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Aminolevulinic Acid (Levulan[®]) in Photodynamic Therapy of Actinic Keratoses

K. Lang, MD, K.-W. Schulte, MD, T. Ruzicka, MD and C. Fritsch MD
Hautklinik, Universitätsklinikum Düsseldorf, Heinrich-Heine University, Düsseldorf, Germany

ABSTRACT

The role of photodynamic therapy (PDT) in the treatment of in situ neoplasias and tumors of the skin is steadily increasing. Its principles of photodynamic action include an intratumoral enriched photosensitizer and light activation. Aminolevulinic acid (ALA) has demonstrated highest efficacy in topical PDT, and has become the most clinically useful. For actinic (solar) keratoses, topical ALA-PDT using Levulan[®] Kerastick[™] (20% topical solution, DUSA Pharmaceuticals) is already postulated to be the treatment of choice. In December 1999, the US FDA approved this topical product for the treatment of actinic keratoses. Levulan[®] is well tolerated and leads to excellent cosmetic results with only minor side effects.

Key Words: aminolevulinic acid, porphyrins, photosensitizer, photodynamic therapy, actinic keratoses

δ -Aminolevulinic acid HCl is an endogenous precursor of highly photosensitizing porphyrin metabolites. Normally, the synthesis of ALA is tightly controlled by feedback inhibition of the enzyme aminolevulinic acid synthase (ALA-S), presumably by intracellular heme levels.^{1,2} Therefore, when exogenous ALA is provided to the cell through topical application, protoporphyrin IX accumulates by bypassing the rate limiting enzyme ALA-S.

In photodynamic therapy (PDT), light absorption by porphyrin metabolites, e.g., protoporphyrin IX, results in an excited state of the molecule and subsequent generation of reactive oxygen species, which can react further to form superoxide and hydroxyl radicals.³ The tissue-specific phototoxic effects resulting from local application of ALA and light irradiation are the basis of photodynamic therapy (PDT) for actinic keratoses (AKs) and other in situ neoplasias.

Pharmacology of ALA

The standard procedure of topical ALA-PDT for skin tumors involves the application of 10-20% ALA in an oil-in-water emulsion, which is then covered by an occlusive dressing to enhance the tissue penetration of the drug and to prevent undesired photobleaching of porphyrins by visible light.

Levulan[®] Kerastick[™]

ALA has been pharmaceutically included into Kerastick[™] (20% topical solution, DUSA Pharmaceuticals).^{4,5} Each Kerastick[™]

applicator has 2 sealed glass ampules containing 1.5ml hydroalcoholic solution vehicle and 354mg ALA. Schering AG, Berlin officially applied for Levulan[®] Kerastick[™] to be used for the treatment of AK in Austria in 2001. Austria is acting as a reference member state for the European application. In the US it is marketed by Berlex Laboratories on behalf of DUSA.

Adverse Effects

Contraindications for PDT include cutaneous photosensitivity, porphyria, and allergies to ALA or to any of its components. Patients who have concomitant disorders that are provoked or aggravated by light should be evaluated cautiously. It is not known whether ALA or its metabolites are excreted in breast milk, therefore, caution should be exercised when treating women who are breastfeeding.

Following topical application of ALA, the treated site becomes photosensitive, and patients should be warned to avoid sunlight or bright indoor light (e.g., examination lamps, theater lamps, tanning beds, or lights at close proximity). Such exposure may result in a stinging and burning sensation and cause erythema and/or edema of the lesions.^{2,6} Topical ALA treatment does not induce systemic accumulation of ALA or porphyrins.⁷

As a result of light exposure during PDT treatments, patients may experience burning pain, stinging, or itching, which is restricted to the illuminated area.⁸⁻¹⁰ The discomfort will peak

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within the first minutes of irradiation. It may continue for several hours, though in a decreasing manner. Local anesthesia or intensive cooling can help to control the pain, especially when disseminated, large, ulcerative, or inflamed areas are treated.

The normal course of clinical response to PDT is usually distinguished by crusting, scaling, pruritus, and healing within 1-4 weeks.¹⁰ Urea preparations can be used to resolve dry crusts and accelerate re-epithelialization.^{11,12} ALA produces very good cosmetic results, often superior to the outcome achieved by cryosurgery¹³, surgery, or topical chemotherapy. Generally, scar formation is minimal or absent. Rarely, residual hyperpigmentation or hypopigmentation of the treated area can occur.

Pharmacokinetics

The application of ALA in PDT for cutaneous disorders was introduced in 1990.¹⁴ The main advantage of this treatment is the absence of generalized cutaneous photosensitivity. The mechanisms of ALA uptake and accumulation in malignant and regenerative cells are not completely understood. Major responsibility for the tumor selectivity of ALA or synthesized porphyrins is the increased permeability of abnormal keratin layers in epithelial skin tumors. The active transport of the compound through plasma membranes was demonstrated in microorganisms and in cell culture.¹⁵ However, additional cell-type dependent uptake mechanisms cannot be excluded. The optimal application time and concentration have already been elucidated by biochemical analyses of ALA-treated skin samples. Epithelial skin tumors such as basal cell (BCC) or squamous cell carcinomas (SCC) reveal maximum porphyrin levels 2-4 hours after topical ALA application.⁶

Light sources

In dermatology, the most commonly used irradiation sources include incoherent light sources that comprise red (570-750nm),⁹

in a complete response (CR) of 90%.¹⁴ In the following years, other investigators, using more professional incoherent light sources, obtained a CR of 80-100% in AKs.¹⁹⁻²¹ The CR rate of AKs located on the face and scalp was significantly higher (91%) when compared with keratoses on the trunk and extremities (45%). The often reported poor clinical response (<30%) of the thick hyperkeratotic lesions⁵ may have been due to ineffective penetration of ALA and consecutive insufficient production of porphyrin molecules.

In a randomized, multicenter, vehicle-controlled, investigator-blinded, light-dose ranging study, maximal therapeutic effects were obtained in ALA-treated AKs irradiated with blue light (BLU-U™, 417 nm) at a dose of 10J/cm² (10 mW/cm²).¹⁶ ALA solution (20%) or the vehicle only was applied to 2 lesions each, on the face and scalp of 36 patients. Lesions were exposed to 2, 5 or 10J/cm² of blue light (417nm) delivered at 3, 5 or 10mW/cm², 14-18 hours after application. Eight weeks after treatment a CR was obtained in 66% of ALA-treated lesions versus 17% of those treated with vehicle and light (p < 0.001). The maximal response (80%) was seen in patients treated with the maximal dose of light (10 J/cm²). Non-responding lesions were re-treated at 8 weeks and by 16 weeks the CR was 85% in ALA-treated lesions. The efficacy of the higher light dose was confirmed in a second phase II study of 64 patients conducted with the same protocol.¹⁶

To establish the optimum concentration of ALA solution, a randomized, vehicle-controlled, investigator-blinded, multicenter study was carried out using ALA 2.5, 5, 10, 20, or 30% wt/vol and blue light (BLU-U™) at 10 J/cm² (10 mW/cm²).¹⁶ ALA was applied to lesions (site not specified) on 124 patients. There were significantly more CR (defined as clearance of 75% of lesions) in the groups treated with 10, 20 or 30% ALA than in the groups treated with 2.5 or 5%. A dose-response trend was evident with a plateau emerging at the 10, 20 and 30% dose levels. The

Study/ Investigator	n	Dose		Area of Lesion	Response time to irradiation	Sessions	
		mW/cm	J/cm ²				
Phase II ¹⁶	36 patients	3,5,10	2,5,10	Face and scalp	20% vs vehicle	66% vs. 17% CR*	1-2
Phase II ¹⁶	64 patients	3,5,10	2,5,10	Face and scalp	20%	80% CR	1-2
Phase III ²²	241 patients**	10	10	Face and scalp	20% vs vehicle	83% vs 14% CR	1-2

Table 1: Clinical Trial results using Levulan® and BLU-U™.

*Maximal response was seen in patients treated with the maximal light dose (10J/cm²).

**All patients showed multiple lesions. The clearance rate was higher for lesions on the face (78%) than on the scalp (50%).

green (545nm),¹⁰ or blue light (417nm,¹⁶ or 400-410nm¹⁷) and laser systems (e.g., argon pumped dye lasers). BLU-U™ has a nominal peak value of 417nm with a spectral range of 402-432nm.¹⁸

Clinical Trials

In 1990, the topical application of 20% ALA to AKs, followed by a single exposure to the light of a filtered slide projector, resulted

researchers concluded that an ALA concentration of 20% produced the best response.

In phase III trials topical ALA 20% was effective in eradicating AKs of the face and scalp in the majority of patients. A total of 241 patients with 4-15 AKs each were enrolled in two randomized, vehicle-controlled, investigator-blinded, multicenter trials²² (see Table 1).

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Vulvovaginal Dryness and Itching

L.J. Margesson, MD

Departments of Obstetrics & Gynecology and Medicine (Dermatology), Dartmouth Medical School, Hanover, New Hampshire, USA

ABSTRACT

Dryness and itching in the vulvovaginal area is an increasing problem as our female population ages and becomes menopausal. This dryness and itching is often the result of estrogen deficiency, and there are typically two types of treatment: Specific Therapy (or hormone replacement therapy), and Nonspecific Therapy. Dermatologists should be able to sort out the causes of the itching and irritation, and understand the approaches to therapy.

Key Words: vulva, vagina, pruritus, estrogen

Dermatologists are not consulted regularly for vulvovaginal problems, but as our aging female population moves into menopause, more and more patients will be complaining of vulvovaginal itching and dryness. Those patients who already have skin conditions affecting their vulvar areas will be more susceptible to irritation and exacerbation of their skin conditions, which include inverse psoriasis, atopic and "sensitive" skin, genital lichen sclerosus, and lichen planus. Dermatologists should be able to sort out the causes of the itching and irritation, and understand the approaches to therapy.

Vulvovaginal Dryness and Itching

Vulvovaginal dryness and itching most commonly occur when there is an absence of estrogen stimulation. Estrogen is needed for the structural and functional integrity of the vagina and the introitus. Without estrogen, the first symptom is dryness. Typically, perimenopausal women develop this dryness long before hot flashes and menstrual cessation. The vagina begins to feel like "sandpaper" and may be accompanied by itching. Signs of this atrophic vulvovaginitis develop slowly and insidiously.

Perimenopause usually starts about 5-7 years before the last menstrual period, but can occur prematurely in the late twenties or thirties.¹ Relative atrophy can also develop postpartum with lactation and with the use of some birth control pills. Onset may be abrupt postsurgery or after chemotherapy.² Tamoxifen, an anti-estrogen used for treatment of breast cancer and malignant melanomas, can cause menopausal symptoms by blocking the estrogen effect in reproductive women. In postmenopausal women, it has an agonistic estrogen-like action.

Along with the dryness and itching, the other complaints of estrogen deficiency, e.g., hot flashes, insomnia, decreased libido, and psychological and cognitive changes eventually occur. Closer to the time of actual menstrual cessation, vaginal atrophic changes may increase to induce marked dyspareunia and urinary incontinence.

Poorly estrogenized vulvovaginal tissue thins, and then loses its normal vaginal secretions and normal flora. The result is an increased susceptibility to trauma from friction or chemical irritants, and to bacterial overgrowth, should it become irritated. Petechiae, telangiectasia, fissuring, and even a purulent discharge may develop. Initially there is vulval itching and then burning.

Estrogen Deficiency in Children

The effects of estrogen deficiency are often overlooked in young girls. In infancy, their genitalia are protected by maternally derived estrogen, but after the first two years of life, they are relatively estrogen deficient. There is relative atrophy, as well as a lack of the normal labial development, which become protective factors for the genital area. However, this atrophic, hypoestrogenic tissue is susceptible to irritants from urine, feces, cleansers and topical products and is susceptible to bacterial overgrowth like in an adult. One of the most common gynecological problems in children is vulvovaginitis. Many of the products used for cleansing and topical relief may just add insult to injury, creating more "contact" (usually of the primary irritant type) dermatitis.³

The Hypoestrogenized Vulva

On examination of the hypoestrogenized vulva, the vulvar trigone (the area of the vulva below the clitoris around the inside of the labia minora and around the hymenal ring) looks atrophic, pale and dry. The vaginal epithelium is dry, light pink to white, thin, and smooth due to loss of rugae. With increased severity, the vulva can show erythema, petechiae, telangiectasia, fissuring and erosion, and the open erosions may even produce a chronic purulent discharge. The pH is elevated at 6.0 - 7.0. The area around the vulva may be secondarily irritated with varying degrees of dryness, scaling and even painful fissures.⁴

Treatment

Treatment is divided into Nonspecific Therapy (i.e., addressing all the general factors that irritate the skin and any underlying conditions that may be further complicating management) and Specific Therapy (i.e., hormone replacement therapy).

Nonspecific Therapy

For Nonspecific Therapy, all irritating soaps and hygiene products should be discontinued along with sanitary pads, and hot constrictive synthetic clothing. Unfortunately, in addition to experiencing dryness, itchiness and irritation in the vulvovaginal area, menopausal women are also often incontinent. This is a major problem in older patients, and a very embarrassing problem that most women try to hide. They wear pads all day and consequently their vulvar area is chronically damp. Unfortunately,

this "diaper dermatitis" is often missed. Patients do not volunteer such information and hide the pads during examinations. Heavy patients often wear constrictive clothing, which further complicates the problem. Because of the combination of urinary incontinence, heat, perspiration and odor, they use irritating cleansing products, "deodorants", and wipes. It is important to take the time to obtain a full history of the products that your patients are using.

systemic estrogens available are estradiol, conjugated estrogen and estropipate. Recently there has been controversy about which progestational agent is safer or more effective. The two progestins are medroxyprogesterone acetate and micronized progesterone. Pure micronized progesterone is felt to be safer and more effective.

Topical replacement therapy includes estriol, conjugated estrogen and estradiol in various forms.

<p>Nonspecific Therapy</p>	<ul style="list-style-type: none"> • Discontinue all hygiene products • Discontinue use of sanitary pads • Discontinue wearing hot, constrictive and/or synthetic clothing • Use only nonirritating cleansers and plain petrolatum • 1% hydrocortisone in petrolatum or triamcinalone 0.1% ointment should be used for mild to moderately severe pruritus and irritation • Treat any underlying dermatological condition
<p>Specific Therapy</p>	<p>Hormone Replacement Therapy</p> <ul style="list-style-type: none"> • Oral – individualized dose, continuous or cyclic, with or without progestin • Vaginal • Transdermal – includes estriol, conjugated estrogen and estradiol in various forms (e.g. Estraderm® Transdermal Systems, Novartis, and Estring® Vaginal Ring, Pharmacia & Upjohn)

Table 1: Two types of therapy recommended for treatment of atrophic vulvovaginitis.

Encourage patients to use loose ventilated cotton type clothing as much as possible, avoiding pantyhose and girdles. Nonirritating cleansers like Cetaphil® lotion (Galderma) should be used to gently cleanse the area. Disposable wipes or feminine deodorant products should be discouraged. For cleansing and soothing irritation, recommend a sitz bath for 5-10 minutes, 2-3 times daily with Burow's solution, mixing 1/2-1 packet of Domeboro® (Bayer) or Buro-Sol® (Stiefel) in 500ml water. A hand-held showerhead is invaluable for cleansing and rinsing the genital area.

If the skin is dry and cracked, use plain petrolatum or even light mineral or olive oil after the soak and while the skin is still damp. If there is mild to moderately severe pruritus and irritation, then topical 1% hydrocortisone in petrolatum or triamcinolone 0.1% ointment may be necessary. Secondary infection from bacteria and yeast may require treatment, and any underlying dermatological condition must be treated. If the patient is not responding, patch testing may be necessary. If incontinence is a major problem, the patient should be referred to a urologist or gynecological urologist for pelvic floor management.

Specific Therapy

Specific Therapy utilizes hormone replacement. However, estrogen replacement can be a confusing and complicated process, because there are many products and regimens available. Adequate estrogen levels can be achieved by taking the hormone orally, vaginally, or by a transdermal route. However, the oral or transdermal routes may not be adequate for the vagina, and a vaginal cream could still be necessary. The oral dose of estrogen needed is individualized, and can be given continuously or in a cyclic fashion, with or without the progestin. If the uterus is present, a progestin must be given to protect the vaginal lining from excess estrogen stimulation. The

Hormone replacement therapy is contraindicated in the presence of:

- estrogen-dependent malignancies
- breast cancer
- thromboembolic disease (The onset may be abrupt postsurgery or after chemotherapy.)
- undiagnosed vaginal bleeding
- endometriosis
- hypertriglyceridemia
- pregnancy.

For those who cannot use hormone replacement therapy, a vaginal lubricant or moisturizer should be considered, such as Replens® (Shire Pharmaceuticals) that will last up to 72 hours. They can be very effective postpartum, during lactation and in premenopausal women.^{5,6,7}

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Conclusion

Levulan® and BLU-U™ are very effective in the treatment of AKs. It is non-invasive and leaves the patients with excellent cosmetic results. The response of AKs to PDT equals the cure rates achieved by other topical treatment modalities, including the use of liquid nitrogen and chemical peels. In summary of the current data, ALA-PDT appears to be most efficient for the treatment of these in situ neoplasias.

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TPP – Canada Institutes Changes to Clinical Trial Regulations

TPP – Canada announced that as of September 1, 2001, some new clinical trial regulations will become effective, resulting in important and long awaited changes in both the clinical trial review and conduct in Canada. These changes include:

- Some Phase I protocols (e.g., bioequivalence, or trials involving healthy volunteers) will have an internal target review time of seven calendar days.
- Following submission of an Investigational New Drug application (IND), the waiting period will be 30 days instead of 60 days.
- Only qualified investigators (i.e., physicians or dentists who are licensed to practice) can undertake clinical trials.
- Prior to starting a clinical trial, the sponsor must supply the names of all Ethics Review Boards and their conclusions
- Clinical trial sites in Canada will be open to TPP inspection and review.
- All clinical trials must be conducted following Good Clinical Practice standards, even trials not requiring an IND.

These changes will have a major impact on how clinical trials will be carried out in the future.

Update on Drugs

Class	Name/Company	Approval Dates and Comments
Photodynamic Therapy	Aminolevulinic Acid <i>Levulan[®] Kerastick[™] photodynamic therapy</i> Draxis Health/DUSA Pharmaceuticals	TPP – Canada issued marketing approval to Draxis Health in June 2001, for this product to treat AKs of the face and scalp. Draxis holds the rights to Levulan [®] in Canada from DUSA Pharmaceuticals.
Monoclonal Antibody	Infliximab <i>Remicade[™]</i> Schering Canada	TPP – Canada approved this monoclonal antibody for marketing in June 2001, for the treatment of severe, active and fistulizing Crohn's Disease in adult patients who have not responded to conventional treatment.
Antifungal Agent	Butenafine HCl <i>Mentax[®]</i> Bertek Pharmaceuticals	The US FDA approved a new indication in June 2001, for this anti-fungal agent. It is now indicated for the treatment of the fungal infection tinea (pityriasis) versicolor caused by the yeast <i>Pityrosporum orbiculare</i> .
Antifungal Agent	Clotrimazole/Betamethasone Dipropionate Taro Pharmaceuticals	The US FDA approved this antifungal/corticosteroid cream in May 2001, in the treatment of a variety of dermatological conditions. It is bioequivalent to Schering-Plough's Lotrisone [®] cream.
Drug News		
Drug Warning	The US FDA issued a warning to consumers in June 2001, to discontinue use of 13 Chinese herbal products containing aristolochic acid because they may present serious health hazards. The products are sold under the <i>Treasure of the East</i> label with the MFG No. 200008 and the manufacturer, Blue Light, Inc., has initiated a recall.	
Drug Warning	The US FDA issued a drug warning in June 2001, stating that myelosuppression, including anemia, pancytopenia and thrombocytopenia, has been reported in patients using Linezolid (Zyvox [®]). Complete blood counts should be monitored weekly in patients who receive this drug, particularly if they: <ul style="list-style-type: none"> • receive it for longer than two weeks • have pre-existing myelosuppression • receive concomitant drugs that produce bone marrow suppression • have chronic infections who have received previous or concomitant antibiotic therapy. 	
Antiacne Agent	The US FDA granted six additional months of marketing exclusivity to Accutane [®] (Isotretinoin, Hoffmann La Roche) in June 2001, through its pediatric exclusivity program. This means that exclusivity for Accutane [®] in the US is in effect until February 7, 2002.	
Drug Interaction	In an article published in <i>Clinical Pharmacology and Therapeutics</i> *, Morii, et al, reported that when mycophenolate mofetil (CellCept [®] , Roche US Pharmaceuticals) and iron ion preparations were administered concomitantly, a remarkable reduction in mycophenolate mofetil absorption was observed. The authors hypothesize that this could be due to formation of a drug-iron complex in the GI tract. They recommend avoidance of simultaneous administration of these products. <p style="margin-top: 10px;">*<i>Clin Pharmacol Ther</i> 68(6):613-6 (2000).</p>	

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