UV-A irradiation Treatment for patient with lupus

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A. Study Purpose and Rationale

Systemic lupus erythematosus is a prototypic autoimmune disease characterized by the production of antibodies to components of the cell nucleus in association with varied clinical manifestations. Because of the marked variability in the presentation of this disease, investigation into the pathogenesis has been directed to understanding both the mechanisms of autoimmunity as well as the basis of its clinical heterogeneity and fluctuating activity.

Lupus affects 1 in 2,000 individuals and is primarily a disease of women between the ages of 15 and 40. Its prevalence varies by racial and ethnic groups, and in the U.S. black and Hispanic individuals have a higher frequency of disease than whites. The disease also shows a hereditary influence with high frequency among first degree relatives.

Pathologic findings occur throughout the body and are manifested by inflammation, blood vessel abnormalities, and immune complex deposition. In particular, the skin is highly affected in lupus with up to 87% of patients experiencing manifestations during the course of the disease. Many therapies to reduce lupus disease activity, including mucocutaneous pathology, exist. The most common being antimalarials such as hydroxychloroquine and chloroquine, as well as azathioprine (a purine analog), dapsone, corticosteroids, and alkylating agents such as cyclophosphamide. The mechanisms of these medications are relatively unclear and research continues on drugs that may be more efficacious and less toxic.

Uncontrolled pilot studies of the effects of ultraviolet radiation (specifically the UV-A1 spectrum (340-400nm)) in decreasing clinical disease activity and autoantibody levels showed a 40% reduction in disease, particularly in reducing rash and pruritis associated with it. The therapy was without side effects and appears to be an effective therapeutic modality for SLE patients.

We expect to see a mean decrease in clinical disease activity from baseline and an improvement in the lab values studied in the patients who will receive irradiation. This improvement is expected because of the differences between long and short wavelengths of light as they penetrate the skin to different depths. UV-B is absorbed for the most part by light absorbing molecules in the epidermis and acts at that site. It is mediated through the targeting of DNA which causes the formation of anti-dsDNA antibodies as well as suppression of cell mediated immunity via activation of Langerhans cells. UV-A and UV-A1 wavelengths act in the dermis where they are primarily absorbed. Blood and lymph circulate through the dermis and as the light reaches the circulating cells, it causes systemic non-DNA changes. Other postulated mechanisms by which UV-A irradiation may be beneficial to the lupus patient include mediator release, virus modulation or enzyme activation. The study seeks to define whether there is a significant difference in clinical disease activity using this treatment modality.

B. Study Design and Statistical Analysis

The study planned is to be a randomized placebo controlled trial of 40 patients with stable systemic lupus erythematosus as defined by the 1982 revised American Rheumatism Association Criteria (of 4 of 11 identifiable criteria for greater than six months: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder, and positive antinuclear antibody titer) and how ultraviolet A1 irradiation effects clinical disease activity. Patients must have stable lupus defined as two months or greater on no medication or on a fixed dose of equal to or less than 40mg prednisone or up to 400mg of plaquenil.

The patients who meet inclusion criteria and sign an informed consent will be randomized to two groups: 1) receiving 60kJ/m2/day of UV-A1 irradiation via a "tanning bed" fitted with UVASUN filters

to absorb all UVB and UVA2 emmisions (as these have been shown to decrease CD4/CD8 Tcell ratios in SLE patients) 2) the placebo group who will receive 60kJ/m2 of normal light via a "tanning bed". The groups will receive three treatments a week for six weeks with follow up for 6 weeks afterward. The subjects must agree to avoid sunlight and wear clothing that covers their skin during daylight. Each group will fill out the study questionnaire at the beginning to the protocol and at the end of the treatment phase (week 6) and at the end of the observation phase (week 12). Laboratory studies will be taken from patients at the time of the questionnaires to assess the following: Hematocrit, WBC, Platelet Count, ESR, Serum Creatinine, and urine will be taken for Urine sediment measurement.

Power was determined by reviewing the available literature on this treatment modality in SLE patients. Molina and McGrath showed in an uncontrolled trial that in three weeks of treatment there was a 2 standard deviation reduction in the SLAM score (from 14 + 4 to 7 + 3.5). Because uncontrolled studies often overestimate effect size, we are proposing a randomized placebo controlled trial with a p value calculated using the change in variability of disease over the expected change in disease (both squared) multiplied by the factor 16.

The changes in clinical scores and laboratory indices before and after UV-A1 irradiation will be calculated using analysis of variance.

C. Study Procedures

Patients will be enrolled in the study for 12 weeks once inclusion criteria have been met. They will undergo an initial history and physical exam.

Questionnaires and blood work will be drawn at week 1, week 6, and week 12

Each visit to the office should take approximately one hour.

D. Study Drugs

The UV-A1 irradiation will be administered in a tanning canopy sunbed. A ALISUN bed, used in a previous study, is a fan-cooled bed that is fitted with 24 FS40 TL/10R lamps enclosed by grids and sheets of plexiglass that freely transmits UV light. UVASUN-pink filters eliminate all ultraviolet wavelengths below 340nm. The irradiance delivered to the skin is approximately 1/6 of the dose necessary to produce minimal erythema in the average Caucasian. The dose is low so as to prevent /minimize unanticipated toxicity, but still see an effect in the outcome analysis. The patients will be turned over midway through each treatment session. The irradiance of the lamps at the body surface is 87W/m2 with average duration of irradiance 12 minutes to result in an average daily dose of 60kJ/m2 and a total dose over 6 weeks of therapy of 1080kJ/m2.

E. Medical Devices

Not applicable

F. Study Questionnaires

Patients will be given the enclosed questionnaire, the SLAM or Systemic Lupus Activity Measure in addition to the Patient Global Rating of their disease activity. The questionnaire is 24 items that are based on 10 clinical parameters found to be specifically useful for assessing lupus activity. They are scored as mild, moderate, and severe on a scale of 0 to 3 (0=none/normal, 1= mild, 2= moderate, 3=severe) These tests will be administered at the beginning of the study, at week 6 and at week 12. The total number of times the patient takes the SLAM is 3.

G. Study Subjects

The inclusion criteria are as follows: men and women ages 20 to 45 with ARA defined SLE per the 1982 criteria who have had disease for greater than 6 months and are on a stable dose of either Prednisone (not to exceed 40mg/day) or Chloroquine (not to exceed 400mg/day) or on no medications for the past 2 months, from whom written consent has been obtained. Also, the patients must abstain from sunlight exposure for the 2 months prior to the study and its duration. Patients with any other chronic disease processes will be excluded. The exclusion criteria includes any one who does not meet the above.

H. Recruitment of Subjects

Patients will be identified and asked to participate by their rheumatologist.

I. Confidentiality of Study Data

All study data will be coded with a unique number for each subject and kept in secured offices.

J. Potential Conflict of Interest

Neither the investigators nor the University has a proprietary interest in the drug or devices under investigation.

K. Location of the Study

Clinical Areas within Columbia Presbyterian Medical Center

L. Potential Risks

The potential risks include a small chance that an exacerbation of lupus will occur, in which case subjects may leave the protocol. In addition, patients may experience claustrophobia from the tanning beds and a small chance of experiencing erythema or redness similar to a sun burn. Long term side effects such as skin cancer are minimal and not specifically known at present.

M. Potential Benefits

The potential benefits include decreased lupus disease activity and a decrease in need for medications relating to the illness as well as decrease in skin manifestations such as redness and rash. In addition, further understanding of the mechanisms of the disease process may be understood by the study.

N. Alternative Therapies

Other drugs such as Prednisone, Hydroxychloroquine, Azathioprine, Dapsone, Cyclophosphamide, and Cyclosporine A may improve clinical lupus activity, but each has its own side effect profile.

O. Compensation to Subjects

At this time there is no compensation for subjects.

P. Costs to Subjects

There will be no costs to subjects for this study.

Q. Radiation or Radioactive Substances

Not Applicable

R. Minors as Research Subjects

Not Applicable

S. References

1. Primer on Rheumatic Diseases Tenth Edition. American Arthritis Foundation, p. 100.

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5. Liang MH, Socher SA, et al. Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. *Arthritis Rheumatology* 1989; 32:1107-1118.