Photodynamic Therapy for Papulopustular Rosacea

STUDY PROTOCOL

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1. STATEMENT OF HYPOTHESIS AND OBJECTIVES:

Rosacea is a chronic inflammatory disorder that is characterized by severe flushing (transient erythema), non-transient erythema, papules, pustules, and telangiectasia. Topical therapy is not always effective in treating symptoms of rosacea. Furthermore, rapid recurrence is common following the use of systemic antibiotics, resulting in the chronic use of these medications to control the disease. Although the exact pathogenesis of rosacea is unknown, treatment for this condition has been investigated based on its similarity to acne and photodamaged skin. Case reports have shown promising results in rosacea patients treated with methyl aminolevulinate photodynamic therapy (MAL – PDT). Other than a case report which observed significant improvement of papules, pustules, erythema, and flushing following 5 - aminolevulinic acid photodynamic therapy (ALA-PDT) treatment of a patient with rosacea, the role of ALA-PDT in the treatment of rosacea has not been reported.

We have designed a pilot study investigating the efficacy of ALA-PDT in treating papulopustular rosacea. The objectives of the study are as follows:

Primary objective:

1. To evaluate improvement of the inflammatory lesions (papules, pustules, nodules), erythema, and telangiectasia of rosacea as assessed by the Investigator's Global Assessment (IGA).

2. To evaluate improvement of the inflammatory lesions (papules, pustules, nodules) of rosacea as assessed by the Inflammatory Lesion Investigator's Global Assessment (ILIGA).

Secondary objectives:

3. To evaluate improvement of rosacea associated erythema as assessed by the Clinical Erythema Assessment (CEA) scale.

4. To evaluate improvement of the inflammatory lesions (papules, pustules, nodules) of rosacea as measured by a difference in inflammatory lesion count.

5. To evaluate improvement of rosacea as assessed by the Patient Overall Assessment Scale.

2. BACKGROUND, SIGNIFICANCE, AND RATIONALE

Rosacea

Rosacea is a chronic inflammatory disorder that is characterized by severe flushing (transient erythema), nontransient erythema, papules, pustules, and telangiectasia. It primarily affects the central third of the face. Secondary features of rosacea include burning or stinging, erythematous plaques, edema, dry appearance, peripheral locations, ocular manifestations, and phymatous changes.[1] It has a prevalence of about 10%. The majority of patients with rosacea are between the ages of 30-60 years of age.[2,3]

There are four subtypes of rosacea (erythematotelangiectatic, papulopustular, phymatous, and ocular); patients may have characteristics of more than one subtype. Although the exact pathogenesis of rosacea is unknown, increased blood flow, excessive sun exposure, hair follicle mites (*Demodex folliculorum and Demodex brevis*), and inflammatory mediators (neutrophils, macrophages, and lymphocytes) are thought to play role.[3]

Treatment for rosacea consists of topical azelaic acid, sodium sulfacetamide, sulfur, topical and systemic metronidazole, antibiotics (erythromycin, clindamycin, tetracycline), and, in resistant cases, isotretinoin. The therapeutic effect of these medications on rosacea is related more towards their anti-inflammatory than their antibacterial actions.[3, 4]

Topical therapy is not always effective in treating symptoms of rosacea. Furthermore, rapid recurrence is common following the use of systemic antibiotics, resulting in the chronic use of these medications in order to control the disease.[4] Pharmacological treatment is partially effective in treating the papulopustular lesions of rosacea, but the treatment of erythema, flushing, and telangiectasia is limited and at times requires the use of lasers, including pulse-dye laser.[5]

Photodynamic Therapy

Photodynamic therapy (PDT) has been used for various dermatological conditions. It involves the administration of a photosensitizer which is absorbed by target cells. Absorption occurs preferentially by hyperproliferative tissue compared to normal tissue. Illumination with a light source of a specific wavelength results in the release of reactive oxygen species within the target tissue and results in the phototoxic destruction of tissue and bacteria.[4,6]

5 - aminolevulinic acid (ALA) and its methylated ester, methyl aminolevulinate (MAL), are two common photosensitizers used in PDT. Both ALA and MAL are converted to protoporphyrin IX (PpIX), a cytotoxic intermediate that destroys tissues through necrosis and apoptosis. ALA, which is activated by blue light (417 +/- 5nm), is approved by the FDA for the treatment of hypertrophic actinic keratoses (AKs) of the face and scalp. It has also been used off-label in treating acne vulgaris, photodamaged skin, sebaceous hyperplasia, and skin cancer. MAL, which is activated by red light, is approved by the FDA for the treatment of nonhyperkeratotic AKs of the face and scalp. MAL is also approved in some European countries for the treatment of superficial and nodular basal cell carcinoma (BCC) and Bowen's disease.[4,6]

Both ALA and MAL – PDT have been effective in treating acne vulgaris. Studies have shown that PDT results in significant reductions in the number of inflammatory acne lesions.[6] The role of PDT in the treatment of acne may be due its antibacterial properties, its ability to damage sebaceous glands, reduce follicular obstruction, and decrease sebum production and gland size.[7,8] Hair follicles and sebaceous glands accumulate *PpIX* after administration of topical ALA. *PpIX* also accumulates more in acne lesions compared to surrounding skin. *Propinobacterium acnes*, a bacteria involved in the pathogensis of acne, produces porphyrins, a metabolic byproduct, which, when activated by light, results in the destruction of the bacteria.[9] Topical ALA causes a preferential accumulation of additional porphyrins in *Propinobacterium acnes,* further enhancing the destructive effect of light.

The mechanism of PDT in the treatment of rosacea is not completely understood. One theory is that rosacea is a folliculitis induced by gram-negative bacteria that are destroyed by a similar mechanism as *Propinobacterium acnes* following PDT. It is uncertain if these gram-negative bacteria also produce endogenous porphyrins.[10] It is possible that PDT could also result in the destruction of *Demodex follicularis*. PDT has also been used in the treatment of actinic keratoses and photodamaged skin. Since rosacea may be induced and worsened by sunlight, the effect of PDT in treating rosacea could be related to its skin rejuvenating properties. The role of PDT in the treatment of neoplastic cells by inducing apoptosis, necrosis, and affecting the microvasculature could be another potential mechanism by which it treats rosacea.[11]

Although the exact pathogenesis of rosacea is unknown, treatment for this condition has been investigated based on its similarity to acne and photodamaged skin. Since follicular inflammation occurs in rosacea and there is a therapeutic overlap between acne and rosacea, the role of PDT in the treatment of rosacea is being investigated. Nybaek et al observed clearing of rosacea in 3 out of 4 patients treated with MAL-PDT. They suggested that a total of two to three treatments with PDT may result in remissions for more than three months following treatment.[4] Katz et al observed significant improvement of papules, pustules, erythema, and flushing following ALA-PDT treatment of a 45 year old female with rosacea.[12]

In light of the above work we have designed a pilot study further investigating the ability of ALA-PDT in treating papulopustular rosacea. If successful, this study could provide further evidence for the use of PDT in the treatment of rosacea. The results of this study may lead to the development of larger studies that are statistically powered to determine improvement of rosacea using ALA-PDT.

3. RESEARCH DESIGN AND METHODS

3.1 Overview of Design

All participants will be patients that have been screened within the Department of Dermatology at the Medical Faculty Associates. Individuals meeting inclusion and exclusion criteria (see Section 3.2) will be randomized to one of three groups (groups A, B, or C); each group will contain 10 patients. Those in group A will have their entire face treated with 20% 5-ALA (Levulan® Kerastick®, Dusa Pharmaceuticals) and Blu-U light (DUSA ®). Those in group B will

have their entire face treated with the vehicle (Kerastick® without 5-ALA) and Blu-U light (DUSA ®). Those in group C will have their entire face treated with the vehicle (Kerastick® without 5-ALA) only. All patients will have their face treated with either 20% 5-ALA (Levulan® Kerastick®, Dusa Pharmaceuticals) or the vehicle (Kerastick® without 5-ALA), which will remain in contact with the skin for one hour and, for those in group A and B, subsequently irradiated with a 417nm blue light set at 10 J/cm^2 from a Blu-U light (DUSA ®) for 16 minutes and 40 seconds. Each subject will receive a total of 4 treatments with a 2-3 week interval between each treatment (See Section 3.4). In addition, the face will be photographed and assessed by a blinded investigator (See Section 4). If ≥ 30% of patients in group A experience improvement in the Investigator's Global Assessment Score (IGA) by at least one point (See Section 3) we will offer subjects in group B and group C one treatment with 20% 5-ALA (Levulan® Kerastick®, Dusa Pharmaceuticals) and Blu-U light (DUSA ®), which will occur 2-3 weeks after the completion of the blinded study period.

3.2 Sample Size, Inclusion and Exclusion criteria

We will enroll a total of 30 patients for this study. Each group (A, B, or C) will contain 10 patients. The inclusion and exclusion criteria for the study are as follows:

Inclusion Criteria:

1. Ages 18-79 years
2. Clinical diagnosis of papulopustular rosacea based on physician evaluation. Only patients with 3-50 papules and/or pustules, and a CEA total score ≥ 5, (See Section 4.1.3) will be enrolled.
3. History of failing at least one conventional treatment for rosacea (metronidazole, sodium sulfacetamide, tetracycline, azaleic acid) or not interested in continuous treatment with these agents.

Exclusion Criteria:

1. < 18 or > 79 years of age
2. Allergy to 5 - aminolevulinic acid (ALA) or any component of the vehicle
3. Use of topical acne or rosacea treatments (on the face) within 2 weeks prior to Treatment 1
4. Use of systemic antibiotics within 1 month prior to Treatment 1
5. Use of topical retinoids (on the face) within 1 month prior to Treatment 1
6. Use of systemic retinoids, including isotretinoin, within 6 months prior to Treatment 1.
7. Use of laser or light based rosacea treatments (on the face) within 1 month prior to Treatment 1
8. Cosmetic procedures (e.g., superficial chemical peels, exfoliation or microdermabrasion of the face) within 2 months prior to Treatment 1
9. Use of topical corticosteroids (on the face) 1 month prior to Treatment 1

10. Use of systemic corticosteroids 3 months prior to Treatment 1
11. Known or suspected history of drug or alcohol abuse within the past 6 months as determined by the medical record or patient interview
12. History of adverse reaction to light exposure
13. History of disorder of porphyrin metabolism
14. Scarring or infection in the area being treated
15. Extensive facial hair that would either impair blue light exposure or interfere with lesion evaluation
16. Inability to make study visits or anticipated poor compliance
17. Pregnant females or nursing mothers. Eligible women of reproductive age will be required to have a negative urine pregnancy test at screening. They will also be required to be on at least one reliable form of effective birth control [examples: barrier method (condoms, diaphragm), oral, injectable, implant birth control or abstinence] during the course of this study and 30 days following the last treatment period.
18. Life threatening illness that would interfere with the patient's ability to complete the study
19. Participation in another clinical experimental therapeutic study within 30 days of screening visit
20. Any history or evidence of severe illness or any other condition that would make the patient, in the opinion of the investigator, unsuitable for the study.

3.3 Screening Phase

Prior to the first treatment session, potential participants will be evaluated for study eligibility. All other inclusion and exclusion criteria must be met prior to study entry/enrollment. The screening phase will be 7-30 days prior to visit 2. If Visit 2 is unable to be scheduled within that window the subject will need to have the inclusion/exclusion reviewed again prior to completing Visit 2.

3.4 Treatment Phase

After the screening phase, subjects (ages 18 – 79 years) with papulopustular rosacea, will be randomized into one of three groups (groups A, B, or C). Each group will contain 10 patients. Those in group A will have their entire face treated with 20% 5-ALA (Levulan® Kerastick®, Dusa Pharmaceuticals) and Blu-U light (DUSA ®). Those in group B will have their entire face treated with the vehicle (Kerastick® without 5-ALA) and Blu-U light (DUSA ®). Those in group C will have their entire face treated with the vehicle (Kerastick® without 5-ALA) only. All subjects will have their face cleansed with acetone; each subjects face should be clean and dry prior to application of 20% 5-ALA (Levulan® Kerastick®, Dusa Pharmaceuticals) or vehicle (Kerastick® without 5-ALA). 20% 5-ALA (Levulan® Kerastick®, Dusa Pharmaceuticals) or vehicle (Kerastick® without 5-ALA) will be crushed and prepared for application after shaking for at least 3 minutes. Topical 5-ALA or vehicle will be liberally applied on skin (entire face) with extra pressure on lesions and allowed to remain in contact with the skin for 1 hour. Those in groups A and B will then have their entire face irradiated with a 417nm blue light set at 10 J/cm^2 from a Blu-U light (DUSA ®) for 16 minutes and 40 seconds. After irradiation, the face will be washed with soap and water and sunscreen will be applied. Each subject will receive a total of 4 treatments with a 2-3 week interval between each treatment session. If ≥30% of patients in

group A experience improvement in the Investigator's Global Assessment Score (IGA) by at least one point (See Section 3) we will offer subjects in group B and group C an additional full face treatment with 20% 5-ALA (Levulan® Kerastick®, Dusa Pharmaceuticals) and Blu-U light (DUSA ®) 2-3 weeks after the completion of the blinded study period. Assessments (Investigator's Global Assessment (IGA), Inflammatory Lesion Investigator's Global Assessment (ILIGA), Clinical Erythema Assessment (CEA) Scale, inflammatory lesion count, and photographs (See Section 4.1.3)) will be performed at baseline, prior to each treatment session, and at study completion by a blinded investigator. A Patient Overall Assessment will be performed prior to every treatment visit (except week 0), and at study completion.

3.5 Study Completion and Withdrawal Criteria

Completion of the blinded component of the study will occur for each individual after 4 treatments with 20% 5-ALA (Levulan® Kerastick®, Dusa Pharmaceuticals) and Blu-U light (DUSA ®) (group A), vehicle (Kerastick® without 5-ALA) and Blu-U light (DUSA ®) (group B), or vehicle (Kerastick® without 5-ALA) only (group C). Participants will have final assessments performed 2 months (+/- 2 weeks) after their last treatment of the blinded period, as outlined in Table 1. If ≥30% of patients in group A experience improvement in the Investigator's Global Assessment Score (IGA) by at least one point (See Section 3) we will offer subjects in group B and group C an additional full face treatment with 20% 5-ALA (Levulan® Kerastick®, Dusa Pharmaceuticals) and Blu-U light (DUSA ®), which will occur 2-3 weeks after the completion of the blinded study period.

Subjects may choose to withdraw from the study at any time and for any reason. The principle and co-investigators may also withdraw any individual that develops worsening rosacea. All serious adverse events that are probably or definitely related to the protocol will be reported to the George Washington University Medical Center Institutional Review Board in accordance with IRB policies and procedures.

3.6 Strength and Limitations of Proposed Research

Strengths of the study include its relatively simple design and the potential for its completion within a short period of time due to the small number of participants (ten).

Limitations of this study include the inability to conduct robust statistical analysis due to its small sample size. However, the results of this project may lead to the development of larger studies that will have the statistical power to detect improvements.

4. DATA VARIABLES, COLLECTION, AND EVALUATION

4.1 Data Variables

The following data will be evaluated in patients fulfilling inclusion and exclusion criteria and who agree to participate in the study.

1. ***Sociodemographic Variables***: Age, gender, race

2. ***Clinical History***:

   a. **Rosacea history**: The patient's disease and treatment history will be obtained. All past and current medications for rosacea will be recorded.
   b. **Past medical history**: All current and past medical conditions will be documented, allowing us to screen for the presence of any condition that, in the opinion of any of the investigators, would make the patient unsuitable for study inclusion. Allergies to medications will also be noted.
   c. **Current medications**: All medications will be recorded.
   d. **Social History**: We will screen for the presence of any drug or alcohol abuse within the past 6 months as determined by the medical record or patient interview.

3. ***Rosacea - specific Variables***: All variables described below will be assessed by the same blinded investigator at various points throughout the study.

a. Investigator's global assessment of rosacea (IGA). The IGA is a subjective 7-point, static scoring system. Scores range from 0 to 6: 0 (clear) = no papules and/or pustules, no residual erythema, no or mild to moderate telangiectasia; 1(minimal) = rare papules and/or pustules, residual to mild erythema, mild to moderate telangiectasia; 2 (mild) few papules and/or pustules, mild erythema, mild to moderate telangiectasia; 3 (mild to moderate) = distinct number of papules and or/pustules; mild to moderate erythema; mild to moderate telangiectasia; 4 (moderate) = pronounced number of papules and/ or pustules, moderate erythema, mild to moderate telangiectasia; 5 (moderate to severe) = many papules and/ or pustules, occasionally with large inflamed lesions, moderate erythema, moderate telangiectasia; 6 (severe) = numerous papules and/or pustules occasionally with confluent areas of inflamed lesions; moderate or severe erythema, moderate or severe telangiectasia. This assessment will be performed at baseline, prior to every treatment visit, and study completion. Improvement will be indicated by a decrease in the IGA score by ≥ 1 point compared to the previous assessment. Worsening will be indicated by an increase in the IGA score of ≥ 1 point compared to the previous assessment.

b. Inflammatory Lesion Investigator's Global Assessment (ILIGA). The ILIGA is a subjective 5-point measure of the overall disease severity. Scores range from 0 to 4: 0 (clear) = no papules/pustules/nodules; 1 (almost clear) = 1 to 2 papules/pustules; 2 (mild) = 3 to 10 papules/pustules; 3 (moderate) = 11 to 19 papules/pustules or ≤ 2 nodules; 4 (severe) = ≥ 20 papules/pustules, or > 2 nodules. This assessment will be performed at baseline, prior to every treatment visit, and study completion. Improvement will be indicated by a decrease in the ILIGA score by ≥ 1 point compared to the previous assessment. Worsening will be indicated by an increase in the ILIGA score of ≥ 1 point compared to the previous assessment.

c. **Clinical Erythema Assessment (CEA) scale**. The CEA scale is an assessment of erythema. It has a score range from 0 to 4: 0 (none) = no redness; 1 (mild) = slight pinkness; 2 (moderate) = definite redness; 3 (significant) = marked erythema; 4 (severe) = fiery redness. The total score is based on the evaluation of all areas of the face (forehead, chin, right cheek, left cheek, and nose). Each of these areas will be scored from 0-4, giving a maximum total score of 20. Improvement will be indicated by a decrease in the total CEA score by ≥ 1 point compared to the previous assessment. Worsening will be indicated by an increase in the total CEA score of ≥ 1 point compared to the previous assessment. The CEA will be performed at baseline, prior to every treatment visit, and study completion.

d **Inflammatory lesion count.** The number of inflammatory lesions (papules, pustules, nodules) will be recorded at baseline, prior to every treatment visit, and at study completion. The inflammatory lesion count will be used to grade the ILIGA (See 4.1.3.a above).

e. **Photographs:** Photographs of the face will be taken at baseline, prior to every treatment visit, and at study completion. These photographs will be used by the blinded investigator in completing the IGA, CEA scale, and in determining the number of inflammatory lesions present.

f. **Patient Overall Assessment Scale.** Patients will assess the overall improvement of their rosacea using a 4-point scale, where 1 = excellent improvement, 2 = good / moderate improvement, 3 = no change, 4 = worsening. This assessment will be performed prior to every treatment visit (except week 0), and at study completion. Improvement will be indicated by a decrease by ≥ 1 point compared to the previous assessment. Worsening will be indicated by an increase in this scale by ≥ 1 point compared to the previous assessment.

4.2 Data Collection

All data variables will be stored in a secure database using coded identifiers in place of name. Most of the data will initially be recorded on approved study forms containing the participant's study ID code. After transfer of data into the computerized database, all paper forms will be kept in a secure locked cabinet within a locked office within the department. Photographs will be stored with a secure electronic file and will be labeled with the participant's study ID code and date they were taken.

4.3 Statistical Considerations

Since this is a pilot study, we will perform only basic descriptive statistical analysis of our results. Due to the small number of subjects, it is unlikely that any statistical test would have the

power to detect a significant difference in any of the measured variables. Instead, we will look for a decrease in IGA, ILIGA, and CEA scores, decrease in inflammatory lesion count, and an improvement in the Patient Overall Assessment Scale. The results of this project may lead to the development of larger studies that will have the statistical power to detect significant differences in these variables after treatment with 5-ALA-PDT.

5. HUMAN SUBJECTS PROTECTION

5.1 Subject Selection

At the time of recruitment, each potential subject will be provided with an informed consent form to read. The potential subject will be allowed to take the consent form home to discuss its content with family members or friends. All individuals will be given a contact number that they may call to obtain answers to any questions regarding the study and their participation. All subjects must sign a consent form prior to any study procedures being performed.

Involvement of special subjects such as pregnant women, institutionalized individuals, prisoners, or impaired and non-competent individuals are not anticipated in this study. Eligible women of reproductive age will be required to be on one reliable form of effective birth control during the treatment period. They will also be required to have a negative urine pregnancy test during the screening period and prior to each treatment session for the duration of the study. Individuals from all racial/ethnic groups, regardless of gender, and those that are economically and educationally disadvantaged are eligible for this study if they meet the eligibility requirements.

5.2 Risks and Benefits

A temporary burning or stinging sensation may occur during light exposure following ALA application. A minority of patients may experience these symptoms after light exposure. Pruritus may also occur.[6]

Patients with AKs and BCC usually experience a phototoxic reaction (edema, erythema, vesicles, crusting, erosions) when treated with ALA-PDT. This is an expected reaction that eventually results in the resolution of the treated lesions. These phototoxic reactions can be associated with pain, burning, and peeling and can last for up to 2 weeks.[6] The severity of the phototoxic reaction increases with longer application times of ALA. Exposure to artificial lights or sunlight within the first 2 days following PDT treatment can result in a more severe phototoxic reaction. To decreases this risk, all subjects will have their faces washed with soap and water and will also have sunscreen applied following PDT treatment. Each subject will be advised to avoid sunlight or artificial light exposure for at least 48 hrs following PDT treatment and to also wear a wide-brimmed hat or other protective apparel to shade the treated area from sun light or other bright light.

Hyperpigmentation and occasionally hypopigmentation may occur following ALA-PDT treatment. These pigment changes usually resolve within six months. In one study, < 3% of patients treated with 5-ALA patch-PDT for AKs showed hypopigmentation after one year.[13] Hyperpigmentation of

healthy skin following ALA-PDT is dependent on the dose of ALA. It usually occurs within 48-72 hours following treatment and increases for the following two weeks. It occurs more frequently in individuals with psoriasis who are treated with PDT. In one study, all twenty-one subjects with psoriasis experienced mild to moderate hyperpigmentation of their psoriasis lesions following PDT. In another study, PDT resulted in hyperpigmentation of psoriasis lesions in seven out eight subjects. Pigmentary change occurs less frequently in patients treated with PDT for non melanoma skin cancer. The Scottish PDT Centre reported that 1% of 762 patients treated with PDT for non melanoma skin cancer developed pigmentary changes. Prolonged hyperpigmentation has been observed when treating hirsutism with PDT.[6,14]

ALA-PDT for the treatment of acne has also been associated with erythema, crusting, discomfort/pain, and hyperpigmentation.[14] In one study, skin exfoliation and postinflammatory hyperpigmentation was observed on the back for 1-3 months following the use of ALA – PDT (1-4 treatment sessions) for the treatment of acne on the back of all 22 subjects.[6] In another study, 20 patients with moderate to severe acne vulgaris of the face had one side of their face treated with ALA-PDT and the other side treated with blue light alone. Patients experienced erythema, pain, stinging, peeling, pruritis, oozing, and pustules on their face. Fifty-five percent of patients experienced stinging and 25% experienced pain during ALA-PDT treatment. ALA-PDT resulted in erythema in 65% of patients, exfoliation in 70%, pruritus in 65%; these symptoms were more severe on acne lesions. These symptoms resolved within a few days following treatment and were less severe on the side of the face treated with blue light alone. Two patients experienced edema, crusting, and oozing and another two patients experienced transient pustular lesions on the side of the face treated with ALA-PDT treatment. Hyperpigmentation was observed in fifty-five percent of patients on the side of the face treated with blue light alone and in 65% of patients on the side of the face treated with ALA- PDT.[15]

Hair loss is another potential side-effect. Localized permanent hair loss, though uncommon, has been observed when treating BCC and Bowen's disease.

Scarring following topical PDT is very rare. Of the 762 patients treated with PDT for non melanoma skin cancer at the Scottish PDT Centre (See Above), only 0.8% developed mild to moderate scarring.[6,14]

Topical PDT has a low risk of carcinogenicity. Porphyrin-like molecules have antioxidant and antimutagenic properties. Only two cases of skin cancer have been reported in patients receiving PDT. The first case involved an 82 year old male who developed melanoma on one of his skin sites 6 months after being treated with seven sessions of PDT, over 4 years, for actinic keratosis and squamous cell carcinoma. Although the development of melanoma in this case was probably coincidental, multiple treatments of PDT has the potential to possibly promote its development. The other case involved a 38 year old male who responded to ALA-PDT for the treatment of SCC in situ of the glans penis. He was started on topical 5-fluorouracil and was later found to have SCC on his penis, which was likely due to incomplete clearance and progression of the SCC in situ. The potential role of PDT in causing this progression is unknown.[14]

Systemic ALA given at higher dosages than that contained in a Kerastick® has been associated with elevated liver enzymes. Elevated liver enzymes have not been associated with the topical application of ALA.

Blue light may cause irreversible damage to the retina. Therefore, during each treatment session, patients will be required to wear protective goggles to decrease this risk.[6]

ALA is a Category C drug. The safety of ALA during pregnancy and the risk to the unborn child are unknown. Therefore, we are not enrolling pregnant women in this study. Women who are able to have children must have a negative pregnancy test result at screen. A repeat pregnancy test must be done if they miss any periods or their menstrual cycle becomes very irregular. If a pregnancy occurs, there may be a risk of miscarriage, birth defects or other unknown medical conditions. All women must use at least one reliable form of effective birth control [example: barrier method (condoms, diaphragm), oral, injectable, implant birth control or abstinence] during the treatment period and for 30 days following the completion of this study. Treatment will be discontinued if a subject becomes pregnant. They will, however, continue to be observed through the conclusion of pregnancy. This observation will entail one telephone call visit at the conclusion of the first trimester, one telephone call visit at the conclusion of the second trimester, and one telephone call at the end of each month thereafter until the conclusion of the pregnancy. With the subject's permission, any serious adverse events, abnormal lab results, or abnormal diagnostic test results pertaining to the subject or her developing fetus, as reported by the subject, will be recorded in our data base and reported to the GWU IRB in accordance to their policies and procedures.

Patients may benefit from study participation by experiencing an improvement of their rosacea. It is still possible that their rosacea may not improve with the treatment under investigation.

5.3 Confidentiality

All information collected as part of this study will be treated as confidential. Subject consent forms and data collection sheets will be stored in a locked office in the MFA Dermatology Department. These documents will be accessible to study investigators only. A computer database will be created. This database will not contain any subject identifiers. The data within the database will be labeled with each subject's study identification number. Database information will be maintained in a password-protected file. All the data included in this study will only be accessible to the investigators listed on the title page, and they will not be released for use by other researchers.

5.4 Adverse Events and Safety Monitoring

Patients will be closely monitored for any adverse events experienced during this study, as described in Section 5.2: Risks and Benefits. Adverse events monitoring will be performed by the principal investigator during each treatment session starting at visit 3, during the blinded and post-treatment period of the study. Any event occurring more than two months after the final treatment will not be considered an adverse event. Patients will be educated as to the possible side effects and complications related to 5-ALA-PDT therapy, and will be instructed to notify any

investigator should they experience signs or symptoms of an adverse event. Because the anticipated risks associated with this study are low, we feel that an independent monitoring board will not be necessary.

All events that meet the Prompt Reporting Requirements (HRP-801) (including but not limited to new or increased risk, harm experienced by the subject, noncompliance with the federal regulations governing human research, and state medical board actions) will be reported to the GW OHR via a Problem Report and Promptly Reportable Information Form (HRP-204) within 5 business days of knowledge of the event.

Table 1: Example Study Schedule of Events*

Week	**Screen**	**W0****	**W3**	**W6**	**W9**	**W17*****
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**
Informed Consent	X					
Clinical History/ Screening Form	X					
Urine Pregnancy Test	X					
IGA	X	X	X	X	X	X
ILIGA	X	X	X	X	X	X
CEA Scale	X	X	X	X	X	X
Inflammatory Lesion Count	X	X	X	X	X	X
Patient Overall Assessment Scale			X	X	X	X
Photographs	X	X	X	X	X	X
Adverse Events			X	X	X	X
Treatment: 5-ALA-PDT (Group A); vehicle - PDT(Group B); vehicle (Group C)		X	X	X	X	

IGA, investigator's global assessment; ILIGA, inflammatory lesion investigator's global assessment; CEA, clinical erythema assessment; 5-ALA-PDT, 5 - aminolevulinic acid (ALA). *Actual schedule and time between treatments may vary for each subject. Each visit's assessment and treatment day may occur 2-3 weeks after the previous treatment/assessment visit. **The first treatment will occur after the washout periods have been met. Re-evaluation of entry criteria will be performed at V2 when more than 30 days have passed since screening or to confirm a washout has been met. *** Final evaluation/study completion will occur 2 months (+/- 2 weeks) after the final treatment session of the blinded period of the study.

REFERENCES:

1. Thiboutot D, Thieroff-Ekerdt R, Graupe K. Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: results from two vehicle-controlled, randomized phase III studies. J Am Acad Dermatol. 2003 Jun;48(6):836-45.
2. Elewski BE, Fleischer AB Jr, Pariser DM. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial. Arch Dermatol. 2003 Nov;139(11):1444-50.
3. Buechner SA. Rosacea: an update. Dermatology. 2005;210(2):100-8.
4. Nybaek H, Jemec GB. Photodynamic therapy in the treatment of rosacea. Dermatology. 2005;211(2):135-8.
5. Pelle MT, Crawford GH, James WD. Rosacea: II. Therapy. J Am Acad Dermatol. 2004 Oct;51(4):499-512; quiz 513-4.
6. Morton CA, McKenna KE, Rhodes LE. Guidelines for topical photodynamic therapy: update. Br J Dermatol. 2008 Dec;159(6):1245-66. Epub 2008 Oct 13.
7. Hongcharu W, Taylor CR, Chang Y et al. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. J Invest Dermatol. 2000; 115:183–92.
8. Pollock B, Turner D, Stringer MR et al. Topical aminolaevulinic acid-photodynamic therapy for the treatment of acne vulgaris: a study of clinical efficacy and mechanism of action. Br J Dermatol. 2004; 151:616–22.
9. Ramstad S, Futsaether CM, Johnsson A. Porphyrin sensitization and intracellular calcium changes in the prokaryote, Propionibacterium acnes. J Photochem Photobiol B. 1997; 40:141–8.
10. Neubert U, Jansen T, Plewig G. Bacteriologic and immunologic aspects of gram-negative folliculitis: a study of 46 patients. Int J Dermatol. 1999 Apr;38(4):270-4.
11. Bryld LE, Jemec GB. Photodynamic therapy in a series of rosacea patients. J Eur Acad Dermatol Venereol. 2007 Oct;21(9):1199-202.
12. Katz B, Patel V. Photodynamic therapy for the treatment of erythema, papules, pustules, and severe flushing consistent with rosacea. J Drugs Dermatol. 2006 Feb;5(2 Suppl):6-8.
13. Szeimies RM, Stockfleth E, Popp G, Borrosch F, Brüning H, Dominicus R, Mensing H, Reinhold U, Reich K, Moor AC, Stocker M, Ortland C, Brunnert M, Hauschild A. Long-term follow-up of photodynamic therapy with a self-adhesive 5-aminolaevulinic acid patch: 12 months data. Br J Dermatol. 2010 Feb 1;162(2):410-4. Epub 2009 Jun 30.
14. Morton CA, Brown SB, Collins S, Ibbotson S, Jenkinson H, Kurwa H, Langmack, McKenna K, Moseley H, Pearse AD, Stringer M, Taylor DK, Wong G, Rhodes LE.Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. Br J Dermatol. 2002 Apr;146(4):552-67.
15. Akaraphanth R, Kanjanawanitchkul W, Gritiyarangsan P. Efficacy of ALA-PDT vs blue light in the treatment of acne.Photodermatol Photoimmunol Photomed. 2007 Oct;23(5):186-90.