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Methyl Aminolevulinate-PDT for Actinic Keratoses and Superficial Nonmelanoma Skin Cancers

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ABSTRACT

Methyl aminolevulinate-hydrochloride cream (Metvix® [in Canada] and Metvixia® [in the US], Galderma) in combination with photodynamic therapy (PDT) provides an effective treatment option for actinic keratoses (AKs), superficial basal cell carcinoma (sBCC), and Bowen's disease (BD). Good clinical outcomes have been reported in the literature. Complete responses (CRs) in AK range from 69% to 93% at 3 months. In sBCC, reported CR rates were from 85% to 93% at 3 months and almost on par with cryosurgery at 60 months (75% vs. 74%). In BD, CR rates were 93% at 3 months and 68% at 2 years. Current evidence has shown that this noninvasive treatment is superior in terms of cosmetic outcome to other management strategies such as surgery. It also offers the advantages of relative simplicity, low risk of side-effects and decreased complications due to scar formation.
Keywords: actinic keratosis; basal cell carcinoma; Bowen's disease; methyl aminolevulinate; PDT; photodynamic therapy

Topical Methyl Aminolevulinate (MAL)-PDT

Photodynamic therapy (PDT) treats superficial skin cancers and pre-cancerous lesions through photosensitized reactions requiring oxygen. Over the past several decades, PDT has been extensively investigated as an experimental therapy for human cancers. There is now growing interest in the use of PDT not only for nonmelanoma skin cancer (NMSC), but also for other skin tumors such as lymphoma, as well as for nononcological indications, such as psoriasis, localized scleroderma, acne, and skin rejuvenation.[1-4] In Europe, as well as in the US, porphyrin-inducing precursors, such as 5-aminolevulinic-acid (ALA) and MAL have been proven effective for the treatment of actinic keratoses (AKs) and basal cell carcinomas.[5-7] Both ALA and MAL induce protoporphyrin IX (PpIX) locally in the skin. Photodynamic therapy combines the simultaneous presence of a photosensitizer activated by an appropriate wavelength of light. For topical PDT, upon illumination, PpIX is transformed to the excited state and then returns to its ground state through a type-II photo-oxidative reaction.[5] In this reaction, these molecules transfer energy to oxygen producing highly reactive oxygen species (ROS), singlet oxygen in particular. ROS accumulates locally within the affected tissue leading to direct cellular damage by apoptosis or necrosis, and indirect stimulation of inflammatory cell mediators.[6]

Previous studies have shown that MAL in combination with red light (570-670nm) has provided good clinical outcomes in the treatment of NMSC (both sBCC and Bowen's disease) and AKs.[7] MAL, the methylated ester of ALA, is a new topical photosensitizer that may offer advantages over ALA in terms of its deeper skin penetration (up to 2mm in depth) due to potentially enhanced lipophilicity and greater specificity for neoplastic cells.[8] In a typical PDT session, the lesion surface is prepared by light curettage of any surface crusts and scales. The 3 hour application of 160mg/g MAL prior to irradiation with 37J/cm^2 from a light-emitting diode system (emission peak of 632nm) corresponds to the time point of the highest ratio of fluorescence depth to tumor depth[2] under occlusion. Two treatments 1 week apart for AKs, sBCC, and BD have been recommended; however, a single treatment session is possible and may be potentially sufficient for very thin AKs. For partially cleared responses, a second treatment course (consisting of two weekly PDT sessions) at 3 months may be considered.[9] This article reviews key published trials of topical MAL-PDT for AK, sBCC, and BD.

AKs

A US randomized, multicenter, double-blind, placebo controlled study was performed in 80 patients with mild-to-moderate AKs on the face and scalp. Forty-two patients (260 lesions) were treated with MAL-PDT and 38 patients (242 lesions) received the placebo cream. MAL was applied for 3 hours followed by illumination with noncoherent red light (75J/cm^2). Treatment was repeated after 1 week. A complete response rate of 89% with MAL-PDT and 38% with placebo was assessed after 3 months follow-up. An excellent or good cosmetic outcome was reported in more than 90% of patients treated with MAL.[10]

ALSO IN THIS ISSUE: **Adapalene 0.1% and Benzoyl Peroxide 2.5%: A Novel Combination for Treatment of Acne Vulgaris (on Page 4)**

Tarstedt et al.[11] reported response rates in an open label, prospective study that compared 2 regimens:

1. A single treatment session
2. 2 MAL-PDT sessions 1 week apart.

One hundred six patients received the single treatment and 105 patients received the second regimen. For thin lesions, clearance rates showed no significant difference (93% with single session vs. 89% with double sessions) For thicker lesions, clearance rates were higher for double sessions (84%) when compared with single treatment (70%). The authors concluded that single treatment is effective for thin AKs. Repeated treatments were needed for thicker or resistant lesions.

In another randomized, multicenter study, MAL-PDT (n=360 lesions) was compared with a single-thaw cycle of cryotherapy (n=421 lesions) or placebo (n=74 lesions). The PDT treatment arm consisted of 2 treatment sessions 1 week apart using 75J/cm^2 with a noncoherent red light (570-670nm). After 3 months, clearance rates for MAL-PDT were significantly higher (91%) compared with cryosurgery (68%) and placebo (30%). Of the MAL-PDT treated patients, 83% were rated as having an excellent cosmetic outcome by an investigator vs. 51% of those treated with cryotherapy; the corresponding patient assessments were 76% and 56% respectively.[12]

A large randomized, intraindividual, right-left comparative study of 119 patients with face/scalp AKs was performed.[14] The aim of the study was to compare 1 MAL PDT session to double freeze-thaw cryotherapy. After a 3-hour application of MAL using 37J/cm^2 with double treatment 7 days apart, cure rates were seen when using MAL-PDT (87%) compared with cryotherapy (76%). Of patients treated with MAL-PDT, 10% required re-treatment after 3 months vs. 21% for cryotherapy. Cosmetic outcome significantly favored MAL-PDT (i.e., 77% vs. 50%).[13] A recent study, however, showed lower efficacy with MAL-PDT (78% clearance) on the extremities compared with cryotherapy (88% clearance).[14]

In a recent multicenter, double-blind, randomized study by Pariser,[15] the efficacy of MAL-PDT using a red light-emitting diode (n=363 lesions) was evaluated vs. placebo (n=360 lesions) for grade 1 (slightly palpable) and grade 2 (moderately thick) AKs on the face and scalp. Lesion complete response rates were significantly superior for MAL-PDT (86.2%) vs. placebo (52.5%). The patient complete response rate was 59.2% for MAL-PDT subjects, and lower for those who had vehicle PDT alone (14.9%). Scalp lesions responded better with MAL-PDT (93%) than did facial lesions (87%). Grade 1 lesions had slightly higher complete response rates than grade 2 lesions (89% vs. 80%). Furthermore, larger lesions with diameters of >20mm had poorer response rates compared with smaller lesions (74% vs. 86%).

When treating AKs, biopsies should be considered for thick, keratotic lesions to rule out squamous cell carcinoma. Calzavara-Pinton et al.[16] have shown that even if squamous cell carcinoma is limited to microinvasive involvement, the treatment outcome is poor.

Superficial BCCs

The recent British Photodermatology Group guidelines for topical PDT concluded MAL-PDT to be effective for sBCC.[9] In an attempt to compare clearance rates and cosmetic outcomes between MAL-PDT (n=60) and double freeze-thaw cryotherapy (n=58) in sBCC, a 5-year European randomized trial was performed in 118 patients. This protocol used MAL applied for 3 hours at 75J/cm^2 with noncoherent red light (570-670nm) for 1 session. Partially treated patients at 3 months were given 2 further MAL-PDT sessions (n=20) or repeat cryotherapy (n=16). Complete clinical response rates after 3 months' follow-up for MAL-PDT were 97% of 102 lesions, while that of cryotherapy was 95% of 98 lesions; the difference between these 2 treatments was not statistically significant. At 5 years' follow-up, clearance rates were similar for the MAL-PDT group (75%) and cryotherapy (74%). Of the lesions initially cleared with MAL-PDT, 22% had recurred vs. 20% after cryotherapy. Cosmetic outcome was judged superior following PDT (87% vs. 49%).[17]

Double MAL-PDT treatment cycles for 'difficult-to-treat' sBCC (and nBCC) were reported by 2 prospective multicenter studies. This included recurrent, large-sized lesions and/or those occurring on the mid-face or ears. In the first study, 87% of patients (n=94) had 'difficult-to-treat' lesions occurring on the face or scalp. The protocol was a single cycle of MAL-PDT (MAL 3h, 75J/cm^2, 570-670nm or 580-740nm, 50-200mW/cm^2) involving 2 treatment sessions 1 week apart. For partially treated lesions after 3 months' follow-up, a second cycle was repeated. Complete clearance at 3 months was 85% for sBCC after histological review (75% for nBCC). After 2 years, the recurrence rate was 22% for sBCC (14% for nBCC). Ninety-four percent of patients were assessed to have a good to excellent cosmetic outcome.[18]

In the second study, efficacy, safety, and cosmetic outcomes were examined in 95 patients with BCCs that were 'difficult-to-treat' and at high risk for surgical complications. A total of 148 BCCs (sBCC and nBCC) were treated with the same PDT protocol (MAL 3h, 75J/cm^2, 570-670nm, 50-200mW/cm^2) with re-treatment for non-complete response lesions at 3 months. Overall, histologically-confirmed lesion complete response rate was 89% (93% sBCC and 82% nBCC) after 3 months' follow-up. Fifteen percent of lesions had histologically confirmed recurrence within 2 years increasing to 20% within 4 years. Ninety-seven percent of patients rated their cosmetic outcome as good to excellent at 3 months.[19]

Bowen's Disease

A large randomized, controlled, multicenter study reported similar clearance response rates following MAL-PDT (86%), single freeze-thaw cryotherapy (82%), and 1 month application of 5-fluorouracil (83%) in 225 patients with histologically confirmed Bowen's disease. MAL-PDT (MAL 3h, 75J/cm^2, 570-670nm, 70-200mW/cm^2) was given as a single cycle 1 week apart. Lesions with a partial response at 3 months were re-treated. Cosmetic outcome was superior for MAL-PDT in 94% of patients vs. 66% with cryotherapy, and 76% with fluorouracil.[20] Clearance rates after 2 years for MAL-PDT was 68% vs. 60% with cryotherapy and 59% with fluorouracil.[7]

Conclusion

MAL is an effective low molecular weight topical porphyrin-inducer that is typically used in combination with a red light-emitting diode for PDT. It offers therapeutic benefit for thin and moderate thickness AKs. It should be considered as a treatment option for superficial BCCs and Bowen's disease, particularly in situations where surgery may be problematic or where patients have multiple lesions. However, long-term cure rates, as mentioned above for Bowen's disease and sBCC, are only 68% and 75% respectively. Because of the appreciable nonresponse and recurrence rates, patients treated with PDT for either disease should be monitored closely during the first 2-3 years after PDT, which is when most lesion recurrences occur. According to studies, patients' high preference for MAL-PDT may be mainly due to its good to excellent cosmetic outcome and general tolerability of side-effects. No direct comparative studies have yet been reported with MAL and ALA. Important parameters, such as the depth of penetration of MAL-PDT, tumor thickness, location, and careful patient selection are key elements for efficacy. In the US, MAL-PDT is currently FDA-approved for the treatment of AKs only, whereas in Canada, MAL-PDT is officially indicated for the treatment of both AKs and sBCCs.

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Adapalene 0.1% and Benzoyl Peroxide 2.5%: A Novel Combination for Treatment of Acne Vulgaris

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ABSTRACT

Topical products commonly used to treat acne include retinoids and antimicrobials, due to their effects on different components of pathogenesis. Accordingly, a fixed combination of adapalene 0.1% and benzoyl peroxide (BPO) 2.5% was developed (Epiduo™, Galderma) and was approved by the US FDA in December 2008 for the treatment of acne. The superior efficacy of this combination was demonstrated in 2 large randomized controlled trials. This paper reviews the evidence for efficacy and tolerability of the combination of the retinoid adapalene 0.1% and BPO 2.5%, a once-daily gel formulation for the treatment of acne.

Keywords: acne; adapalene; antibiotics; benzoyl peroxide; retinoids

Adapalene, a receptor-selective naphthoic acid derivative with retinoid-like properties, has comedolytic, anticomedogenic, and anti-inflammatory effects. Benzoyl peroxide (BPO) is a highly lipophilic oxidizing agent with bacteriocidal and keratolytic effects. The addition of adapalene with BPO does not result in chemical or photo-instability of the combined product. Retinoids are considered first line therapy for mild comedonal and inflammatory acne.[1] In dermatological practice, topical retinoids are the class of agents most commonly used as topical monotherapy for acne. When 2 topical agents are used, the agents most frequently selected are retinoids and BPO, either alone or with antibiotics.[2] In view of the primary role of these 2 classes of topical agents, a single formulation comprising both is rational and may increase adherence and improve overall efficacy.

Review of Clinical Studies

Dose-ranging Studies

Individually, topical retinoids and BPO are potentially irritating agents and a combination product may increase this potential. In an irritancy study[3] comparing adapalene 0.1% gel, tazarotene cream 0.05%, and tretinoin microsphere gel 0.04% used in combination with 2 different clindamycin/BPO products under occlusion, the adapalene 0.1% gel was reported to be the least irritating. This 3-week randomized, controlled intraindividual study involved test site applications at the back under occlusion. The tolerability of 2 different combination clindamycin/BPO topical products followed 8 hrs later by adapalene 0.1% gel, tazarotene cream 0.05%, and tretinoin microsphere gel 0.04% was evaluated. Regardless of the type of clindamycin/BPO combination, the mean cumulative irritancy index and erythema scores were significantly lower for sites involving adapalene gel. The combination of adapalene 0.1% and BPO 2.5% was selected for further development based on a cutaneous tolerability study[4] evaluating adapalene 0.1% combined with either BPO 2.5% or 5%. In that study, 60 healthy subjects were randomized into a 3 week split-face trial with daily application of adapalene 0.1% + BPO 2.5%, adapalene 0.1% + BPO 5%, BPO 2.5% or 5%. This study showed that irritation scores (total sum score comprising erythema, dryness, pruritus, and stinging/burning) for adapalene 0.1% + BPO 2.5% were lower than for the combination product containing BPO 5%, and similar to BPO 5% alone.

Randomized-Controlled Trials (See Table 1)

A Phase II/III randomized, double-blind, parallel group study[5] of adapalene 0.1% + BPO 2.5% gel, adapalene 0.1% gel, BPO 2.5% gel, or vehicle gel used nightly for 12 weeks involved 517 acne patients enrolled in a 2:2:2:1 ratio, respectively. The combination arm was significantly more effective in achieving a facial acne global grade of clear/almost clear (i.e., 28% vs. 16% vs. 15% vs. 10%, respectively). The differences were significant against the BPO (P=0.003) and vehicle (P=0.02) arms, and borderline for adapalene itself (P=0.08). Significant improvements in the lesion counts were observed for the combination compared with monotherapy and vehicle arms. Total acne lesions were reduced by 51% (median 78 at baseline to 40 at end of study), inflammatory lesions by 63% (27 to 17), and noninflammatory lesions by 51% (44 to 22). Overall local tolerability of the combination was similar to that for adapalene alone, with a somewhat higher percentage of subjects in the combination group having erythema, dryness, and/or stinging/burning. Mean tolerability scores, based on erythema, scaling, dryness, and stinging/burning, peaked at the first week and declined thereafter. Mean symptom scores were mild or less for all treatment arms.

A subsequent larger Phase III double-blind, randomized-controlled trial[6] (RCT) with similar trial design involving 1668 patients randomized into the same 4 treatment arms in a 1:1:1:1 ratio was performed. Results demonstrated that the combination was more effective in achieving clear/almost clear global scores (30% vs. 20% for adapalene 0.1% gel , 22% for BPO 2.5% gel and 10% for vehicle gel), and in reducing acne counts. Total acne counts were reduced by 56% (median 76 at baseline to 35 at end of study), inflammatory lesions by 62% (27 to 11), and noninflammatory lesions by 54% (44 to 20). A significant reduction in all lesion counts were noted within the first week of treatment compared with vehicle. Local intolerability adverse events were mild-to-moderate

in all treatment arms and peaked during the first week. However, more patients in the adapalene + BPO combination group experienced signs and symptoms of local intolerability compared with the other treatment groups. The number of patients with adverse events leading to discontinuation was slightly higher with the combination compared with adapalene monotherapy, BPO monotherapy, and vehicle groups: 11 (2.7%) vs. 4 (1.0%), 5 (1.2%), and 2 (0.5%), respectively. The most frequent treatment-related adverse event was dry skin, which was higher in the combination and adapalene groups than in the BPO monotherapy and vehicle groups (i.e., 6.0%, 4.3%, 1.9%, and 2.2% respectively).

Long-term Safety and Efficacy

The long-term tolerability and safety of adapalene 0.1% + BPO 2.5% gel was evaluated in 452 acne subjects over 12 months.[7] Of these, 327 completed the study (72%). No subjects discontinued due to lack of efficacy, while discontinuation due to adverse events was 2%. Overall, treatment was well tolerated with mean scores for local intolerance (comprising erythema, dryness, scaling, and burning/stinging) reported as mild or less in all study visits. The mean worst scores of subjects were consistent with mild irritation. The highest irritation scores were recorded at the first week and subsequently declined thereafter. The most common adverse event was dry skin (17%). Efficacy, based on the intent to treat population with last observation carried forward, was 65% reduction in total, 70% in inflammatory, and 66% in noninflammatory lesion counts.

Conclusion

The combination of adapalene 0.1% + BPO 2.5% gel in a single formulation is a novel topical agent for the treatment of mild-to-moderate inflammatory acne. The clinical efficacy and tolerability of this fixed dose combination over 12 weeks has been shown in 2 large high quality RCTs. Furthermore, long-term tolerability and ongoing efficacy has been demonstrated in a 12-month study.

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Study	Summary	Epiduo™	Adapalene 0.1% in Vehicle Gel	BPO 2.5% in Vehicle Gel	Vehicle Gel
Thiboutot, et al.[5]	number of patients	149	148	149	71
	success rate (%)	28	16	15	10
	P-value (vs. Epiduo™)		0.008	0.003	0.002
	total lesions (median % change)	-51	-35*	-36*	-31*
	inflammatory lesions	-63	-46*	-44*	-38*
	noninflammatory lesions	-51	-33*	-36*	-38*
Stein-Gold et al.[6]	number of patients	415	420	415	418
	success rate (%)	30	20	22	11
	P-value (vs. Epiduo™)		<0.001	0.006	<0.001
	total lesions (median % change)	-56	-47**	-48**	-28**
	inflammatory lesions	-62	-50**	-56**	-34**
	noninflammatory lesions	-54	-49**	-44**	-29**
Pooled outcomes	number of patients	564	568	564	489
	success rate (%)	28	18	19	10

Table 1: Efficacy of Epiduo™ and its components on success rate and lesion reduction in acne (success defined as investigator global scores of clear or almost clear). * P <0.001; ** P < 0.017

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Update on Drugs

Name/Company	Approval Dates/Comments
Benzyl Alcohol Lotion 5% Sciele Pharma	The US FDA approved this prescription medication in April 2009 for the treatment of head lice infestation for use in patients 6 months of age and older.
Red Light Technology Device + Methyl Aminolevulinate Cream *Aktilite® CL 128 + Metvix®* Photocure/ Galderma	Health Canada approved this LED-based narrow band red light technology device in combination with methyl aminolevulinate in April 2009 for the treatment of actinic keratosis and superficial basal cell carcinoma.

Drug News

Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals, Inc. announced in April 2009 that a Phase III trial evaluating sorafenib tablets (Nexavar®) in patients with unresectable Stage III or Stage IV melanoma was stopped early following a planned interim analysis by the independent Data Monitoring Committee (DMC). The trial was sponsored by the National Cancer Institute (NCI) and led by the Eastern Cooperative Oncology Group (ECOG) under a Clinical Trials Agreement between NCI and Bayer and Onyx. The DMC concluded that the study would not meet the primary endpoint of improved overall survival among patients receiving sorafenib in combination with the chemotherapeutic agents carboplatin and paclitaxel vs. patients receiving placebo plus the chemotherapeutic agents. The treatment effect was comparable in each arm. There were no unexpected serious side-effects, though the final analysis of the data will occur per protocol and statistical analysis plan. Bayer and Onyx will further review the findings of this analysis to determine what, if any, impact these data might have on other ongoing sorafenib melanoma trials. Data from this study are expected to be presented at an upcoming scientific meeting.

In a study presented at the 2009 Annual Meeting of the American Academy of Allergy, Asthma & Immunology*, researchers at Mount Sinai Hospital in New York studied 14 patients with persistent atopic dermatitis who received traditional Chinese medicine at Ming Qi Natural Health Center in Manhattan between August 2006 and May 2008. The treatments consisted of Erka Shizheng Herbal Tea, a bath additive, creams, and acupuncture. The study authors utilized 2 measures: the SCORAD index to gauge atopic dermatitis severity and the Dermatology Life Quality Index (DLQI) to calculate impairment to life quality. Baseline median scores for SCORAD and DLQI were 89 and 17, respectively. After a median 8 months of treatment, the median scores fell to 11 for SCORAD and 1 for DLQI. In all but 1 patient, SCORAD measures decreased between 60% to 90% after 3.3 months of treatment. More than 50% improvement in DLQI scores was documented in all but 1 patient after 2.4 months. Patients also reported a reduction in the use of steroids, antibiotics, and antihistamines within 3 months of being treated with traditional Chinese medicine. There were no abnormalities of liver and kidney function observed. While the researchers concluded that the use of traditional Chinese medicine is safe and effective for patients with persistent atopic dermatitis, especially those with a severe case and significant life quality impairment, it is still recommended to speak with a physician before taking any complementary or alternative medicines.

* Wisniewski J, Nowak-Wegrzyn A, Steenburgh-Thanik H, et al. Efficacy and safety of traditional Chinese medicine for treatment of atopic dermatitis (AD). *J Allergy Clin Immunol* 123(Suppl 2):Abstract #131 (2009 Feb).