

Photodynamic therapy with methylaminolevulinate 80 mg/g with and without occlusion improves acne vulgaris

P22

Robert Bissonnette¹, Catherine Maari¹, Simon Nigen¹, Nathalie Provost¹, Chantal Bolduc¹, Per Fuglerud²

¹Innovaderm Research, Montreal Canada, ²Photocure ASA, Oslo, Norway

ABSTRACT

Aims: To study the safety and efficacy of methylaminolevulinate (MAL) at 80 mg/g with and without occlusion followed by red light exposure 90 minutes later for the treatment of facial acne vulgaris.

Methods: Patients with at least 10 inflammatory lesions on each side of the face and a Global Acne Severity score of at least 3 were recruited. MAL (80mg/g) was applied on the entire face except the nose and the peri-orbital area. Patients were randomized to receive occlusion on the left or right side of the face and to red light exposure 90 minutes later to either 25 J/cm² or 37 J/cm². MAL-PDT was performed 4 times at 2 week intervals.

Results: A total of 44 patients were enrolled in this study. Inflammatory lesions were reduced from baseline to Day 126 (12 weeks after last treatment) by median of 31.7%, 59.4%, 58.1% and 55.8 % for patients randomized to 25 J/cm² without occlusion, 25 J/cm² with occlusion, 37 J/cm² without occlusion and 37 J/cm² with occlusion respectively. MAL-PDT was in general well tolerated and only two patients discontinued their participation in the study due to adverse events. Pain intensity and post PDT erythema were generally lower on the side without occlusion.

Conclusions: PDT performed 90 minutes after MAL application with or without occlusion was well tolerated and effective in reducing the number of inflammatory lesions in patients with facial acne vulgaris.

INTRODUCTION

Methylaminolevulinate (MAL) is a photosensitizer precursor that is transformed into photoactive porphyrins after topical application. Photodynamic therapy (PDT) with MAL at 160 mg/g is currently approved in several countries for the treatment of actinic keratoses, basal cell carcinoma and/or Bowen's disease (1). For these indications red light exposure is performed 3 hours after MAL cream application under occlusion. Small randomized trials performed with MAL under occlusion followed by red light exposure 3 hours later have shown that MAL-PDT is effective in the treatment of acne vulgaris (2-5). However, these treatment parameters were not well tolerated as many patients experienced severe pain and erythema sometimes associated with a pustular eruption.

Photocure ASA developed a new cream formulation containing 80 mg/g of MAL for the treatment of acne vulgaris. The objective of the current trial was to study the safety and efficacy of MAL at 80 mg/g with and without occlusion in combination with 25 J/cm² or 37 J/cm² of red light for the treatment of facial acne vulgaris.

METHODS

Study Design: Forty four patients with acne vulgaris, 18 years of age or older and with at least 10 inflammatory lesions on each side of the face and a Global Acne Severity score greater or equal to 3 were recruited for this single-blind, single center (2 locations) study. The washout periods were 2 weeks for topical facial acne treatments, 4 weeks for systemic antibiotics or phototherapy and 1 year for isotretinoin.

Patients were randomized (1:1:1:1) to be exposed to either 25 J/cm² of red light with occlusion on the right side, 25 J/cm² of red light with occlusion on the left side, 37 J/cm² of red light with occlusion on the right side or 37 J/cm² of red light with occlusion on the left side. The contralateral side of the face was treated with the same fluence but without occlusion. The intent-to-treat (ITT) and safety populations consist of all patients enrolled in the study who received at least one MAL application.

Efficacy Evaluation:

Efficacy of MAL-PDT treatment was assessed by counting inflammatory (papules, pustules and nodules) and non-inflammatory (open and closed comedones) acne lesions on each side of the face. Global Acne Severity was also rated using a 5-point global assessment. The results were analyzed as success (0 or 1) or failure (2, 3, 4).

Treatment: Patients received four MAL-PDT treatments at 2-week intervals. A thin layer of MAL cream at 80 mg/g (Visonac™ Photocure ASA) was applied to both sides of the face excluding the nose and a peri-ocular region of 1-2 cm. Opsite (Smith and Nephew) was applied to one side of the face. After an incubation period of 90 minutes, both sides of the face were exposed to either 25 J/cm² or 37 J/cm² of red light (Aktilite CL 128) at 45 mW/cm² or 90 mW/cm², respectively.

Safety Assessments: Safety was evaluated by adverse events reporting, evaluation of pain during light exposure, evaluation of erythema after light exposure and evaluation of hyperpigmentation and hypopigmentation.

Statistical Analysis:

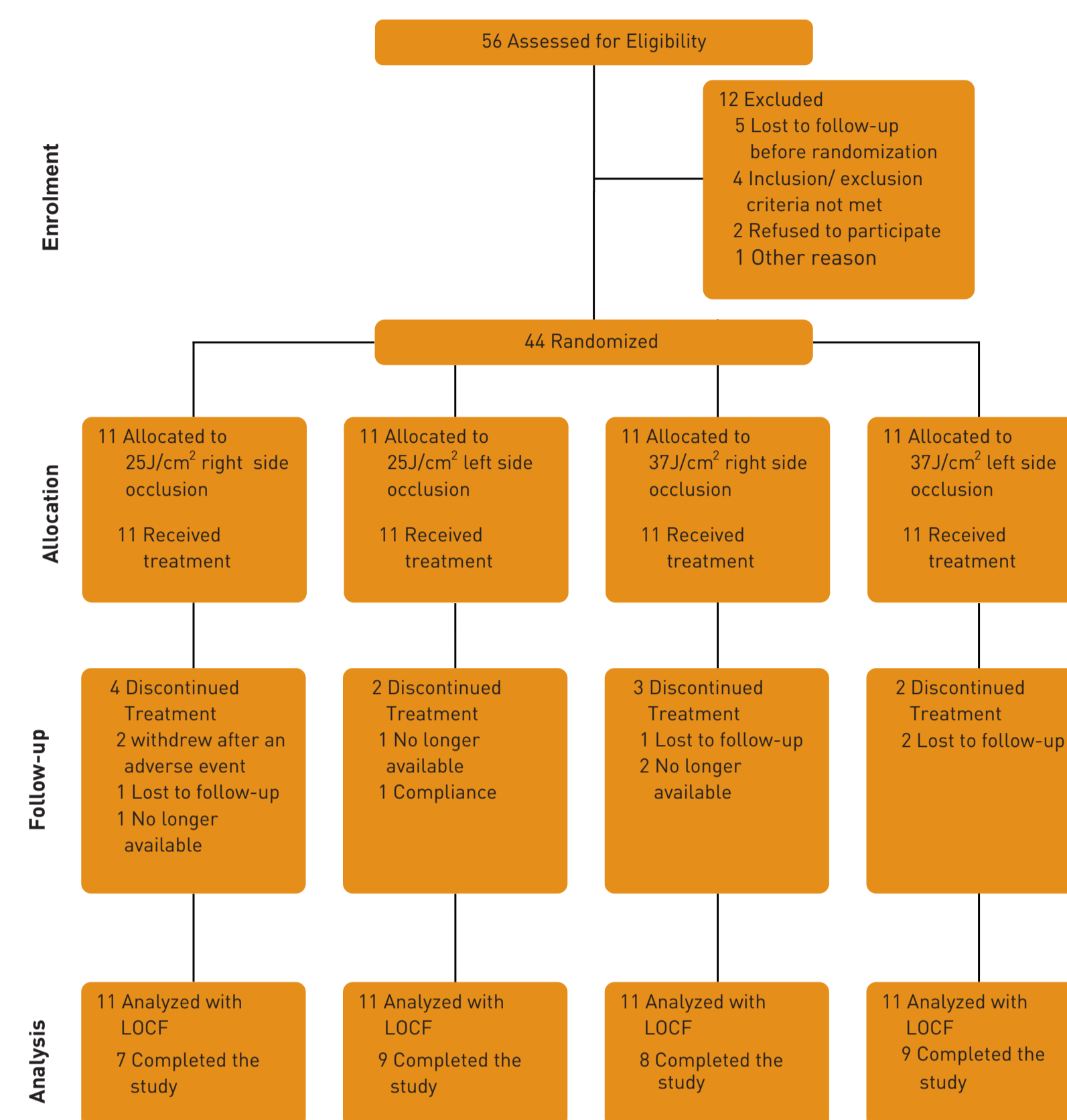
Evaluation of statistical significance was done by comparing confidence intervals. Differences were considered statistically significant when confidence intervals were non-overlapping. Global Acne Severity scores were converted to a failure or success result where success was defined as a Global Acne Severity score of 0 (clear) or 1 (almost clear). The last observation was carried forward (LOCF) for missing data

RESULTS

Patient Disposition:

A total of 44 patients were treated and 33 completed the study (Day 126). Patient disposition in presented in Figure 1

Figure 1. Patient disposition



Efficacy Analysis

Inflammatory lesions: There was a decreased in the mean number of inflammatory lesions after MAL-PDT with or without occlusion for all four groups. The median percentage was reduced from baseline to Day 126, 12 weeks after last treatment, by 31.7%, 59.4%, 58.1% and 55.8% for patients randomized to 25 J/cm² without occlusion, 25 J/cm² with occlusion, 37 J/cm² without occlusion and 37 J/cm² with occlusion respectively. There was a significant reduction of inflammatory lesions at Day 126 for all groups except for patients treated at 25 J/cm² without occlusion. There was no statistically significant difference between the mean number of inflammatory lesions for the side without occlusion and the side with occlusion, irrespective of the red light fluence used (Table 1).

Table 1. Mean number of inflammatory lesions irrespective of red light fluence.

Day	Mean [95% CI]	
	No-Occlusion 25 J/cm ² and 37 J/cm ²	Occlusion 25 J/cm ² and 37 J/cm ²
Day 0	15.68 [13.07-18.29]	16.14 [13.85-18.42]
Day 14	12.41 [10.10-14.72]	11.73 [9.99-13.46]
Day 28	10.75 [8.92-12.58]	10.77 [8.93-12.61]
Day 42	10.43 [8.42-12.45]	9.16 [7.22-11.10]
Day 70	9.82 [7.80-11.84]	9.23 [7.23-11.23]
Day 126	9.80 [7.80-11.79]	9.02 [6.89-11.15]

Non-inflammatory lesions: There was a very slight decrease in the number of non-inflammatory lesions for all groups between Day 0 and Day 126, but no statistically significant difference was observed (Table 2).

Table 2. Mean number of non-inflammatory lesions.

Day	Mean [95% CI]			
	Non-Occlusion 25 J/cm ²	Occlusion 25 J/cm ²	Non-Occlusion 37 J/cm ²	Occlusion 37 J/cm ²
Day 0	10.82 [7.03-14.61]	11.32 [7.93-14.71]	14.59 [7.81-21.37]	15.09 [8.87-21.31]
Day 14	8.41 [4.17-12.64]	8.68 [5.40-11.96]	14.77 [8.77-20.77]	15.41 [9.60-21.21]
Day 28	7.36 [4.37-10.35]	7.91 [4.68-11.14]	14.00 [7.95-20.05]	14.32 [8.38-20.26]
Day 42	8.36 [5.13-11.60]	9.00 [5.58-12.42]	13.59 [7.63-19.55]	13.91 [7.99-19.83]
Day 70	8.59 [5.63-11.55]	8.73 [5.62-11.83]	13.36 [7.29-19.43]	12.91 [6.62-19.20]
Day 126	8.59 [5.69-11.49]	7.50 [4.89-10.11]	12.68 [5.78-19.59]	12.18 [5.75-18.61]

Global Acne Severity: Five patients had a score of 0 or 1 at either Day 70 or Day 126, 3 were in the 37 J/cm² group without occlusion, 1 was in the 25 J/cm² group with occlusion and 1 patient in the 37 J/cm² group with occlusion. Successful improvement as defined by an improvement of at least two grades in Global Acne Severity evaluation was observed only in patients exposed to 37 J/cm², 4 were in the group without occlusion and 2 in the group with occlusion.

Safety Analysis

No serious adverse event occurred during this study. Two patients withdrew from the study due to adverse events. One withdrew because of a pustular eruption on the face following MAL-PDT. The second patient withdrew due to pain during light exposure.

The majority of adverse events observed were expected local side effects following PDT (Table 3). Application site pain was the most frequent adverse event and occurred either during or after light exposure and was more frequently reported on the side where MAL was applied under occlusion. Application site erythema, observed by patients after leaving the study site, was reported more frequently on the side without occlusion regardless of the light exposure. However when erythema intensity was evaluated immediately after PDT by a blinded assessor it was more intense on the side with occlusion.

Hypopigmentation was not observed in this study. Fifteen mild adverse events of transient hyperpigmentation were reported in a total of 7 patients. They all resolved before the end of the study.

Table 3. Summary of adverse events

Adverse events	25 J/cm ² n=154		37 J/cm ² n=169	
	No Occlusion	Occlusion	No Occlusion	Occlusion
Application site dryness	0	1	0	0
Application site erythema	15	5	14	7
Application site pain	39	60	48	59
Application site pruritus	2	2	0	0
Application site scab	1	1	0	0
Application site Pustular reaction	1	1	0	0
Application site paresthesia	3	4	6	6
Application site blister	0	0	0	1
Application site desquamation	0	1	0	0
Other adverse events	18		28	

DISCUSSION

This study used a cream with MAL at 80 mg/g, which is less concentrated than the commercially available MAL (160 mg/g) used to treat skin cancer and actinic keratoses. A shorter incubation time of 90 minutes was used and as opposed to previously published studies PDT was performed without occlusion on half of the face which is more convenient for patients and physicians. MAL-PDT treatment was effective in reducing the number of inflammatory lesions in patients with facial acne vulgaris. After four MAL-PDT treatments, the mean number of inflammatory lesion was significantly lower at Day 126 as compared to baseline for patients treated with 37 J/cm² with or without occlusion. Moreover, no significant difference in reduction of inflammatory lesions was observed when comparing the side with occlusion to the side without occlusion. Although the mean number of non-inflammatory lesions was lower at Day 126 as compared to Day 0, there was no statistically significant difference in the number of non-inflammatory lesions for all groups.

The effect of a lower red light dose, 25 J/cm², was also evaluated. Reduction in inflammatory lesions was on average lower with the 25 J/cm² fluence as compared to 37 J/cm², suggesting that it might be preferable to use 37 J/cm² when MAL is used at 80 mg/g with an incubation time of 90 minutes for the treatment of acne.

MAL-PDT was in general well tolerated by patients and only two patients withdrew because of skin adverse events. Treatment performed without occlusion was associated with fewer skin adverse events, less immediate erythema and less pain than treatment with occlusion.

CONCLUSIONS

PDT performed 90 minutes after MAL application with or without occlusion is well tolerated and effective in reducing the number of inflammatory lesions in patients with facial acne vulgaris.

REFERENCES

- Braathén LR, Szeimies RM, Basset-Seguín N, *et al*. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. International Society for Photodynamic Therapy in Dermatology, 2005. *J Am Acad Dermatol* 2007;56:125-43.
- Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. *J Am Acad Dermatol* 2006;54:647-51.
- Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using methyl aminolevulinate: a blinded, randomized, controlled trial. *Br J Dermatol* 2006;154:969-76.
- Horfelt C, Funk J, Fröhm-Nilsson M, *et al*. Topical methyl aminolevulinate photodynamic therapy for treatment of facial acne vulgaris: results of a randomized, controlled study. *Br J Dermatol* 2006;155:608-13.
- Haedersdal M, Togsverd-Bo K, Wiegell SR, *et al*. Long-pulsed dye laser versus long-pulsed dye laser-assisted photodynamic therapy for acne vulgaris: A randomized controlled trial. *J Am Acad Dermatol* 2008;58:387-94.

Disclosure of conflicts of interest:

Dr. Robert Bissonnette, Dr Catherine Maari, Dr. Simon Nigen, Dr. Nathalie Provost and Dr. Chantal Bolduc have received honoraria, research grants, and/or have been an advisor to the following companies:

Allergan, Dusa Pharma, Galderma, La Roche-Posay, Photocure ASA, QLT, Quest Pharmatech and Stiefel.

This study was funded by Photocure ASA.