerization.[1] Therefore, treatments need to address the complete disease burden across the entire affected field to reduce the likelihood of disease recurrence or progression to invasive SCC.

International Journal of Dermatology 2019, **58**, 1040–1044

Imiquimod 3.75% is a field-directed treatment for AK, which detects and treats clinical and subclinical lesions across an entire sun-exposed field.[6] This immune response modifier activates both innate and adaptive immune responses to eradicate AK lesions.[7] Treatment of AK with imiquimod leads to the unmasking of previously invisible subclinical lesions and, therefore, to a transient increase in lesion count to the maximum lesion count during treatment (L_{max}). A pooled analysis of the pivotal clinical studies showed that the reduction in the number of AK lesions from L_{max} to the end of the study after the application of imiquimod 3.75% was 92%.[8] Further analysis of the data from these studies has demonstrated that the reduction in lesions is similar between patients with differing disease severities and different Fitzpatrick skin types.[9,10] It has also been reported that effective reduction in clinical and subclinical lesions over the entire treated area is associated with sustained long-term lesion clearance.[11] Local skin reactions (LSR) were found to be the most common side effects during treatment with imiquimod 3.75%. In cases of severe LSR, temporary interruption of treatment may be needed and has not been found to be associated with loss in efficacy.[12]

The objective of the current study was to evaluate the safety and efficacy of topical application of imiquimod 3.75% in a cohort comprising the first 15 patients to use this treatment in Greece.

Materials and methods

This prospective case-series study was conducted between November 2015 and November 2016 at the Department of Dermatology and Venereology, University of Athens Medical School, Andreas Sygros Hospital, Athens, Greece. The study was approved by the Ethics Committee (Scientific Board) of Andreas Sygros Hospital on November 12, 2015, and was conducted in accordance with the principles of the Declaration of Helsinki.

To be eligible for enrollment, patients had to provide written informed consent and have 5–50 AK lesions in an area larger than 25 cm^2 on either their full face or balding scalp. AK lesions were defined as: rough, flesh to brown colored erythematous papules and macules with an adherent white to yellow scale on sun-damaged skin; palpable or visible; and hypertrophic or non-hypertrophic.

The treatment regimen was in accordance with the Food and Drug Administration-approved prescribing information.[13] Patients applied imiquimod 3.75% to the entire affected area once daily for 2 weeks. This was followed by a 2-week treatment-free interval after which patients repeated application of imiquimod 3.75% once daily for a further 2 weeks.

Patients' AK lesions were evaluated by the same physician at baseline (Week 0), at the end of the first treatment cycle (Week 2), and 2 weeks after completion of the second treatment cycle (Week 8). As the application of imiquimod 3.75% leads to the unmasking of subclinical lesions, efficacy was analyzed by determining the median percentage and median absolute reductions in AK lesions from the maximum visible lesion count at baseline (Week 0) and at the end of the first treatment cycle (Week 2; i.e., from L_{max}) to the end of the follow-up period (Week 8).

The tolerability of imiquimod 3.75% was evaluated by investigators assessing LSR at Week 2 and Week 8. Erythema, edema, weeping/exudate, flaking/scaling/dryness, and scabbing/crusting were evaluated as none, mild, moderate, or severe. The presence or absence of erosions was also determined.

The results for the cohort are presented using descriptive statistics.

Results

Patient cohort

The baseline demographics and clinical characteristics of the 15 patients enrolled in this study are summarized in Table 1. The mean (standard deviation [SD]) age of the patients was 75.3 (8.9) years (range: 57–85 years). Most of the patients were male (12/15) with an equal split between patients who had Fitzpatrick skin types II (8/15) and III (7/15). The median number of AK lesions at baseline was 25 (range: 8–50). In terms of previous AK treatment, two patients in the cohort had received prior cryotherapy. Ten patients applied imiquimod 3.75% to both their face and scalp, four patients to their face only, and one patient applied treatment to the scalp only.

Efficacy

The median lesion counts over time for the cohort are shown in Figure 1. There was an increase in the number of lesions after the first treatment cycle as imiquimod 3.75% unmasked previously undetectable subclinical lesions from a median of 25 at baseline to a median L_{max} of 29 (range: 9–50) at Week 2. Two weeks after the second treatment cycle (i.e., at Week 8), the median number of AK lesions had decreased to five (range: 0–29).

The median percentage reductions in lesions from baseline and L_{max} to the end of the study (Week 8) were 84% and 87%, respectively. The median absolute reductions in lesions from baseline and L_{max} to the end of study were 16 and 23, respectively.

Tolerability

At Week 2, most LSR were of moderate severity. Erythema and flaking, scaling, or dryness were noted in all patients. Seven patients

Table 1 Baseline demographics and clinical characteristics

Characteristics	*N* = 15
Mean age (SD), years	75.3 (8.9)
Male, *n* (%)	12 (80)
Fitzpatrick skin type, *n* (%)	
II	8 (53)
III	7 (47)
AK lesions, median (range)	25 (8–50)

AK, actinic keratosis; SD, standard deviation.

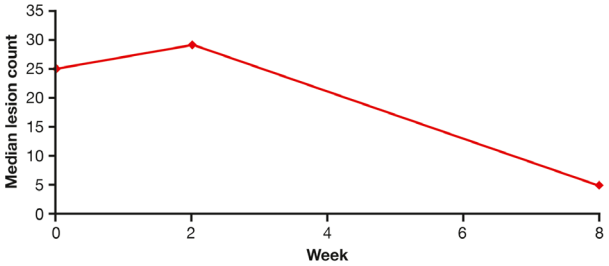

Figure 1 Median lesion counts over time for the cohort of 15 patients treated with imiquimod 3.75%

Table 2 Local skin reactions with imiquimod 3.75%

	Severity, *n* (%)			
Adverse events	**None**	**Mild**	**Moderate**	**Severe**
Week 2				
Erythema	0 (0)	2 (13.3)	7 (46.6)	6 (40)
Edema	2 (13.3)	7 (46.6)	5 (33.3)	1 (6.6)
Weeping/exudate	2 (13.3)	2 (13.3)	9 (60)	2 (13.3)
Flaking/scaling/dryness	0 (0)	10 (66.6)	4 (26.6)	1 (6.6)
Scabbing/crusting	2 (13.3)	0 (0)	6 (40)	7 (46.6)
	Absent		**Present**	
Erosions	2 (13.3)		13 (86.6)	
Week 8				
Erythema	3 (20)	10 (66.6)	1 (6.6)	1 (6.6)
Edema	12 (80)	3 (20)	0 (0)	0 (0)
Weeping/exudate	14 (93.3)	1 (6.6)	0 (0)	0 (0)
Flaking/scaling/dryness	1 (6.6)	13 (86.6)	1 (6.6)	0 (0)
Scabbing/crusting	13 (86.6)	2 (13.3)	0 (0)	0 (0)
	Absent		**Present**	
Erosions	10 (66.6)		5 (33.3)	

experienced moderate and six patients with severe erythema, while 10 patients experienced mild flaking, scaling, or dryness and four moderate. Edema was present in 13 patients, which was mild, moderate, or severe in seven, five, and one patient, respectively. Thirteen patients had weeping or exudate, which was moderate in intensity in nine cases. Of the 13 patients who experienced scabbing or crusting, six cases were moderate and seven were severe. Thirteen of the 15 patients experienced erosions (Table 2).

By the end of the study at Week 8, most LSR were mild in intensity or had resolved completely. Three patients presented with edema, one patient with weeping or exudate, and two with scabbing or crusting; all of these LSR were mild in intensity. Erythema was recorded in 12 patients, 10 of which were mild in intensity. Fourteen patients had flaking, scaling or dryness, which was mild in 13 cases and moderate in one case. Five patients experienced erosions (Table 2).

None of the patients required a rest period during treatment to manage LSR, and there were no systemic symptoms from the treatment.

Patient examples

The first patient example is shown in Figure 2. This 72-year-old male patient had Fitzpatrick Skin Type III and 18 AK lesions at baseline. At the end of the first treatment cycle, the number of AK lesions had increased to an L_{max} of 23. Two weeks after the second treatment cycle, the number of AK lesions had decreased to three, representing an 83.3% decrease from baseline and an 87% decrease from L_{max}. At the end of the first treatment cycle, this patient experienced moderate erythema, flaking/scaling/dryness, and weeping/exudates, severe scabbing/crusting, and mild edema. Erosions were present. Most of these LSR had resolved by Week 8 when the patient only had mild erythema and mild flaking/scaling/dryness. Erosions were not present.

A second 80-year-old male patient with Fitzpatrick skin type III is shown in Figure 3. This patient had 31 AK lesions at baseline, increasing to 36 at Week 2 as imiquimod 3.75% unmasked previously invisible subclinical lesions and decreasing to five at Week 8 as imiquimod 3.75% cleared the lesions. This patient had an 83.9% reduction in lesions from baseline and 86.1% reduction in lesions from L_{max} to the end of the study. At the end of the first treatment cycle, this patient experienced severe erythema, flaking/scaling/dryness, and scabbing/crusting, and moderate weeping/exudate and edema. Erosions were present. At Week 8, most of these LSR had resolved with only mild erythema and flaking/scaling/dryness remaining. Erosions were no longer observed.

A third 78-year-old male patient with Fitzpatrick skin type II is shown in Figure 4. This patient had 38 AK lesions at baseline, increasing to 41 at Week 2 as imiquimod 3.75% unmasked previously invisible subclinical lesions, and decreasing to 15 at Week 8. This patient had a 60.5% reduction in lesions from baseline and 63.4% reduction in lesions from L_{max} to the end of the study. At the end of the first treatment cycle, this patient experienced moderate erythema and mild flaking/scaling/dryness, while scabbing/crusting, weeping/exudate, and edema were not observed. At Week 8, the patient experienced only mild flaking/scaling/dryness.

Discussion

The patients enrolled in the current study represent the first patients treated with imiquimod 3.75% in Greece. The population in Greece is exposed to the sun all year round, which has led to AK becoming a substantial problem. Despite the prevalence of the Mediterranean skin type, a notable proportion of Greeks are fair-skinned and so at higher risk for developing AK.[3] A study of 400 AK patients in Greece showed that AK mainly affects men over 60 years old, that the disease is most commonly located on the face and scalp, and that AK usually presents as multiple lesions.[14] In this study, the most important risk factors for AK were Fitzpatrick skin types II and III, as well as signs of photoaging and outdoor work/activity.[14]

Results from real-life studies of dermatological treatments such as ours are important as they complement the data obtained by randomized clinical trials. Patient populations

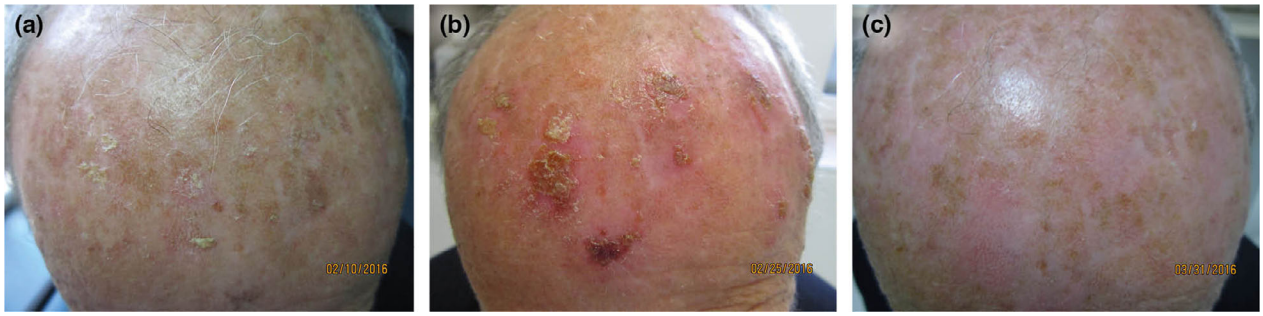

Figure 2 Patient example 1: (a) baseline; (b) Week 2, end of first treatment cycle; (c); Week 8, 2 weeks after second treatment cycle

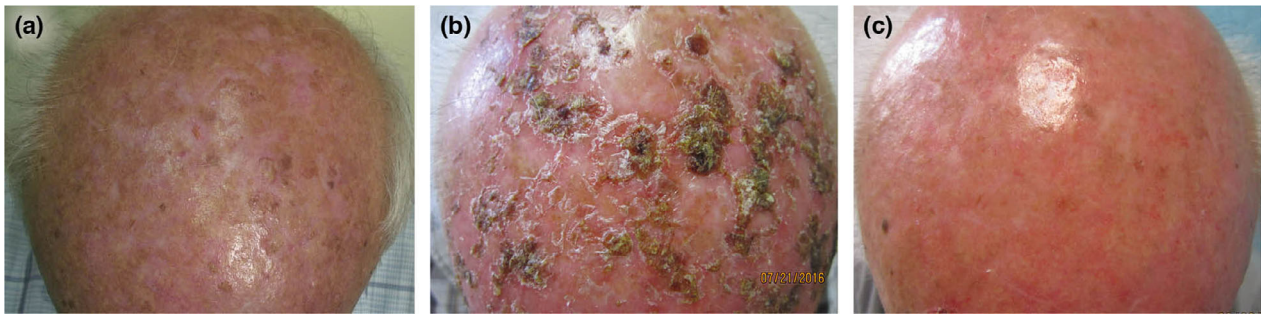

Figure 3 Patient example 2: (a) baseline; (b) Week 2, end of first treatment cycle; (c); Week 8, 2 weeks after second treatment cycle

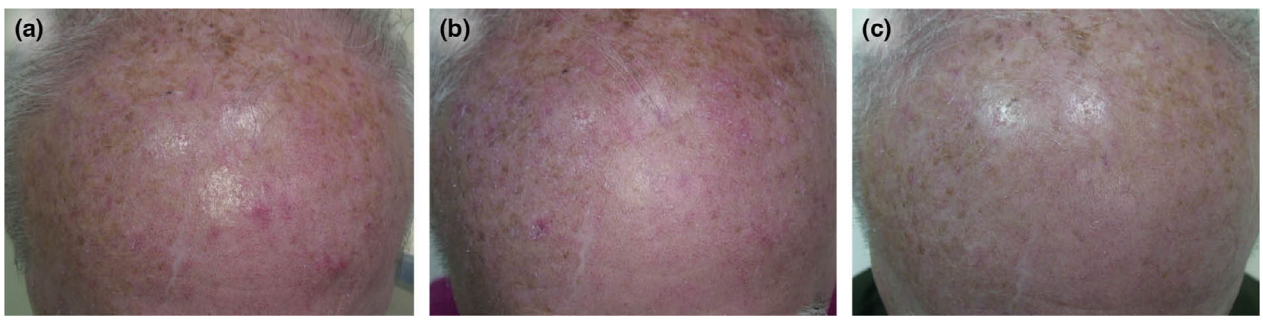

Figure 4 Patient example 3: (a) Baseline; (b) Week 2, end of first treatment cycle; (c); Week 8, 2 weeks after second treatment cycle

enrolled into randomized clinical trials have to meet strict eligibility criteria and may not be representative of patients seen in real-life clinical practice. For example, the pivotal clinical studies of imiquimod 3.75% enrolled patients with 5–20 AK lesions,[8,15] whereas our study included patients with 5–50 AK lesions as the former criteria would exclude many patients seen in daily clinical practice in Greece.

Both clinical and subclinical lesions were effectively cleared by the two treatment cycles of imiquimod 3.75%; the median percentage reductions in lesions from baseline (Week 0) and L_{max} to the end of study (Week 8) were 84% and 87%, respectively. The efficacy results in our study are in line with those reported in the overall population of patients recruited into the pivotal studies of imiquimod 3.75%. Swanson *et al.* reported a median reduction of 81.8% in lesion counts from baseline to 8 weeks posttreatment in 160 patients with AK treated with imiquimod 3.75%.[15] Similar efficacy was also reported in real-life daily practice studies of imiquimod 3.75% conducted in the UK and Italy.[16,17]

The 'highlight phenomenon', referring to the highlighting of subclinical lesions by treatment, was reproduced in our series of patients. The efficacy data in our study showed an initial 16% increase in AK lesions as imiquimod 3.75% unmasked previously invisible subclinical lesions. However, in a previous study assessing the efficacy of imiquimod 3.75%, the number of AK lesions doubled during treatment.[8] This difference may be attributed to the fact that patients with 5–20 AK lesions were enrolled in that study and thus a less broad field could be affected compared with our study, where patients with more AK lesions (5–

50) were enrolled. The median percentage reduction in AK lesions from L_{max} to study end was 92.2% in the previous study, slightly higher than the reduction of 87% shown here.[8]

Imiquimod 3.75% shows comparable efficacy to imiquimod 5%, although the treatment regimen of the former is simpler, shorter, and associated with less severe adverse effects.[18,19] Additionally, compared with imiquimod 5%, the 3.75% formulation is approved for the treatment of a larger surface area (up to 200 cm^2) and is therefore able to target more AK lesions in a sun-damaged field.[18,19]

Imiquimod 3.75% was, in general terms, well tolerated, and none of the patients required a rest period from treatment. All patients experienced some kind of LSR at the end of the first treatment cycle, which started to subside 2 weeks after the end of the second treatment cycle. These results are in line with those from the pivotal clinical and other real-life clinical studies.[8,15–17] Swanson *et al.* observed LSR in almost all patients, with erythema being the most common.[15] LSR, in particular erythema, are considered to indicate that treatment with imiquimod 3.75% is having a beneficial effect.[16,17] It is important that patients know that LSR are likely to occur during treatment to optimize treatment adherence and minimize unnecessary clinic visits.[16]

The principal limitation of our real-life study was the small number of patients who were enrolled. Our aim was to determine the initial efficacy and tolerability of imiquimod 3.75% in Greece, rather than conducting a more comprehensive evaluation (imiquimod 3.75% is not currently approved in Greece). An additional limitation was the relatively short duration of patient follow-up. In the pivotal clinical studies of imiquimod 3.75%, patients were followed up for 8 weeks after the second treatment cycle.[8,15] Additional follow-up to 1 year showed sustained efficacy, with a median percentage reduction in AK lesions from L_{max} of 97.2%.[11] Moreover Hanke *et al.* showed that complete clearance was sustained 14 months after the last dose of imiquimod 3.75% in 17 of the 42 patients (40.5%).[20]

In conclusion, the results of this prospective case-series study in Greece indicate that imiquimod 3.75% can effectively detect and clear both clinical and subclinical AK lesions across an entire sun-exposed field on face and/or scalp after two 2-week treatment cycles with a 2-week interval of no treatment. LSR were common but well tolerated and seemed to correlate with clinical outcome. Overall, imiquimod 3.75% is a new field-directed therapy that is effective and safe for treating clinical and subclinical AK lesions located on sun-damaged areas.

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