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Comparative study of imiquimod 3.75% vs. photodynamic therapy for actinic keratosis of the scalp

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Abstract

Background/purpose: To assess efficacy, tolerability, adverse effects, recurrence, and aesthetic results of imiquimod 3.75% vs. photodynamic therapy with 5-aminolaevulinic acid (MAL-PDT) for actinic keratosis (AK).

Methods: A small randomized, intraindividual right-left pilot study for AK treatment of multiple scalp lesions was performed. Patients were treated with imiquimod and subsequently MAL-PDT (on opposite sides of the scalp) 14 days apart. Study end points were evaluated with clinical and dermoscopic examinations at 1, 3, 6, and 12 months.

Results: Nine male bald patients were enrolled. Imiquimod achieved a slightly higher overall clearance rate than MAP-PDT (68.1% vs 56.5%). According to AK degree of severity, clearance rates were greater for degree I and III with imiquimod (68.8%, 64.5% and 75% with imiquimod vs. 48%, 69.8%, and 66.7% for MAL-PDT, respectively). At 12 months, a slightly higher total recurrence rate was noted for imiquimod compared with MAL-PDT (9.9% vs. 8.6%); new lesions were 2 degree I for imiquimod and 4 degree I for MAL-PDT. For both treatments, pain was moderate/strong (even if MAL-PDT seems to be less tolerable) adverse effects are common and transient; aesthetic results excellent.

Conclusion: Both imiquimod and MAL-PDT were effective in the reduction in the number of AK. In the long-term, both present a good effectiveness maintained over time with excellent aesthetic results. A combination or sequential therapy could optimize the management of the cancerization field.

KEYWORDS

actinic keratosis, imiquimod 3.75%, photodynamic therapy

1 | INTRODUCTION

The spontaneous evolution of actinic keratosis (AK) includes regression, persistence, or progression to in situ or invasive squamous cell carcinoma (SCC). The relative risk of developing SCC increases in proportion to the number of AK lesions.[1] The most practice and easy way to classify AK is the grading system proposed in 1991 by Olsen et al[2] who identify three different lesions: AK I is better palpated than visualized, AK II is visible, and AK III is hyperkeratotic. In clinical practice, a useful diagnostic aid can be provided by dermoscopy.[3]

TABLE 1 Epidemiological data and number/grade of AK treated with imiquimod 3.75% and MAL-PDT

Patients	Age	Sex	Phototype	Nr/grade of AK treated with imiquimod 3.75%	Nr/grade of AK treated with MAL-PDT
1	76	M	II	11 I, 5 II, 1 III	7 I, 11 II, 2 III
2	87	M	II	8 I, 8 II	5 I, 8 II, 2 III
3	79	M	II	10 I, 2 II, 1 III	9 I, 4 II, 1 III
4	76	M	III	10 I, 1 III	8 I, 2 II
5	79	M	II	10 I	13 I
6	87	M	II	5 I, 5 II, 3 III	7 I, 2 II
7	85	M	II	16 I, 2 II	13 I, 4 II
8	72	M	II	2 I, 5 II, 2 III	3 I, 11 II, 1 III
9	85	M	II	8 I, 4 II	10 I, 1, II
Total AK				80 I, 31 II, 8 III **119 tot.**	75 I, 43 II, 6 III **124 tot.**

The MAL-PDT has been the gold standard therapy for AK management for years[4] given the large skin areas able to be treated with high response rates and great cosmetic outcomes. Points of weakness are that is time consuming, needs physician's care and is often reported by patients as painful. Therefore, new topical agents have been assessed to improve and simplify multiple AK treatment. Imiquimod 3.75% (imiquimod) aroused much interest for its application in cancerization field therapies.[5-7] Imiquimod is a powerful topical able to modify the immune response. It acts at the cellular level by binding to the toll type membrane receptors that play an important role in activating both innate and adaptive immune responses and induces apoptotic mechanisms in AK lesional cells.[8] For this reason, a clinically visible inflammatory response during the application of the drug predicts good therapeutic efficacy.

In order to evaluate efficacy, recurrence, tolerability, adverse effects, and aesthetic results of imiquimod compared with MAL-PDT, we conducted a small randomized intraindividual right-left pilot study for the treatment of multiple AK in patients with extensive cancerization field of the scalp.

2 | PATIENTS AND METHODS

Nine male bald patients who visited the Dermatology Unit of University of Parma from January to April 2018 were recruited. Inclusion criteria were multiple AK (at least three in each therapeutic area) and age over 18. The exclusion criteria included immunosuppression, topical treatment in the same studied area in the previous 3 months, and hereditary diseases that predispose to development of skin cancer. AK was classified following the clinical classification proposed by Olsen et al[2]

Treatment area of each patient was photographed, and all lesions were mapped on a template. After a gentle curettage of the most hyperkeratotic lesions, we performed a single session of MAL-PDT on the right or left side of the scalp, randomly. As we previously described,[9] the protocol for MAL-PDT provided the topical application of methyl aminolevulinate cream (Metvix® Cream, Galderma) on the entire side of the scalp to be treated. After 3 hours, the occlusive dressing and residual cream were removed. Wood's light was used to verify the correct absorption of MAL in each lesion, and the skin was exposed to red light with a continuous spectrum emitted by a diode lamp (Aktilite®, Galderma) at a power of 37 J/cm^2 and at a distance of 5 cm from the skin surface.

After two weeks from MAL-PDT, treatment with imiquimod (Zyclara® Cream, Meda Pharma) was carried out on the untreated area of the scalp directly by the patient. Protocol provides daily application of the cream with a gentle massage to promote absorption on the entire cleaned treatment area for 14 days continuously without any coverage. Then, after a rest period of 14 days, another daily treatment of 14 days.[7] We suggest the patient to perform medication in the evening before bedtime to avoid sun exposure. It was decided to perform MAL-PDT and imiquimod treatments 14 days apart and not together in the same session to minimize patient discomfort and to avoid any effects of one technique on the other. Throughout the follow-up, patients were not allowed to perform any other treatment so as not to influence the results. It was only recommended to apply a sun protection factor spf 50 + on the whole scalp in case of sun exposure.

Efficacy was evaluated counting residual AK at 1 month. Outcomes were classified as poor, partial, or optimal according to the number of lesions reduction < 25%, ≥25%, and < 75% or ≥75%, respectively. Furthermore, pictures of the treated areas were taken to better compare the results. Further visits at 3, 6, and 12 months were performed to check long-term efficacy, any recurrence, any new lesions, late adverse effects, and aesthetic results. During and immediately after PDT treatment and at the first follow-up visit after the imiquimod treatment, patients were asked questions about pain and a visual analog scale (VAS) of 0 to 10 was draw up: 0 represented a well-tolerated treatment and 10 mean severe pain and poorly tolerated procedure. Responses were grouped as follows: good tolerance (0-3), acceptable tolerance (4-7), and poor tolerance (8-10). Patients were also asked to report any skin adverse effects like erythema (mild/moderate/severe), edema, erosion/crust, or any systemic effect like flu-like symptoms.

The aesthetic results, that is, the possible presence of persistent erythema, pigmentation alterations, scars, and areas of atrophy, were assessed at twelve months and classified as poor, good, or excellent.

The statistical analysis of the data was performed with the Jamovi 0.9.4.2 open source statistical package (https://www.jamovi.org/download.html). For the comparisons between the groups relating to continuous variables, both parametric tests (Student's t test) and non-parametric tests (Wilcoxon W test) were used. $P < .05$ was considered statistically significant.

3 | RESULTS

Nine male patients were enrolled. The mean age was 80, 7 years (range 72-87). Fitzpatrick skin-type II 8 patients and III 1 patient (Table 1). A total of 119 AK were treated with imiquimod and 124 with MAL-PDT. Among AK of the imiquimod protocol, 80 were degree I, 31 II, and 8 III. In PDT group, 75 AK were degree I, 43 II, 6 III.

The residual AK in both treated areas was clinically counted at one, three, and six months (Table 2). The one-month data remained unchanged during the subsequent follow-up visit. The result obtained with imiquimod was 38 residual lesions out of 119 divided into 25 degree I, 11 II, and 2 III. As regards MAL-PDT, the total residual AK was 54 out of 124, of which 39 were degree I, 13 II, and 2 III. As consequence, the overall clearance rate (evaluated counting healed lesions on the total AK) was 68.1% in the half of scalp treated with imiquimod, corresponding to 81 healed out of 119 initials. The rate relating to MAL-PDT was 56.5% equivalent to 70 AK healed on 124 initials. Both results indicate partial response according to the scale of clinical evaluation used to evaluate the effectiveness of therapy. Descriptive statistical analysis of these data reported an average of the total clearance rates of the two techniques and a standard deviation, both expressed in percentages, equal to 67.4 ± 16 for imiquimod and 54 ± 19 for MAL-PDT. The comparison analysis by T Test of these results did not reveal statistically significant differences ($P > .05$).

The clearance rates related to each degree of AK were calculated. Those following the use of imiquimod were 68.8% for degree I (55 AK healed of 80; partial response), 64.5% for degree II (20 AK healed of 31; partial response), and 75% for degree III (6 AK healed of 8; optimal response). As regards, MAL-PDT data obtained were 48% for AK I (36 AK healed of 75; partial response), 69.8% for AK II (30 AK healed of 43; partial response), and 66.7% for III degree lesions (4 AK healed of 6; partial response). The descriptive statistical analysis of these data reported an average of the clearance rates relative to degree I AK of the two techniques and a standard deviation, both expressed in percentages, equal to 65.8 ± 15.4 for imiquimod and 44.8 ± 18.6 for MAL-PDT; the comparison analysis by T Test of these results revealed statistically significant differences ($P = .004$—Wilcoxon W test). As regards degree II AK, on the other hand, an average of the relative clearance rates of the two techniques and a standard deviation, both expressed in percentages, equal to 70 ± 29.9 for imiquimod and 66.2 ± 34.9 for MAL-PDT were calculated; the comparison analysis by T Test of these results did not reveal statistically significant differences ($P > .05$). Statistical analysis for degree III AK was not possible due to small number of lesions treated (8 treated with imiquimod and 6 with MAL-PDT).

During the last check-up at twelve months, the initially healed AK which eventually recurred were counted. After the application of imiquimod a total of 8 AK occurred, of which 7 degree I and 1 degree II while after MAL-PDT there were 6 total recurrent AK of which 5 degree I and 1 degree II. Through these counts, it was possible to obtain the total recurrence rates for imiquimod and MAL-PDT, which were 9.9% and 8.6%, respectively (Table 3). In addition, the

TABLE 2 Number of residual and healed AK after treatment. % = clearance rates

	IMIQUIMOD			MAL-PDT		
Patients	Nrof residual AK	Nr and % of healed AK		Nrof residual AK	Nr and % of healed AK	
1	7	10	58.8%	3	17	85%
2	4	12	75%	8	7	46.7%
3	1	12	92.3%	7	7	50%
4	6	5	45.5%	7	3	30%
5	3	7	70%	5	8	61.5%
6	6	7	53.9%	3	6	66.7%
7	3	15	83.3%	5	12	70,6%
8	2	7	77.8%	8	7	46.7%
9	6	6	50%	8	3	27.3%
Total	38	81	68.1%	54	70	56.5%
Nr/Grade (N = 9)	25 I 11 II 2 III	55 I 20 II 6 III	68.8% 64.5% 75%	39 I 13 II 2 III	36 I 30 II 4 III	48% 69.8% 66.7%

TABLE 3 Reccurrence rate (%) and new lesions after imiquimod 3.75% and MAL-PDT calculated at 12-month time point

	Patients										
	1	2	3	4	5	6	7	8	9	Total AK recurred	% AK recurred
	Recurrence										
Imiquimod 3.75%	1 (I)	1(I)	0	2(I)	0	2(I)	1(I)	0	1 (II)	**8 (7 I; 1 II)**	**9.9%**
MAL -PDT	0	1(II)	0	0	1(I)	1(I)	0	2(I)	1(I)	**6 (5 I; 1II)**	**8.6%**
	New lesions									**Total new AK**	
Imiquimod 3,75%	0	2(I)	0	0	0	0	0	0	0	**2 (I)**	
MAL-PDT	0	2(I)	0	0	0	0	2(I)	0	0	**4(I)**	

total number of new lesions was calculated: 2 AK in imiquimod area and 4 in MAL-PDT (Table 3). All new lesions were degree I.

Concerning pain felt by the patients, calculated through the VAS score, none reported a score between 0 and 3 (equivalent to a mild intensity) and this result was valid for both. A VAS score between 4 and 7 (corresponding to moderate intensity), was reported by seven patients (77.8%) for imiquimod and by five patients (55.6%) for MAL-PDT. VAS score between 8 and 10 (equivalent to a severe intensity) was reported by two patients (22.2%) after imiquimod and four patients (44.4%) after MAL-PDT. Only two patients (22.2%) reported greater pain during treatment with imiquimod than the other patients, in whom MAL-PDT was the method that triggered the most pain (Table 4). The mean VAS score for imiquimod was equal to 6 (range 4-8), while for MAL-PDT was 7 (range 4-10).

As regards to adverse effects, the most frequent were erythema, burning sensation, appearance of edema, erosions, scabs, and systemic flu-like symptoms (fever, asthenia, headache, joint pain). Following imiquimod, all patients (100%) developed a severe erythematous reaction, while in MAL-PDT area a moderate erythematous reaction developed in seven patients (77.8%) and mild in two patients (22.2%). Burning sensation was reported in all nine patients (100%) during the application of both techniques. Edema, erosions, and crusts occurred in all patients (100%) in the half of the scalp treated with imiquimod; instead, hemi-skin treated with MAL-PDT developed edema in only three patients (33.3%) and erosions and crusts in two others (22.2%). The appearance of systemic flu-like symptoms was reported in six patients (66.6%) during the application of imiquimod and in none during treatment with MAL-PDT (Table 4). At the last control visit at twelve months, the entire scalp of the patients was inspected to check for the presence of persistent erythema, pigmentation alterations, scars and, atrophy areas. An excellent aesthetic result was obtained with both (Table 4).

TABLE 4 Pain, adverse effects and cosmetic outcome after imiquimod 3,75% and MAL-PDT

		Number of patients and percentage	
		Imiquimod 3.75%	**MAL-PDT**
Pain	Mild	None	None
	Moderate	7 (78%)	5 (56%)
	Severe	2 (22%)	4 (44%)
Erythema	Mild	None	None
	Moderate	None	2 (22%)
	Severe	9 (100%)	7 (78%)
Burning sensation		9 (100%)	9 (100%)
Edema		9 (100%	3 (33%)
Erosions/scabs		9 (100%)	2 (22%)
Systemic flu-like symptoms		6 (67%)	None
Cosmetic outcome	Poor	None	None
	Good	None	None
	Excellent	9 (100%)	9 (100%)

4 | DISCUSSION

This study provides the first intraindividual comparison of two of the most used and established techniques for AK treatment. Imiquimod showed a total clearance rate of 68.1%, a value lower than data of the literature. Swanson et al in 2010[7] and then Stockfleth et al in 2014[10] showed an average three-month total clearance rate of 81.8% for imiquimod, with a complete cure rate (fully healed patients out of the total number of patients examined) equivalent to 35.6% and a partial cure rate (partially healed patients with a reduction in the number of lesions ≥ 75% of the total number of patients examined) by 59.4%. In our study, none showed complete remission, while four out of nine patients (44.4%) reported partial recovery. MAL-PDT lead to a total clearance rate of 56.5%, equivalent to a partial response. As for imiquimod treatment, this value was lower than those found in previous studies showing average total clearance rates at one month ranging between 82% and 89%.[11,12] Furthermore, the intraindividual comparative study between TCA 50% and MAL-PDT[13] also showed a total clearance rate higher for MAL-PDT (79.7%) compared with the present study. We ipothesize that the immune status of single patient and the small sample size could influence these results. Indeed, curiously emerged that patients with bad response to imiquimod also have a bad response to MAL-PDT and the other way around. As known, a dysregulation of the immune system could be associated with a more aggressive behavior of AK. A small study on immunosuppressed patients showed a lower clearance rate

(46%) than immunocompetent patients when treated with imiquimod, and the result was maintained up to 1 year after the end of treatment.[14] So, probably preliminary study on immune system of sample size could identify who will have a good response to treatment. Obviously, further studies on this topic with a larger number of patients are needed.

Concerning clearance rates for each degree of AK, imiquimod treatment presented similar efficacy for I, II, and little higher for III AK. On the other hand, MAL-PDT showed greater efficacy for II degree lesions, followed by III and lastly by I. Therefore, it may be reasonable to devise a combination treatment so to get the best of both. In analyzing the three different degree of AK, we found dermoscopy as useful tool in addition to clinical parameters. As described,[3,13] dermoscopic features for AK are background erythema, red pseudonetwork, structureless white-yellow areas, white scales, and keratotic follicular openings. The reduction/disappearance of these parameters indicates efficacy of treatment. Interestingly, background erythema is the feature that lasts longer so it could be still present at the first follow-up visit but tends to disappear thereafter. So, this parameter alone does not indicate persistence of AK rather it must be seen as a local reaction probably related to efficacy itself of the treatment applied.

Our results show that imiquimod and MAL-PDT have a modest number of recurrent lesions in the long-term, indeed recurrence rates of AK at twelve months were 9.9% and 8.6% for imiquimod and MAL-PDT, respectively. In addition, recurred AK tends to present to a lower degree. Taken together, imiquimod and MAL-PDT present a good effectiveness maintained over time, as already reported in the literature.[9,15,16] Concerning new lesions at twelve months, both treatments were highly effective with only 2 new AK degree I in imiquimod areas and 4 degree I in MAL-PDT sides. This last result fully complies with the studies performed so far assessing that MAL-PDT is able to prevent new AK in both immunocompetent and immunosuppressed patients with an extensive field of cancerization.[17,18] No data are available in literature about imiquimod.

Concerning pain, our findings are similar to literature data. Indeed, moderate/strong pain is one of the most common adverse effects of imiquimod in all its available concentrations, that is, 5%, 3.75%, and 2.5%[7,19,20] and lasts for the entire treatment period. Similar data have been found for MAL-PDT in other intraindividual comparative studies with TCA in which PDT proved to be more painful than the compared techniques but only during first minutes of treatment.[9,12,21] Therefore, MAL-PDT is globally more tolerated since pain is limited to the irradiation phase only.

Most common transient adverse effects after both treatments were burning sensation, severe erythema, edema, erosions, and crusts. According to Stockfleth et al,[22] local skin reactions are the expression of the epidermal immune response and means that the drug is starting to determine the beneficial therapeutic effects. They were more severe and last longer in the imiquimod areas especially during the first treatment cycle and resolved spontaneously within a maximum of 15 days from the suspension of therapy. Whereas, after MAL-PDT they resolved within only 7 days. In addition, unlike MAL-PDT, imiquimod leads to transient systemic flu-like symptoms (fever, fatigue, headache, joint pain) in most patients.

Concerning aesthetic results, imiquimod and MAL-PDT are associated with the best aesthetic results compared with cryotherapy, 5-fluorouracil, and trichloroacetic acid both at 50% and 35%, as already reported in previous studies.[9,12,19,23-26] This makes the use of imiquimod and MAL-PDT even more suitable in the treatment of AK spread over large skin surfaces, especially in body areas such as the head, where an optimal aesthetic result is mandatory.

In conclusion, imiquimod and MAL-PDT are both effective and lead to a significant reduction in AK. We suggest a combination or sequential therapy to optimize the management of the cancerization field. This study provides the first half-side comparison of imiquimod 3.75% and MAL-PDT but has some limitations. It is an open and not controlled trial of a small sample size. Thus, further studies with more patients are needed.

CONFLICT OF INTEREST

We state explicitly that conflicts of interest do not exist.

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