Protocol Version: 12/20/12

Low-Dose UVA1 Radiation in Cutaneous Lupus Patients

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1. OBJECTIVES

Cutaneous lupus erythematosus (CLE) produces distressing symptoms including itch, pain, and disfigurement. Therapeutic options are limited and involve a significant degree of risk due to their side effect profile. To address this deficiency, we propose an open-label study to determine the efficacy of low dose UVA1 phototherapy in treating cutaneous lupus patients. This will be complemented by safety, quality of life, and immunological studies to assess the value of treating cutaneous lupus patients with low dose UVA1 phototherapy.

Primary Aim: To determine the effect of low dose UVA1 phototherapy on CLE lesions.

- Hypothesis: CLE patients treated with low dose UVA1 phototherapy will experience clinical improvement.

Secondary Aims

Aim 1: To determine the safety of low dose UVA1 phototherapy in CLE patients.

- Hypothesis: UVA1 phototherapy will have minimal side effects in CLE patients.

Aim 2: To assess effect of low dose UVA1 phototherapy on the quality of life of CLE patients

- Hypothesis: UVA1 radiation will have minimal side effects.

Aim 3: To assess immunologic effect of low dose UVA1 phototherapy in CLE patients

- Hypothesis: UVA1 radiation will decrease levels of circulating autoantibodies and T_H1 cells, and decrease T cells, B cells, and plasmacytoid dendritic cells in skin.

2. BACKGROUND

Approximately 70% of SLE patients have cutaneous manifestations including malar erythema.[1] Cutaneous lupus erythematosus has been classified into three major subtypes: acute cutaneous lupus (ACLE), which is defined as patients with SLE who fulfill at least four out of the 11 criteria outlined by the American College of Rheumatology,[2] and cutaneous lesions, subacute cutaneous lupus erythematosus (SCLE), which is manifested by psoriasiform or annular lesions in photosensitive areas, and chronic cutaneous lupus erythematosus, with discoid lupus (DLE) being the most common subtypes.[3]

Ultraviolet light therapy (phototherapy) is an established, first line therapy for several immunologically mediated disorders, including psoriasis, cutaneous T-cell lymphoma, and vitiligo. Two main types of phototherapy are currently available: UVB (290-320 nm) and UVA (320-400 nm). The UVB spectrum produces sunburn erythema and is the predominant source of photosensitivity in lupus erythematosus. UVA produces far less erythema and because of its longer wavelength, penetrates to the deep dermis where it can interact with antigen presenting cells (APCs) and T cells, potentially exerting systemic effects. UVA is subdivided into UVA1 (340-400 nm) and UVA2 (320-340 nm). UVA1 generally does not provoke photosensitive diseases.[4]

The mechanism of action of UVA1 in human SLE is unclear, but initial trials of low dose UVA1 in SLE patients demonstrated a significant decrease in the frequency of peripheral blood interferon γ-producing T_H1 and T_C1 cells and a decrease in T_H1 /T_H2 and T_C1/T_C2 ratios.[5] Furthermore, UVA1 irradiation induced death of SLE peripheral

blood mononuclear cells, and decreased immunoglobulin production in a dose-dependent manner. [6]

Preliminary data demonstrate safety and efficacy of low-dose UVA1 (6-20 J/cm^2) in SLE.[7-9] Several open label and three randomized, controlled, crossover trials from two research groups report benefit from UVA1 in SLE patients based on various systemic disease activity measures at doses ranging from 6-12 J/cm^2 for 3-9 weeks.[7-10] However, the cutaneous changes in response to UVA1 treatment were not an outcome measure and were not carefully assessed. The recent validation of the Cutaneous Lupus Activity and Severity Index (CLASI) allows for a prospective trial to determine the efficacy of UVA1 in cutaneous lupus. The CLASI is based largely on physician examination of skin lesions and consists of an activity score and a damage score. It is also weighted based on the most frequently involved body surface areas to better reflect disease activity.

In these trials, no serious adverse events occurred. Polderman reported that two patients developed mild transient photosensitivity reactions with irradiation of 12 J/cm^2.[9] In both patients, dose reductions to 6 J/cm^2 allowed continuation of therapy. Adverse events for other diseases have been minimal. With UVA1 doses several fold greater than those used for SLE (typically used for scleroderma and atopic dermatitis), the most common problems have included transient erythema, recurrence of herpes simplex virus reactivation, and polymorphic light eruptions.[12] Although difficult to assess at this time, UVA1 has not shown any clear link with skin cancer.[13] Extensive experience with all types of UV therapy, including UVA1, indicates that phototherapy is significantly less toxic than treatment with immunosuppressive drugs. In fact, UVA1 irradiation is not absorbed by DNA (as compared with UVB which directly damages DNA bases). In a trial assessing photosensitivity in subacute cutaneous lupus erythematosus patients, no induction of lesions was seen in response to repeated doses of 20 J/cm^2 of UVA radiation, and the skin of one patient cleared.[14]

In sum, all three published randomized, controlled trials indicate that UVA1 is potentially safe and efficacious for SLE. The short duration of treatment and follow-up in these studies further limits their applicability to cutaneous lupus, a disease typically characterized by a relapsing and chronic nature. Moreover, none of these studies used the most accepted tool for measuring cutaneous lupus burden, the CLASI. Furthermore, most CLE patients are frequently seen in a dermatology setting where phototherapy may be available, making UVA1 a potentially practical therapy. Whether UVA1 is tolerated and efficacious in CLE remains an important unanswered question.

3. CONCISE SUMMARY OF PROJECT

This is an open-label trial to assess the efficacy, safety, and immunologic effects of UVA1 phototherapy on patients with cutaneous lupus erythematosus. Fifteen patients will be recruited to receive low dose (20 J/cm^2) UVA1 phototherapy treatment three times per week for 10 weeks followed by an eight-week observation phase. In the event that a patient experiences adverse events (e.g. erythema) with the 20 J/cm^2 dose, the dose will be decreased to 6 J/cm^2. If symptoms persist, the patient will be withdrawn from the study. Patients will be allowed to continue on their current medications throughout the study. Patients will be assessed prior to, during, and at the end of UVA1 treatment; and at the end of the observation period. Any adverse events and symptoms of SLE flares will be assessed simultaneously. Serological studies will be completed prior to treatment, during the treatment phase, and at the end of the observation phase. Optional skin

biopsies will be performed at the beginning and end of the active treatment phase. Gene expression studies will be conducted on blood and skin samples with the intent of understanding the mechanism of action for UVA1 treatment in cutaneous lupus.

4. ELIGIBILITY CRITERIA

Criteria for Inclusion of Participants

1. Age > 18 years at enrollment.

2. Diagnosis of cutaneous lupus confirmed by clinicopathological correlation.

3. CLASI activity score of $\geq$2.

4. Stable dose of antimalarials (hydroxychloroquine, quinacrine, or chloroquine) for 60 days.

5. Stable dose of immunosuppressive medications (e.g. mycophenolate mofetil, methotrexate, low dose prednisone<10 mg daily) for at least 30 days.

6. Stable use of topical medications including steroids (e.g. triamcinolone, clobetasol) and steroid-sparing agents (e.g. tacrolimus) for at least 30 days,

7. Patient must be able to speak and read English or Spanish at a 6th grade reading level. A translator will be available with additional consent forms in Spanish.

8. All races, ethnic backgrounds, and genders will be eligible.

9. Ability to give informed consent: Patients must be able to give informed consent or they will give assent with guardian consent.

Criteria for Exclusion of Participants:

1. Current rash consistent with acute cutaneous lupus (butterfly rash).

2. Contraindication to UVA1 phototherapy, including personal history of melanoma or non-melanoma skin cancer, history of other photosensitive disorders (e.g. porphyria cutanea tarda, polymorphous light eruption, xeroderma pigmentosum, etc.), or history of any type of organ transplant (solid organ or bone marrow).

3. Current use of frequently photosensitizing medication (e.g. tetracycline, doxycycline, isotretinoin).

4. Current or <2 months prior use of UVA1 phototherapy prior to enrollment.

5. Inability to receive UVA1 treatment safely and effectively (e.g. claustrophobia, wheelchair-bound, difficulty understanding instructions).

6. Nursing mothers, pregnant women, and women planning to become pregnant while on study are to be excluded.

7. Participants with a disease history deemed consistent with drug-induced lupus by study investigators.

5. STUDY PROCEDURES (See Appendix for Table of Study Visits)

Treatments will be delivered using Daavlin 4 Series Phototherapy Unit (Daavlin Company, Bryan, Ohio). The unit uses Philips color / 10 phosphor lamps (Phillips International, Eindhoven, The Netherlands) and an acrylic UVB-blocking filter. Photons are emitted at wavelength 340-400 nm. Participants will receive UVA1 treatment three times per week for a total of 10 weeks. An initial test dose of 6 J/cm^2 will be administered, followed by a test dose at 12 J/cm^2. Treatments will thereafter be 20 J/cm^2 for the remainder of the 10-week period. All participants will be required to wear UV protective, opaque goggles. Men will be required to shield their genitalia using an athletic supporter. Additionally, one or more active lesions will be covered during treatment. Treatments will be carried out during the fall and winter months.

An erythema/overdose protocol will be incorporated as follows:

Prevention: Participants will be counseled to avoid further exposure to ultraviolet light. Use of SPF 30 or higher broad spectrum sunscreeen, sun avoidance, and sun protection will be required.

Treatment: Participants will be instructed to report all erythema to the study coordinator immediately. Prior to each treatment, trained nurses will interview patients for symptoms of lupus flare. The patients will be assessed by a dermatologist to determine if sunburn erythema or acute cutaneous lupus/LE-related photosensitivity is present. All such episodes will by recorded as adverse events. Patients deemed to have a lupus flare, defined as having a Systemic Lupus Erythematosus Disease Activity Index with modifications from the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA SLEDAI) score increase of >3, will be withdrawn from the study. Patients deemed to have adverse events related to UVA1 radiation (e.g. erythema) will have a dose reduction to 6 J/cm^2 for the duration of the study. If these symptoms recur or persist with this dose reduction, the patient will be withdrawn. Phototherapy sessions missed for non-adverse event-related reasons will be rescheduled at the earliest available date.

In order to accomplish the study aims, several variables will be measured. Participants will receive an interview, complete questionnaires, undergo a dermatologic exam, have photographic documentation, and provide blood samples at all of the study visits (see attached schedule). Skin biopsies will be optional. The outcome measures also require repeat administration of the SELENA-SLEDAI and the CLASI. Each test requires 5-10 minutes for administration.

Study Visit 1 – Initial Enrollment (Week 1, Before UVA1 Phototherapy):
The patients will have:

- Informed consent
- Full medical/family history and physical examination
- Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) - a measure of cutaneous lupus disease activity
- Systemic Lupus Erythematosus Disease Activity Index with modification from the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA-SLEDAI) - a measure of systemic lupus disease activity.

- **Sub-Study Procedure:** Optional 4 mm punch biopsies (three; affected-treated, affected-untreated, and unaffected skin) – Patients will have a 4 mm punch biopsy of the active (erythematosus) border of up to two lesions and site-matched (to the affected-treated site) unaffected skin (excluding lesions on the face due to cosmetic concerns). The biopsy will be performed using standard sterile technique. Skin will be closed with a single 3-0 or 4-0 polypropylene or nylon suture. Skin biopsies will be used for DNA/RNA extraction and protein expression studies.
- Clinical photography of involved areas with labeling of $\geq$1 active cutaneous lesion(s) to be covered during phototherapy, referred to as the "shielded cutaneous lupus lesion."
- 40 cc of blood draws - Blood will be collected from a vein in the subject's arm for autoantibody titers, complete blood count with differential, BUN and creatinine, DNA/RNA extraction and protein expression studies. The collection will take place during a scheduled research-only clinic visit by a support staff person or an investigator who has been formally trained to conduct venipuncture.
- Skindex-29+3 (modified to include cutaneous lupus-specific questions) – A quality of life survey
- Physician assessments – Study investigators will give a score from 1-10 on overall, activity, and damage aspects of each patient's skin disease, as well as general health.
- Phototherapy orientation – The phototherapist will orient all patients to the safety protocols of the unit. Subjects will wear standard UV protective goggles and shield their genitals. A symptom questionnaire assessing symptoms of lupus flare, photosensitivity, and changes in medications will be provided at the initial phototherapy orientation. Participants will be asked to review this at home prior to each UVA1 treatment session. This questionnaire will also be reviewed at each UVA1 treatment session by the phototherapy nursing staff.
- Delivery of UVA1 phototherapy – Patients will receive UVA1 phototherapy according to the protocol stated in Table 1. **The time required to complete UVA1 treatment will be <30 minutes.**

Table 1. UVA1 Phototherapy Standard Protocol
1. Explain treatment to patient.
2. Patients should be treated three times per week.
3. Prior to each treatment session, review lupus flare and photosensitivity questionnaire.
4. Treat whole body except for genitals and "shielded cutaneous lupus lesion."
5. Goggles should be worn at all times by the patient and the phototherapist.
6. Unit should be a fixed distance from patient. • Whole body – 8-9 inches
7. Patient to apply sunscreen to nipple/areola and cover genitals.
8. Set unit to deliver appropriate dose ($\leq$20 J/cm^2).
9. Dose as follows: a. Initial dose at 6 J/cm^2 b. Second dose at 12 J/cm^2 c. Third dose and all doses thereafter at 20 J/cm^2 in the absence of adverse effects
10. Prior to treatment, always review patient's medications.

11. Prior to each treatment, inquire for any erythema or symptoms of lupus flare.
12. UVA1 light can induce HSV (cold sores) especially if patient has a personal history. If this occurs, notify the physician for treatment and possible prophylaxis.

Study Visit 2 –UVA1 Treatment Phase (Week 6, After 15 UVA1 Phototherapy Treatments)

The same assessment and procedures will be performed as in Study Visit 1 with the exception of informed consent, phototherapy orientation, and optional skin biopsies.

Study Visits 3 - End of UVA1 Treatment Phase (Week 11, After 30 UVA1 Phototherapy Treatments)

The same assessment and procedures will be performed as in Study Visit 1 with the exception of informed consent and phototherapy orientation.

Study Visit 4 - End of Observation Phase (Week 19, 8 Weeks After UVA1 Phototherapy Treatment Ends)

The same assessment and procedures will be performed as in Study Visit 1 with the exception of informed consent, phototherapy orientation, and optional skin biopsies.

6. TREATMENTS

Investigational Therapy and Reference Therapy

Investigational Agent - low dose UVA1 phototherapy 3 times per week for 10 weeks

Reference therapy - none

Treatment Assignment

After obtaining informed written consent, subjects meeting criteria for inclusion will begin low dose UVA1 phototherapy in escalating doses, as described, up to 20 J/cm^2.

Concomitant Therapy

Patients will be allowed to continue their concomitant systemic and topical treatments, providing that they meet the inclusion criteria. However, systemic lupus flares will result in removal from the study.

Criteria for Removal from Study

- Missed treatments: If the patient misses $\geq$3 treatments, they will be removed from the study.
- Development of lupus flare, as determined by SELENA-SLEDAI score increase of at least three.
- Intolerance to UVA1 phototherapy despite dose reductions (e.g. induction of UVA1-related skin eruption such as solar urticaria or polymorphic light eruption).

In each case, the principal investigator will assess the patient and determine appropriate therapy outside the auspices of the study. These events will be recorded.

7. SOURCES OF RESEARCH MATERIAL

Skin Biopsy

4 mm punch biopsies (three; affected-treated, affected-untreated, and unaffected skin) of up to 15 patients will be performed under local anesthesia by an investigator who has been formally trained to perform a skin biopsy. The biopsies will be performed using standard sterile technique. Skin will be closed with a single 3-0 or 4-0 polypropylene or nylon suture. These biopsies will take place during Study Visits 1 and 3 during a scheduled research-only clinic visit. The investigator will avoid cosmetically sensitive areas such as the face for biopsies, unless the patient permits.

Blood

Approximately 40 cc of blood will be collected from a vein in the subject's arm at the Study Visits during a scheduled research-only clinic visit by a support staff person or an investigator who has been formally trained to conduct venipuncture.

Patient Data

Other data used in the research will be obtained from the subjects' medical records and in-person interviews. The data sought will include the subject's age, gender, race, age of diagnosis, contact information, disease location, presentation and history, associated symptoms, past and current treatments, personal history of autoimmune diseases, family history, and quality of life assessments. At return study visits, subjects will update the investigators on changes to their disease history, associated symptoms, treatments, quality-of-life assessments, and will be assessed for adverse events. At each Study Visit, an investigator will perform a skin examination, obtain severity index scores for cutaneous and systemic lupus (i.e. CLASI, SELENA-SLEDAI), provide physician's assessment of disease activity, and obtain photographs.

8. LABORATORY PROCEDURES

Differences in gene expression before and after UVA1 treatment may yield insight into possible mechanisms of action for UVA1 treatment in cutaneous lupus. To investigate expression of individual genes, DNA and RNA testing will be conducted on both blood and skin samples. Planned experiments include microarray analyses to generate global expression patterns of multiple genes and RT-PCR for verification of gene expression. Skin biopsy and blood samples may also be used for assessment of protein expression using immunohistochemistry and flow cytometry, respectively.

9. RECRUITMENT

A total of 15 patients will be recruited from the University of Texas (UT) Southwestern Medical Center at Dallas (Professional Office Building 1 Dermatology Clinic), the already established UT Southwestern Cutaneous Lupus Registry (IRB #082010-241, "Molecular Studies in Cutaneous Lupus") and the Parkland Health and Hospital System (Parkland Dermatology Clinic). To date, >150 cutaneous lupus patients have been recruited to the UT Southwestern Cutaneous Lupus Registry. Referring physicians will be asked to discuss the study with prospective participants. If they are interested, the physician can provide the study center's contact information. The study coordinator/doctor will explain the purpose of the study, length of the study, procedures involved in the study, and the risks/benefits of the study to prospective participants either in person or by telephone. After all questions have been answered and the participant agrees to participate the consent form will be signed. Based on current practice in our center, we anticipate completing enrollment within the first two years of the study.

During the recruiting and consenting process, the investigators will adhere to UT and Food and Drug Administration (FDA) guidelines. The purpose, the duration, the procedures (blood and skin biopsy sample collections), and the risks/benefits of the study will be explained to each potential subject by the investigators. Subjects will be given a copy of the consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization to read. They will be given ample time for questions and answers to their questions by the investigator. The signed consent and HIPAA forms will be kept in secure files by the investigators, and copies will be given to the subjects. The collection of study samples will not start until the subject signs the consent and HIPAA forms. (*Note: This is in addition to the consent form and post-biopsy instructions given to the subjects for skin biopsy.)*

10. TRAINING IN THE POLICES PROTECTING THE RIGHTS AND WELFARE OF HUMAN SUBJECTS IN RESEARCH

All the investigators have completed their Human Subjects Protections training and HIPAA training in compliance with UT Southwestern policies and procedures. They will adhere to the UT and the FDA guidelines while conducting this research project to assure study integrity.

11. POTENTIAL RISKS

UVA1 light treatments: There are several potential risks of ultraviolet light exposure:

Short-term risks:

- Marked hyperpigmentation or tanning, erythema, pruritus, photosensitive eruptions, and recrudescence of herpes simplex infection (HSV).

- Flaring of lupus disease, which may include having new skin lesions, increased fatigue, and joint pains.

Long-term risks:

- The most common is aging of the skin: Repeated and prolonged exposure to ultraviolet light induces changes in the skin, which appear as premature aging. These include thinning and wrinkling of the skin in addition to freckling.

- Less common is injury to eyes: Ultraviolet light can injure the subject's eyes. Subjects will be required to wear protective eye shields (goggles) at all times during their UVA1 treatments.

- Rare is skin cancer: Repeated and prolonged exposure to ultraviolet light can increase the subject's risk of skin cancer. This includes exposure from natural sunlight, UVB phototherapy, PUVA or tanning salons. Actinic keratoses (sun-damage spots) can also occur with any long-term exposure to ultraviolet light. Only one case report of UVA1-treated patients developing skin cancers has been reported.[15]

- The risk of skin cancer is particularly increased in the genital area, especially in men. Because of this, subjects must shield the genital areas during each treatment

Biopsy: The most common side effects associated with biopsies of the skin are pain at the site, bleeding, bruising at the site, scarring at the site and infection at the site.

Sample of blood: The patient may experience discomfort, bleeding, and/or bruising. The patient may feel dizzy or faint. On a rare occasion, an infection could develop at the site where the blood was collected.

Stress: The patient could experience stress from participating in this kind of research. Knowing that researchers have personal information about them may trouble the patient.

Loss of confidentiality: It is possible that identifiable health information may be accidentally shared and subject confidentiality is lost. Every effort will be made to make sure the subject's information is kept confidential (including the covering of tattoos, birthmarks, etc. in photographs in order to conceal the subject's identity).

12. SUBJECT SAFETY AND DATA MONITORING

Subject safety: Goggles will be worn at all times by the patient during UVA1 phototherapy. The patient will apply sunscreen to nipples/areolas and cover genitals. A symptom questionnaire assessing symptoms of lupus flare, photosensitivity, and changes in medications will be provided at the initial phototherapy orientation. Participants will be asked to review this at home prior to each UVA1 treatment session. This questionnaire will also be reviewed before each UVA1 treatment session by the phototherapy nursing staff. Patients will be assessed for erythema by phototherapy nursing staff prior to UVA1 treatment. Any observed erythema will be reported to the PI. Furthermore, suggestion of a lupus flare on the questionnaire will trigger immediate reporting to the PI prior to any further treatment. If a flare is verified based on investigator assessment, the patient will be withdrawn from the study. A lupus flare will be defined by having an increase in the SELENA-SLEDAI score of at least three. In the event of photosensitivity reported on the questionnaire, the PI will be notified and will evaluate the patient. If a reported reaction is deemed to be sunburn-type erythema, the dose of UVA1 will be decreased to 6 J/cm^2 and held at that dose throughout treatment. If symptoms persist, the patient will be withdrawn from the study. The patient's medications will always be reviewed prior to initiation of UVA1 phototherapy, but no dose change will be instituted for photosensitizing medications, given the low dose of UVA1 in this study. UVA1 light can induce HSV (cold sores) especially if the patient has a personal history. If this occurs, the PI will be notified for treatment and possible prophylaxis.

Local anesthetic is used before a skin biopsy procedure. In both the blood draw and the biopsy, guidelines are used for a sterilized procedure. All personnel performing biopsies and phlebotomy are fully trained with experience.

In the event of a patient experiencing stress from participating in this type of research, referrals for the proper counseling will be available.

Data Monitoring: All identifiable information will be kept in separate data logs and data tables. Subject specimens and samples will be labeled with unique identifiers with no identifiable information on them. Data will not be shared with investigators outside the ones listed on this project summary, yet, if shared, this data will be de-identified.

Data Safety and Monitoring Plan: The PI (Benjamin Chong, MD) will be solely responsible for the data and safety monitoring. Data to be monitored includes: study accrual rate, experience of study participants, study attrition including participant withdrawals/dropouts, pattern of adverse events and/or unanticipated events, patterns of protocol deviations and/or violations, and changes in risk/benefit. Frequency of data monitoring and analysis will occur quarterly.

13. PROCEDURES TO MAINTAIN CONFIDENTIALITY

Collection of samples:

A master file with the subject's demographic information (name, sex, race, age, contact information, birth date, diagnosis, medical record number, and surgical pathology number) will be developed, stored separately from the subject's samples and questionnaire data, and assigned a unique identification number. The identification numbers will be used to identify all samples collected during the course of the study. All information collected will be stored according to UT, FDA, and state guidelines, and all research utilizing subjects' samples must be approved by the IRB at UT Southwestern.

Storage of samples:

Each blood and skin biopsy sample will be stored in the UT Southwestern Department of Dermatology laboratory (NL8.110N) in a locked -80ºC freezer with the subjects' unique identification number, a unique sample number, and date of collection. The samples stored will be under the supervision of the primary investigator and research associate(s). The samples will be stored until all test procedures have been completed, or until the samples are no longer considered viable. At the study closure, any remaining samples will be destroyed according to the UTSW laboratory policy and procedures. The subjects' identifiers will also be destroyed after final data analysis.

Linkage of sample to the donor subject:

The sample number will be linked to the database number in a separate log, and this link will not be broken throughout the course of the study.

Use of samples:

These samples will be used for a study within the Department of Dermatology by the PI (Benjamin Chong, MD) at UT Southwestern Medical Center.

Reports of DNA results:

Only the PI will receive the results of the DNA testing. The subject or their legally responsible representative, physician, family members, medical-insurance provider, life-insurance provider, and employer will *not* receive these results. The subject will give explicit, properly-informed written consent for the release of the DNA test results to the primary investigator as part of the consent process.

Approval of sample use:

The PI will be responsible for patient samples. No other investigator will receive samples.

Computer security:

The computer storing the donor-subject's identity is not linked to the internet and database access is password-protected.

Publication of private information:

Private information may be released to the investigator if the subject gives his/her consent/assent. No information will be published which would reveal the subject's identity.

Release of a donor-subject's sample to a third party for purposes other than research:

There are *no* conditions when a sample will be labeled with the patient's initials could be released to the donor-subject, family member, physician, insurance provider, or employer for any use.

Future contact with donor-subjects:

Subjects with cutaneous lupus will be invited to continue follow-up for future research participation. A subject's family members may be invited to participate in research if it is determined they have a history of cutaneous lupus. The subject will be given the investigator's contact information, and they will be invited by the proband to call the investigator to learn about the study.

Removal from the study:

A subject's sample and related data may be removed from the database if the subject chooses to no longer participate in the study, or has been incorrectly diagnosed with cutaneous lupus. Once enrolled in this study, the tissue and blood specimens will not be available for destruction or returned to the subject at their request.

14. ADVERSE EVENTS

Adverse events will be assessed by principal and co-investigators of the study at least quarterly. The PI, Benjamin Chong, MD, is responsible for reporting adverse events to the IRB.

15. POSSIBLE BENEFITS

The subject may experience improvement in their cutaneous lupus activity. In addition, both safety and efficacy of this potential treatment will be assessed for future therapeutic trials in patients with cutaneous lupus. Indirect benefits would include a sense of altruism in contributing to cutaneous lupus research, and added time spent with the investigators.

16. COSTS TO SUBJECTS

There will be no additional costs for the patient. Patients will receive $250 for their participation as compensation for the time commitment. If they undergo skin biopsies at Study Visit 1 and 3, they will receive an additional $100, for a total of $350. Payments will be made in five equal installments, after week 2, 4, 6, 8, and 10 of UVA1 treatment ($50±20 (depending on whether skin biopsies were performed)). Early withdrawals due to adverse effects will receive pro-rated compensation. Participants who withdraw early for other reasons will not receive financial compensation. Additional travel, parking, lost-wages, and child-care expenses will not be covered for the patients enrolling in the study.

17. RISK/BENEFIT ASSESSMENT

The physical, psychological, social, and/or economic risks to subjects are reasonable in relation to the anticipated benefits to the subjects in relation to the importance of the knowledge that may result.

18. BIOSTATISTICS

Assuming that the standard deviation is 25%, a sample size of 12 achieves 83% power to detect a difference of 20% with a significance level (alpha) of 0.05 using a one-sided one-sample t-test. However, we are planning to recruit a total of 15 to account for 20% attrition rate due to lost to follow-up and lack of tolerance to UVA1 therapy.

19. REFERENCES

1. Patel P, Werth V. Cutaneous lupus erythematosus: a review. Dermatologic clinics. 2002;20(3):373-85, v.
2 Tan EM, Cohen AS, Fries JF, Masi AT, Mcshane DJ, Rothfield NF, et al. Special Article - the 1982 Revised Criteria for the Classification of Systemic Lupus-Erythematosus. Arthritis and Rheumatism. 1982;25(11):1271-7.
3. Gilliam JN, Sontheimer RD. Distinctive cutaneous subsets in the spectrum of lupus erythematosus. J Am Acad Dermatol. 1981;4(4):471-5.
4. Walker D, Jacobe H. Phototherapy in the age of biologics. Semin Cutan Med Surg 2011; 30(4): 190-8.
5. Szegedi A, Simics E, Aleksza M, Horkay I, Gaal K, Sipka S, et al. Ultraviolet-A1 phototherapy modulates Th1/Th2 and Tc1/Tc2 balance in patients with systemic lupus erythematosus. Rheumatology (Oxford) 2005; 44(7): 925-31.
6. Polderman MC, van Kooten C, Smit NP, Kamerling SW, Pavel S. Ultraviolet-A (UVA-1) radiation suppresses immunoglobulin production of activated B lymphocytes in vitro. Clin Exp Immunol 2006; 145(3): 528-34.
7. McGrath H,Jr. Ultraviolet-A1 irradiation decreases clinical disease activity and autoantibodies in patients with systemic lupus erythematosus. Clin Exp Rheumatol 1994; 12(2): 129-35.
8. Polderman MC, Huizinga TW, Le Cessie S, Pavel S. UVA-1 cold light treatment of SLE: a double blind, placebo controlled crossover trial. Ann Rheum Dis 2001; 60(2): 112-5.
9. Polderman MC, le Cessie S, Huizinga TW, Pavel S. Efficacy of UVA-1 cold light as an adjuvant therapy for systemic lupus erythematosus. Rheumatology (Oxford) 2004; 43(11): 1402-4.
10. McGrath H, Martinez-Osuna P, Lee FA. Ultraviolet-A1 (340-400 nm) irradiation therapy in systemic lupus erythematosus. Lupus 1996; 5(4): 269-74.
11. Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S, Kantor J, Kim E, Militello G, McGinnis K, Richardson S, Treat J, Vittorio C, Van Voorhees A, Werth VP. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. J Invest Dermatol. 2005 Nov;125(5):889-94.
12. Dawe RS. Ultraviolet A1 phototherapy. Br J Dermatol 2003; 148(4): 626-37.
13. Wallenfang K, Stadler R. Association between UVA1 and PUVA bath therapy and development of malignant melanoma. Hautarzt. 2001;52(8):705-7.
14. Lokitz ML, Billet S, Patel P, Kwon EJ, Sayre RM, Sullivan KE, et al. Failure of physiologic doses of pure UVA or UVB to induce lesions in photosensitive cutaneous lupus erythematosus: implications for phototesting. Photodermatol Photoimmunol Photomed 2006; 22(6): 290-6.

20. APPENDIX

Procedures	Screening	Week 1	Week 6	Week 11	Week 19
Chart review	X	X	X	X	X
Medical history	X	X			
Informed consent		X			
Demographics	X	X			
Inclusion / Exclusion criteria review	X	X			
Disease history	X	X	X	X	X
Medication history and review	X	X	X	X	X
Review of systems	X	X	X	X	X
Past medical history	X	X			
Family history		X			
Smoking history		X			
Photosensitivity history and risk factors	X				
SELENA-SLEDAI administration		X	X	X	X
CLASI administration	X	X	X	X	X
Skindex-29 administration		X	X	X	X
Fitzpatrick phototyping	X	X			
Clinical assessment (with physical exam)	X	X	X	X	X
Photographs		X	X	X	X
Blood draws		X	X	X	X
Pregnancy test	X				
Optional biopsies		X		X	