Dermatol Ther (Heidelb) (2017) 7:525–533
DOI 10.1007/s13555-017-0199-9

ORIGINAL RESEARCH

High Patient Satisfaction with Daylight-Activated Methyl Aminolevulinate Cream in the Treatment of Multiple Actinic Keratoses: Results of an Observational Study in Australia

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Received: July 24, 2017 / Published online: September 13, 2017

ABSTRACT

Introduction: Actinic keratoses (AK) are treated to reduce the risk of progression to squamous cell carcinoma and for symptomatic and cosmetic benefits. The objective of this observational study was to generate real-life data on the use of daylight photodynamic therapy with methyl aminolevulinate cream (MAL DL-PDT) in treating mild to moderate facial/scalp AK.

Methods: A multicenter, prospective, observational study was conducted in Australia in patients receiving a single treatment of MAL DL-PDT for mild to moderate AK. Efficacy was assessed 3 months after treatment by investigator-assessed improvement and patient- and physician-completed satisfaction questionnaires. Adverse events were recorded throughout the study.

Results: Overall, 81 patients were enrolled of mean age 62.7 years, mostly men (76.5%) with skin phototype I (64.2%) or II (35.8%) and a long history of AK (mean duration 16.8 years). Most had multiple lesions (82.7% had >10 lesions) of predominantly grade I (75.3%). At 3 months after treatment, almost half the patients (46.8%) required no further treatment. The proportions of patients and physicians satisfied to very satisfied with the MAL DL-PDT treatment were 79.7% and 83.3%, respectively. After receiving the treatment, 74.1% of patients indicated via the questionnaire that they were not bothered at all by the pain. Related AEs were reported in 48.1% of patients, mainly mild erythema (44.4%).

Conclusions: In clinical practice in Australia, the use of MAL DL-PDT in treating multiple mild to moderate non-hyperkeratotic AK of the face and/or scalp results in high levels of patient and physician satisfaction reflecting the good efficacy and tolerability of this almost painless, convenient procedure.

Trial Registration: ClinicalTrials.gov identifier, NCT02674048.

Funding: Galderma R&D.

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Keywords: Actinic keratosis; Australia; Daylight-activated photodynamic therapy; Methyl aminolevulinate cream; Observational study

INTRODUCTION

Australia has the highest prevalence of actinic keratoses (AK) worldwide affecting up to 60% of adults, especially elderly, fair-skinned men with outdoor lifestyles [1, 2]. AK are more common with age, chronic sun-exposure, and immunosuppressive drugs; regular sunscreen use is effective in preventing the development of AK [3].

It is often desirable to treat AK to reduce the risk of progression to (in situ and) invasive squamous cell carcinoma (SCC) [4]; improvement in associated symptoms and skin appearance are additional benefits of treatment. The various treatment options mainly include destructive therapies (e.g., cryosurgery, electrosurgery or excisional surgery), topical therapies (e.g., 5 fluorouracil, imiquimod, diclofenac, ingenol mebutate), photodynamic therapy (PDT) with photosensitising topical agent (e.g., methyl aminolevulinate cream; MAL), and combination therapies [5]. Patient satisfaction with some treatments, especially destructive therapies, can be affected by considerable treatment discomfort and residual scarring.

A structured expert consensus statement on AK recently rated MAL DL-PDT as the preferred option for patients with multiple AKs on both small and large fields due to its efficacy and tolerability profile [6]. Methyl aminolevulinate cream (Metvix®; Galderma) with red light [conventional-PDT (c-PDT)] is indicated for the treatment of thin or non-hyperkeratotic and non-pigmented AKs on the face and scalp, superficial and/or nodular basal cell carcinoma, and squamous cell carcinoma in situ (Bowen's disease). More recently, MAL DL-PDT has been approved in many countries for the treatment of face and scalp AK. In previous randomized, controlled, phase 3 studies conducted in Australia and Europe, MAL DL-PDT was demonstrated to be a simpler, less painful procedure with similar high efficacy and better safety compared to MAL c-PDT [7, 8]. In the Australian trial, MAL DL-PDT resulted in higher overall subject satisfaction compared to MAL c-PDT, with 100% of subjects satisfied to very satisfied with DL-PDT versus 85.7% for c-PDT [7]. Similarly, in the European trial, 96.2% of subjects satisfied to very satisfied with DL-PDT (including 64.8% very satisfied) versus 83.1% (18.9% very satisfied) for c-PDT [8].

For patients who require treatment of multiple AK that can easily be exposed to daylight, MAL DL-PDT may be particularly suitable, especially since there is sufficient daylight in Australia to use it throughout the year and during most weather conditions [9].

The objective of this observational study was to generate real-life data on the use of MAL DL-PDT in clinical practice in Australia in the treatment of mild to moderate facial/scalp AK and to assess patient and physician satisfaction.

METHODS

Study Design

This was a prospective, observational study conducted in 6 centers in Australia between September 2015 and March 2016. Physicians experienced with MAL PDT (with red light) were invited to participate, and the prescription of MAL DL-PDT was at the sole discretion of the prescribing physician. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation-Good Clinical Practice principles and in compliance with local regulatory requirements. The study was reviewed and approved by the appropriate Independent Ethics Committees and written informed consent was obtained from all patients prior to study initiation. The study is registered at ClinicalTrials.gov identifier NCT02674048.

Patients

Eligible patients were aged 18 years or older and had been prescribed MAL DL-PDT as part of

their routine medical care to treat mild to moderate AK on the face and/or scalp.

Treatment

A single treatment of MAL DL-PDT was administered.

Assessments

At baseline, the number of AK lesions and the global severity of AK lesions were assessed by the physician. A follow-up visit for re-assessment as per clinical practice was proposed after 3 months, and efficacy was assessed on a 6-point global improvement scale from 1 (clear) to 6 (worse). After 3 months, patients completed questionnaires and each physician completed a questionnaire when all their study patients had completed the study. Post-treatment pain was assessed on a numerical rating scale from 0 (no pain) to 10 (extreme pain). Adverse events were recorded throughout the study.

Statistical Methods

All collected variables were descriptively summarized without replacement of any missing values (observed data only).

RESULTS

Study Population

A total of 81 patients were enrolled with a mean age of 62.7 years, the majority were male (76.5%) and all had skin phototype I (64.2%) or II (35.8%) (Table 1). Among the patients who had received previous treatment for AK (93.8%), the mean duration of past treatments was 16.8 years. Almost all subjects (97.4%) were naïve to DL-PDT, with 2.6% and 18.4% of patients having received DL-PDT and c-PDT, respectively (Table 1). All patients had multiple lesions, including 82.7% with >10 lesions, and half the patients (49.4%) had >20 lesions. Most patients (75.3%) had predominantly grade I

Table 1 Baseline demographic and clinical characteristics

	Patients, *n* (%) *n* = 81
Age (years)	
Mean ± SD	62.7 ± 10.7
Gender	
Male	62 (76.5%)
Skin phototype	
Type I	52 (64.2%)
Type II	29 (35.8%)
Previous AK treatment received	76 (93.8%)
Cryotherapy	68 (89.5%)
Fluorouracil	47 (61.8%)
Imiquimod	30 (39.5%)
Ingenol mebutate	16 (21.1%)
Conventional PDT	14 (18.4%)
Surgery	13 (17.1%)
Diclofenac	8 (10.5%)
Laser	5 (6.6%)
Peelings	3 (3.9%)
Daylight PDT	2 (2.6%)
Other	2 (2.6%)
Past medical history of AK treatments (years)	
Mean ± SD	16.8 ± 10.4
Median (min–max)	15.5 (1.0–43.0)
Number of lesions	
<5	3 (3.7%)
5–10	11 (13.6%)
11–20	27 (33.3%)
>20	40 (49.4%)
Global severity of the lesions	
Majority of grade I	61 (75.3%)
Majority of grade II	11 (13.6%)
Well balanced mix of grade I and II	9 (11.1%)
Grade III lesions present	7 (8.6%)

Table 1 continued

	Patients, *n* (%)*n* = 81
Location of lesions	
Entire face	60 (74.1%)
Scalp	31 (38.3%)
Forehead	14 (17.3%)
Nose	9 (11.1%)
Cheek	8 (9.9%)

AK actinic keratosis, *PDT* photodynamic therapy

lesions, which were mainly located over the full facial area (74.1% of patients) (Table 1).

The vast majority of patients (97.5%) completed the study and attended a follow-up visit at around 3 months.

The study physicians were experienced dermatologists (mean of 19 years clinical practice) regularly treating patients for AK (mean of 63 AK patients per week). The main reasons given by the physicians for using MAL DL-PDT treatment were treatment location (in 100% of patient cases), number of AK lesions (96.3%), efficacy to clear AK (96.3%), and because the area to be treated was large (95.1%) (Table 2).

MAL DL-PDT Procedure

The entire field was prepared before the MAL cream application in the vast majority of patients (97.5%), mainly using a skin abrasive pad (55.6%), microdermabrasion (37%) and/or curettage of individual lesions (34.6%) (Table 2). Sunscreen was applied in most cases (85.2%) with about half (46.4%) applying sunscreen before skin preparation and about half (52.2%) after skin preparation. In almost all cases (98.8%), MAL cream was applied to the entire field. Patients spent a mean duration of 2 h outside in the daylight. Post-treatment skin care was recommended to all patients, especially moisturizer, sunscreen and/or cleanser. According to the patient questionnaire results, the weather was mainly sunny in most cases

Table 2 Methyl aminolevulinate cream daylight photodynamic therapy (MAL DL-PDT) treatment procedure

	Patients, *n* (%) *n* = 81
Physician-provided data	
Major consideration for choosing MAL DL-PDT	
Location of lesions	81 (100%)
Number of lesions	78 (96.3%)
Efficacy to clear AK	78 (96.3%)
Large area to be treated	77 (95.1%)
Tolerability	72 (88.9%)
Maintenance of AK clearance	70 (86.4%)
Patient adherence	57 (70.4%)
Cosmetic benefits	41 (50.6%)
Cost	32 (39.5%)
Preparation of skin before MAL application	81 (100.0%)
On entire field	79 (97.5%)
On lesions only	2 (2.5%)
Method of skin preparation	
Skin abrasive pad	45 (55.6%)
Microdermabrasion	30 (37.0%)
Curette	28 (34.6%)
Other[a]	7 (8.6%)
Sunscreen applied	69 (85.2%)
After skin preparation before MAL	36 (52.2%)
Before skin preparation	32 (46.4%)
After MAL	1 (1.4%)
Location of MAL application	
On entire field	80 (98.8%)
On lesions only	1 (1.2%)
Time between MAL application and daylight exposure (min) ($n = 53$)	
Mean ± SD	6.2 ± 4.7
Min–max	0–20

Table 2 continued

	Patients, *n* (%) *n* = 81
Time of daylight exposure (h) (*n* = 53)	
Mean ± SD	2.0 ± 0.1
Min–Max	1.8-2.5
Post-treatment care recommended	81 (100.0%)
Moisturizer	80 (98.8%)
Sunscreen	78 (96.3%)
Cleanser	77 (95.1%)
Patient-provided data	
Weather during daylight exposure (*n* = 78)	
Sunny	46 (59.0%)
Mixed sunny/cloudy	24 (30.8%)
Cloudy	8 (10.3%)
Temperature during daylight exposure (*n* = 80)	
15–20 °C	7 (8.8%)
20–25 °C	29 (36.3%)
25–30 °C	37 (46.3%)
>30 °C	7 (8.8%)
Time spent in the shade	51 (63.0%)
Mean time in the shade ± SD (min) (*n* = 51)	44.3 ± 41.7
MAL removed after daylight exposure (*n* = 80)	71 (88.8%)

AK actinic keratosis, *MAL* methyl aminolevulinate cream, *DL-PDT* daylight photodynamic therapy

[a] More than one method could be used and *other* were heavy gauze and gauze with scraping

(59%) and almost two-thirds of patients (63%) spent some time in the shade (Table 2).

Efficacy

In this patient population with multiple lesions, almost half of the patients (46.8%) required no further treatment at month 3 and physician-assessed global improvement at 3 months graded the vast majority of patients (88.6%) as at least much improved. Of the patients requiring re-treatment at 3 months, the most frequently received treatment was cryotherapy (88.1%) for a few residual lesions.

Patient Satisfaction

Most patients (79.7%) were overall satisfied or very satisfied with the treatment when questioned at 3 months (Fig. 1). Most patients were satisfied or very satisfied with the effectiveness of the MAL DL-PDT treatment and with the appearance of the treated area of their skin (77.2% and 75.9%, respectively) (Fig. 2). Of the patients who had previously been treated for AK, 7 out of 10 (68.2%) considered that MAL DL-PDT was better than their previous treatment (Fig. 3a). Overall, 8 out of 10 patients (80.8%) would consider using MAL DL-PDT again (Fig. 3b).

Physician Satisfaction

Overall, physicians were satisfied/very satisfied (83.3%) with the treatment at the end of the study (Fig. 1), and all physicians indicated that they would use MAL DL-PDT treatment again in the future.

Safety

After receiving the treatment at baseline, the mean pain level was very low at 1.6 on a 0–10

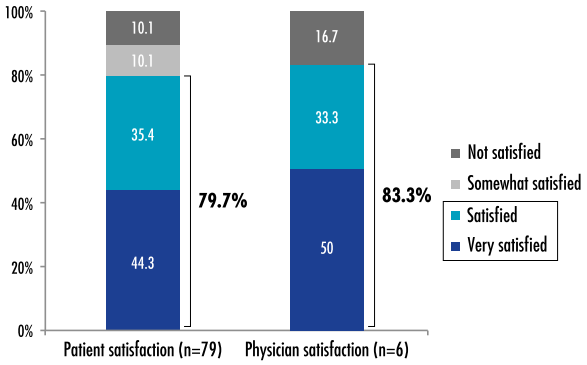

Fig. 1 Overall satisfaction with daylight-activated methyl aminolevulinate treatment according to patient and physician questionnaires at end of study

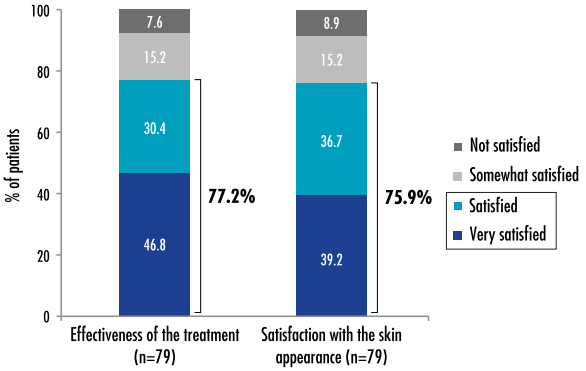

Fig. 2 Patient satisfaction with the treatment effectiveness and the appearance of their treated skin at end of study

scale and 74.1% of patients indicated in the patient questionnaire that they were not bothered at all by pain (Fig. 3c).

Related AEs were reported in nearly half (48.1%) of patients, most frequently mild erythema (44.4%). No event was assessed as serious by the investigators during the study, but one related AE (SCC) was reclassified as serious by the sponsor. All other AEs were mild except for one patient with moderate skin exfoliation at month 3 and one patient who experienced severe related phototoxic reactions post-treatment (erythema, pain of skin, photosensitivity reaction, pruritus, skin burning sensation, skin irritation) that resolved within 4 days of intensive moisturizer use.

Most patients (69.3%) indicated they were not bothered at all by side effects, and the mean duration of downtime due to skin reactions was only 3.6 days. At the end of the study, all the physicians (100%) indicated they were satisfied with the tolerability of MAL DL-PDT.

DISCUSSION

In this observational study, 80% of patients were satisfied or very satisfied with the MAL DL-PDT treatment, and this was despite the fact that MAL DL-PDT is not reimbursed in Australia. In a randomized, controlled trial in Australia in a similar patient population (mean age 66.9 years, 75% men) with a high number of lesions at baseline (mean 14.8), albeit mostly mild lesions, the overall patient satisfaction was

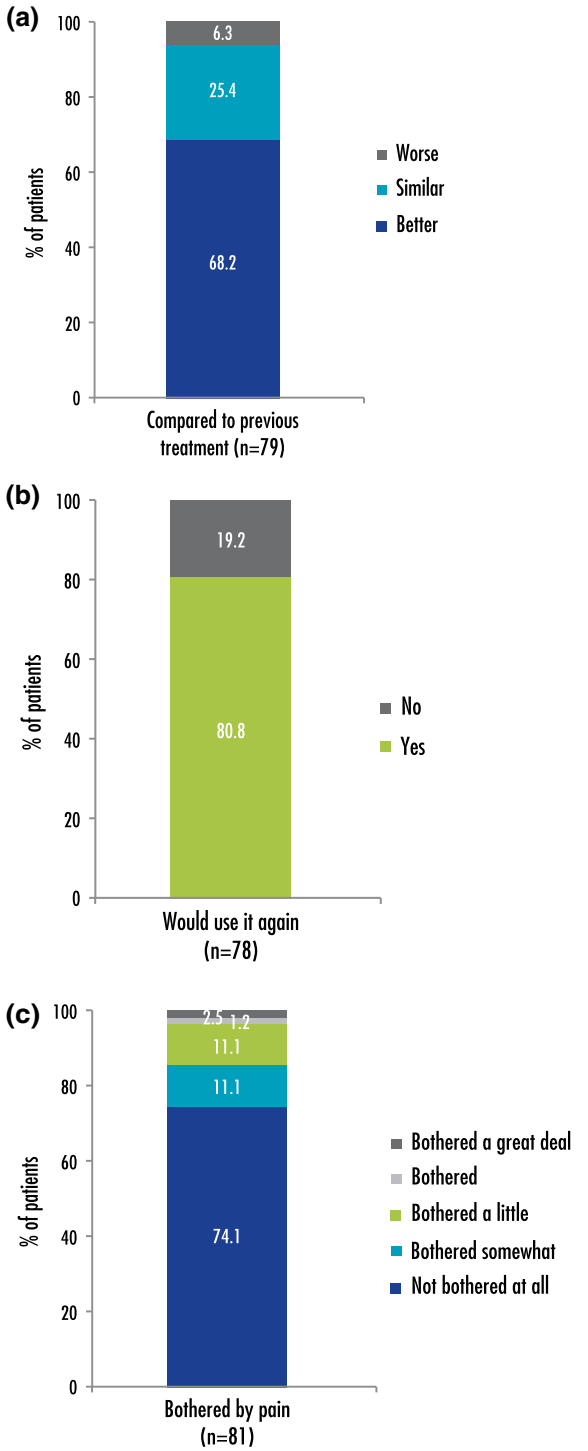

Fig. 3 Patient responses when asked **a** How does daylight-activated methyl aminolevulinate compare with your last treatment for actinic keratosis? **b** Would you use daylight-activated methyl aminolevulinate again? and **c** How bothered were you by any pain?

even higher, with all subjects either satisfied (50%) or very satisfied (50%) [7].

In these patients with a long history of AKs, but mostly naïve to MAL DL-PDT (97%), factors that may have contributed to the high patient and physician satisfaction include the convenient single treatment session, short time to healing, high tolerability and low pain, as well as the excellent cosmetic outcome and good efficacy. Despite a high number of AK at baseline, 47% of patients required no further treatment 3 months after a single session of MAL DL-PDT, and those patients requiring further treatment at month 3 were mainly treated by cryotherapy (88%) for a few residual lesions.

In the vast majority of cases, the entire field (98%) was prepared before application of the MAL cream to the entire field (99%), as recommended by the Australian MAL DL-PDT consensus recommendations [10]. In patients with multiple lesions over large areas, field-directed therapy is appropriate given the importance of treating both clinically visible and subclinical lesions [11, 12]. Pretreatment of hyperkeratosis before application of the MAL cream was carried out exclusively by mechanical methods, with no reports of chemical methods (more than one method could be used). A previous study with c-PDT demonstrated that, although urea or salicylic acid had similar efficacy to curettage, the tolerability was slightly lower with more pain and higher rates of erythema [13].

The MAL DL-PDT procedure was well tolerated and almost painless, with 74% of patients indicating they were not bothered at all by any pain. This is quite remarkable since the treated areas were very large and the entire face was affected in 74% of patients. Related AEs were mostly mild skin reactions that resolved rapidly, and over two-thirds of patients (69%) indicated that they were not bothered at all by side effects. One serious AE of SCC was reported, which highlights the importance of investigating suspicious lesions at baseline and closely following up high-risk patients, especially those with a long history of AK, previous history of non-melanoma skin cancer and high number of lesions at baseline. Local immunosuppression induced by PDT (with aminolevulinic acid or MAL) has been described in healthy human volunteers [14], albeit a reduced risk was observed with lower light intensities (such as daylight) [15]. However, treating patients with AK and skin cancers is a different situation than healthy skin. In skin cancers, PDT may stimulate the immune response resulting in high efficacy [16], possibly by attracting host leukocytes into the tumor and increasing antigen presentation [17], or through systemic, antigen-specific anti-tumor immunity [18, 19]. A 24-week randomized, controlled trial conducted in Australia with MAL DL-PDT reported no serious AEs over the entire study period, and 79% of patients reported they were not bothered at all by side effects [7].

Limitations of this study are the non-interventional nature and lack of a control group. However, the results are consistent with those from a randomized controlled trial conducted in 7 investigational centers in Australia [7].

CONCLUSION

This real-life observational study confirms that MAL DL-PDT is used in the treatment of diagnosed AK according to Australian MAL DL-PDT consensus recommendations. The results provide evidence supporting the high levels of patient and physician satisfaction, as well as good efficacy and tolerability, of MAL DL-PDT for the treatment of multiple mild to moderate non-hyperkeratotic AK of the face and/or the scalp.

ACKNOWLEDGEMENTS

Sponsorship for this study and article processing charges was funded by Galderma R&D. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. Editorial and medical writing assistance was provided by Helen Simpson, PhD, of Galderma R&D.

Disclosures. J.A. See received financial support from Galderma R&D for conducting the

study. K. Gebauer received financial support from Galderma R&D for conducting the study. J.K. Wu received financial support from Galderma R&D for conducting the study. S. Manoharan received financial support from Galderma R&D for conducting the study, has been on advisory boards or been a speaker for Allergan, Inova, Leo, Avita, Endymed, Syneron Candela, and L'Oreal Paris Skincare. J. Sullivan's medical practice (Holdsworth House) received financial support from Galderma R&D for conducting the study. N. Kerrouche is a full-time employee of Galderma R&D.

Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available as it is proprietary data. All of the conclusions drawn in the manuscript are based on data included in the publication and supporting literature has been provided.

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