PROTOCOL TITLE:

Topical treatment for superficial disseminated actinic porokeratosis: A Single-blinded Comparison Between Lovastatin/Cholesterol and Lovastatin

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NCT04359823

1.0 Objectives / Specific Aims

- The purpose of this study is to evaluate the effectiveness of cholesterol/lovastatin versus lovastatin alone to treat porokeratosis. Our working hypothesis is that both topical cholesterol/lovastatin and lovastatin alone are helpful in treating patients with disseminated superficial actinic porokeratosis (DSAP).
- Aims:
  - 1. To evaluate the response to treatment with topical cholesterol/lovastatin and lovastatin alone in a series of patients with the diagnosis of DSAP.
  - 2. To characterize lesion patterns following topical treatment and patterns of lesion regression.

2.0 Background

Porokeratosis is a premalignant condition with a malignant transformation rate of 7.5%[1]. Variants include disseminated superficial actinic porokeratosis (DSAP), disseminated superficial porokeratosis, porokeratosis of Mibelli, porokeratosis palmaris et plantaris disseminate, porokeratosis ptychotropica, and linear porokeratosis.

Porokeratosis is a rare condition involving clonal proliferation of abnormal keratinocytes that can be inherited or acquired. DSAP is the most common type of porokeratosis. It is described as a well circumscribed, erythematous macule with a peripheral rim of hyperkeratosis, also referred to as the coronoid lamella. While typically benign, lesions may develop into squamous cell carcinoma or Bowen's disease[1]. The lesions typically spare the palms and soles and are most prevalent on the extensor surfaces and back. DSAP typically presents in patients in their 30s and 40s who have a history of extensive ultraviolet radiation exposure. It is estimated to occur in a female to male ratio of 1.8:1[2].

The exact pathogenesis for DSAP is currently unknown, however, the mevalonate genetic pathways are suspected to play a role in development. In one study, at least one mutation in the mevalonate pathway was found in 98% of familial cases and 70% of sporadic cases[3]. Treatment usually consists of destruction of the lesion utilizing cryotherapy, photodynamic therapy, carbon dioxide lasers, 5-fluorouracil. However, recent observations have suggested that various porokeratosis variants arise in areas affected by second-hit mutations in genes encoding components of the mevalonate pathway. Consequently, investigators from Yale University successfully treated a series of patients with topical cholesterol/lovastatin which resulted in complete clearance of DSAP lesions after 4 weeks of treatment[4].

It is hypothesized that statins will block the accumulation of toxic metabolites in the mevalonate pathway, while topical cholesterol will provide the essential nourishment to the cells[4]. This study will provide a larger sample size and allow us to observe more definitive outcomes of the stain/cholesterol therapy.

3.0 Intervention to be studied

Noninvasive in vivo imaging techniques have become an important diagnostic aid for skin cancer detection. Dermoscopy, also known as dermatoscopy, epiluminescence microscopy, incident light microscopy, or skin surface microscopy, is performed using a handheld instrument called a

dermatoscope or dermoscope, which has a transilluminating light source and standard magnifying optics (10×). The dermatoscope facilitates visualization of subsurface skin structures located within the epidermis, dermoepidermal junction, and papillary dermis, which are otherwise invisible to the unaided eye. Colors and structures visible with dermoscopy are required for generating a correct diagnosis.

Dermlite dermatoscopes are approved by the FDA.

We will utilize 2% cholesterol and 2% lovastatin ointment. It will be compounded by a pharmacist. Ointment will be applied on lesional skin with occlusion twice daily. Cholesterol and lovastatin are not approved by the FDA to be used in porokeratosis but are used off-label by physicians for the treatment of DSAP.

Pharmacology

Cholesterol is an animal sterol found in the body tissues (and blood plasma) of vertebrates. It can be found in large concentrations within the liver, spinal cord, and brain. Cholesterol is an important component of the membranes of cells, providing stability. Cholesterol is distributed universally in all animal tissues. It can be derived either from intestinal absorption of dietary cholesterol or from synthesis de novo within the body. Cholesterol itself in the animal system is the precursor of bile acids, steroid hormones, and provitamin D3.

Lovastatin is a lactone metabolite isolated from the fungus Aspergillus terreus with cholesterol-lowering and potential antineoplastic activities. Lovastatin is hydrolyzed to the active beta-hydroxyacid form, which competitively inhibits 3-hydroxyl-3-methylgutarylcoenzyme A (HMG-CoA) reductase, an enzyme involved in cholesterol biosynthesis. In addition, this agent may induce tumor cell apoptosis and inhibit tumor cell invasiveness, possibly by inhibiting protein farnesylation and protein geranylgeranylation, and may arrest cells in the G1 phase of the cell cycle. Studies suggest that less than 5% of the oral dose reaches the general circulation as active inhibitors and the time to peak serum concentration is 2-4 hours. Lovastatin undergoes extensive first-pass metabolism so the availability of the drug in the system is low and variable. The peak concentrations of lovastatin when a dose of 10-40 mg is administered are reported to range from 1.04-4.03 ng/ml and an AUC of 14-53 ng.h/ml. This indicates that lovastatin presents a dose-dependent pharmacokinetic profile.

Lovastatin is a HMG-CoA reductase inhibitors that has been used topically for the treatment of skin disorders such as acne, seborrhoea, rosacea, rhinophyma, atopic dermatitis, contact dermatitis and ichthyosis (US Patent 5,730,992 1998 and US Patent 6,126,947 2000). Topical lovastatin at 49 mM (20 mg/ml) in 95% ethanol is well-tolerated with limited side effects. Muscle breakdown may occur resulting in signs and symptoms such as myalgias, fasciculations, cramping, myopathy, rhabdomyolysis and increased levels creatine kinases in the blood. The ethanol component may induce mild skin dryness. It was effective in the treatment of acne vulgaris, thus supporting the expectation of absorption through the skin. Lovastatin is known to cause reversible cell cycle arrest and effective concentrations depend on cell type and experimental conditions, but cell culture

concentrations of 2 to 20 μM (0.8–8.0 μg/ml) for up to 72 h result in reversible cell cycle arrest with cells beginning to cycle after 6 hrs[5,6].

4.0 Study Endpoints

- Percentage of clearance of disseminated superficial actinic porokeratosis lesions after 12 weeks of therapy
- Validated scale changes: Patient Quality of Life (RAND36, DLQI), Physician Global Assessment Scale (DSAP-PGA), Actinic Keratosis Field Assessment Scale
- Clearance of coronoid lamella on dermoscopy (or photograph) after 12 weeks of therapy.

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria

- All patients 18 years and older with the diagnosis of disseminated superficial actinic porokeratosis.

Exclusion Criteria

- Patients with allergies or contraindications to lovastatin or cholesterol
- Female patients currently pregnant or lactating.
- Patients requiring their medications to be delivered to Alabama (Chemistry Rx does not dispense medications to this state)
- Female patients with plans to become pregnant.
    - Patients actively taking approved forms of long-term contraception (oral contraceptives, implantable intrauterine devices, or other hormone eluting implants) will be allowed to participate as long as they have no plan to become pregnant during the course of the study. A urine pregnancy test will be administered to these patients to confirm that they can be included in the study.

6.0 Number of Subjects

Approximately 50 subjects will be recruited.

7.0 Setting

- **Study Sites**
- Virtual video chat forums with patients living in the USA.
- Medical University of South Carolina
    - Dermatology Clinics

8.0 Recruitment Methods

Recruitment will occur after standard of care visits to the Dermatology Clinics, virtual visits, and chart review of eligible patients.

For standard of care visits, the first person to tell eligible patients about this study will be someone directly involved in their patient care. If they are interested, the aforementioned clinician and study team members will approach the patients without coercion and with the emphasis on the voluntary aspect of being on this study. Subjects will also be told in a caring manner that no matter what their decision is, it will not affect how their doctor cares for them as a patient or their care in general.

Patients discovered via chart review will be contacted to be informed of the potential research opportunity under the same aforementioned conditions. Only patients who have indicated they are willing to be contacted for research opportunities on their MUSC profile will be eligible for this form of contact. In this instance the first person to contact them may not be someone directly involved in their patient care.

Potential subjects who contact the study team members directly will also be considered for participation in the study. In this event, these potential subjects must have heard about the study through indirect information sources (clinicaltrials.gov, DSAP support groups, or other means by which the study team members did not directly advertise the study for purposes of recruitment). If they are interested, the aforementioned study team members will respond to them via email, and subsequently approach the patients virtually without coercion and with the emphasis on the voluntary aspect of being on this study. Subjects will also be told in a caring manner that no matter what their decision is, it will not affect how their doctor cares for them as a patient or their care in general.

9.0 Consent Process

Written informed consent will be obtained from subjects. Informed consent will be obtained in a private room within the clinics or privately via virtual visits. All subjects will undergo a prescreening call by study team members during which they are informed of the details of the study, eligibility concerns, and given the opportunity to ask and questions or address concern about the study. They will be sent the consent form immediately afterward, allowing them ample time to review the document before meeting the study team in person or virtually during visit 1 (week 0). During visit 1, the trained study team member performing consent will then review the consent form with them once again and address any questions before the sign the document and return it to the team via email. Virtual consenting will be performed on REDcap. Only trained research team members will be obtaining informed consent. Training will be performed by Alan Snyder and only those who are trained will perform informed consent after they sign the study training log. No waiting period will be necessary between informing the subjects and obtaining the consent; however, subjects will be allowed to take home the unsigned consent form for review prior to signing it if needed.

The virtual consent process for patients who contact study team members directly about potential interest in participating is summarized below:

1. subjects contact our study team after hearing about our study from indirect sources

2. Interested subjects are called by one of our study team members for a prescreening call in which we determine if they are eligible to participate in our study. This is also an

opportunity for Q&A for potential participants who may want eligibility information or details about the study prior to an official enrollment visit.

3. Potential subjects are securely emailed a copy of the IRB-approved ICF and scheduled for an official enrollment video visit that is mutually agreeable for the investigators and potential participant. The time period between this email and the enrollment visit will provide participants ample time to review the ICF in detail so that they have the opportunity to prepare additional questions during the official enrollment visit.

4. Investigators and potential participants engage in a video chat for consenting, in which REDCap will be used for execution of the consent process. Study participants will have the option to have the signed ICF sent to their personal email after it is signed by both parties.

6. Subsequently, Visit 1 will proceed following the procedures in our protocol

10.0 Study Design / Methods

- Potential subjects will be approached for informed consent as directed in sections 8.0 and 9.0. Pertinent project information, risks, and time commitment will be relayed to subjects. If subjects show interest in participating, they will be given consent forms to either sign or bring home for consideration. A urine pregnancy test will be administered to these patients to confirm that they can be included in the study.
- If the patient is eligible for the study, he or she will be randomly assigned to one of two groups. They will have a 50/50 chance of being in either group. Neither the researchers nor you will make the choice to which group you are assigned. The two groups are Group A (cholesterol/lovastatin) and Group B (lovastatin only). The patient will not be informed of which group they are in and will not be informed of what their study medication is, allowing single-blinding. Researchers will not be masked.
- Enrolled subjects will be followed up at monthly intervals for three months via virtual check-in using an MUSC approved HIPAA compliant technology. At each visit, participants will undergo brief, limited physical examination (in order to determine disease severity and affected body surface area); additionally, clinical photographs of the lesion will be obtained in clinic or shared virtually with the investigators via secure email (sent to MUSC Outlook email). The physical exam will occur in-person or by using the virtual visit technology, which allows us to see the patient and visualize their skin findings.. Photographs will be stored in the coded study-specific medical record for further analysis of lesion features.
- At each visit a Patient Quality of Life, Physician Global Assessment Scale, and Actinic keratosis Field Assessment Scale will be administered.
- Patients will be contacted via virtual check-in visits at weeks 4, 8, and 12. Patients will be asked about compliance and any adverse effects experienced. Patients are also encouraged to contact Alan Snyder at any given point during the study if they think they are experiencing study-related side effects. Immediate consultation will follow to determine the severity of such event and necessary impacts on patient health and participation. Participants will also be contacted by phone by study team member to assess for any adverse effects at weeks 2 and 6 of treatment.

- Compounded topical medication prescribed to subjects will be self-applied twice daily. These medications will be prepared by Tidewater Pharmacy in Mount Pleasant, SC or Chemistry Rx in Philidelphia, PA. They will be prepared so the study will remain single-blinded (only investigators know which study drug they are receiving) and associated costs will not be covered by the research budget. The cost of the medication will be approximately $85 when dispensed by Tidewater Pharmacy, or $110 when dispensed by Chemistry Rx. The differences in costs are attributed to shipping and pharmacy fees.
- Both pharmacies will be compounding the drugs to be used in this study, and the compounding formula (recipe) will be identical between these two compounding pharmacies.
- Enrollment and prescription drug delivery to other states will not be performed until the respective state pharmacy boards confirm the legality of clinical telehealth interventions and out-of-state pharmacy prescriptions. All state and federal guidelines will be followed according to their regulations and recommendations.
- Patient prescriptions will be called in to their respective pharmacies by credentialed study team members after enrollment is completed. Individual prescriptions will be called in to the aforementioned pharmacies so that the pharmacies can individually ship the medication to the respective participant. Both pharmacies are well aware of the study protocol and procedures for sending the prescription. This will occur by standard procedure of calling medications for patients:
    - 1. The study team member will call the pharmacist to inform them that a participant has been enrolled and ready to receive one of the two single-blinded drugs. The lovastatin/cholesterol combination has been assigned the arbitrary codename “RDC100”, and the lovastatin alone medication has been assigned the arbitrary codename “RDC15”. On the prescription label there will be the codename, application instructions, and storage instructions.
    - 2. Per standard procedure of calling in a prescription, the study team member will verbally inform the Tidewater/Chemistry Rx pharmacist of the patient name, birthday, and phone number so that the medication can be prescribed and so that the patient can be contacted by the pharmacist for shipping and payment purposes.
    - 3. The pharmacist will contact the patient over the phone in order to complete the medication payment over the phone and to identify the address to which the medication will be sent to.
    - 4. The subject will inform the study team member upon receival of the medication, confirm that they received the correct, randomized medication.
    - 5. All of the information related to drug disposal and reception will be recorded on the coded Drug Accountability Sheet, which is located separately in the secure box drive.

- Medications will be able to be shipped to all continental US states by Chemistry Rx, except Alabama. This is because Chemistry Rx does not have the license to dispense to Alabama. Therefore, any participant reliant upon an Alabama address to receive their medication will not be allowed to participate in this study.
- Dermoscopic and clinical photographs will be subsequently analyzed for the presence of cornoid lamella. The team will record any additional dermoscopic or clinicals feature that may arise during the analyses.
- Frequency of dermoscopic and clinical features will be analyzed against clinical involution to find possible predictors.
- Procedures during the day of imaging:

  The doctor will identify the lesion(s) that will be analyzed.

  The lesion(s) will be measured and clinical and dermoscopy photographs will be taken. Facial images might be taken to assess lesions on the head area.

Schedule of events:

Event	Screening Baseline Visit 1	Week 4 (virtual)	Week 8 (virtual)	Week 12 (virtual)
Informed consent	X			
Eligibility Assessment	X			
Demographics	X			
Physical Examination	X			
Clinical photograph & Scale (3x) administration	X	X	X	X
Dermoscopic photograph	X			
Adverse events monitoring	X	X	X	X

11.0 Data Management

- Continuous data will be summarized using descriptive statistics (number of values, means, standard deviation, median, minimum and maximum). Categorical data will be summarized using frequency tables (frequencies and percent).

- We are comparing before and after photographs from the same patient, hence we employ analysis by paired t-test to compare baseline data with data after treatment.
- Coded dermoscopic and clinical photographs may be obtained for further analyses. Files with patient images will be stored in a secure departmental drive that will only be accessible to study team members by their unique MUSC ID and password.
    - Photos shared directly via email to study team members will be also be uploaded to the participants respective coded folder on the Box drive.
    - These emailed photos (sent by the participant personal email) must be de-identified close up photos of the participants legs or arms, and sent only to study team members secure MUSC-assigned Outlook email addresses. Photos that do not fit this criteria will be deleted upon receival and not used in the study.
- All subject medical record information and data collection will be coded and stored on an MUSC Box drive only accessible to study team members, and will be protected by two-factor authentication.

12.0 Withdrawal of Subjects

1. Any adverse effect during patient's treatment will require a thorough review of the adverse event by the study team members. Depending on the severity of the adverse event, the participant may be recommended to withdrawal from the study. The research team will continue to follow the patient until resolution of said adverse event has resolved.

2. Upon subject's verbal notification, the study team will evaluate the adverse event, they will proceed to document it and evaluate for subject safety. They will determine if subject is suitable to continue in the study.

3. Information will be provided about safe discontinuation of the drug and if any clinical review needs to occur. For evaluation and reporting purposes, researchers may conduct an exit interview and ask subjects about the reason for early withdrawal.

4. Subjects can participate in the study as long as they want. Subjects may verbally notify investigators if they wish to voluntarily withdrawal from the study and they will be removed immediately.

13.0 Risks to Subjects

- We anticipate minimal side effects and local irritation to be minimal. Muscle toxicity is a known adverse effect of statins. Patients will be notified during enrollment to watch out for common signs and symptoms such myalgias, fasciculations, cramping, myopathy and increased levels of CK. If an adverse event occurs, the subject must notify the study team members at their earliest convenience. Upon the subject's verbal notification to the study team, the study team will evaluate the adverse event and will proceed to document it and evaluate for subject safety. They will determine if subject is suitable to continue in the study.

- If there is an increased frequency of any concerning adverse event in particular, all enrolled participants in the trial will be sent an individual notice.
- There is a risk for possible breach of confidentiality as photographs of face may be taken to assess lesions on the head. However, all measures to keep information protected will be taken.
- There is a risk of emotional discomfort while the subject takes the questionnaires.
- A cumulative data assessment will be conducted every other month throughout the study's duration by study team members. A report that includes any available efficacy data, as well as a record of anticipated adverse events, will be compiled and submitted to the IRB at that time. Any event meeting the criteria of an unanticipated problem involving risks to subjects or others will be immediately reported to the MUSC IRB, as required by HRPP 4.7- Unanticipated Problems and Adverse Events Policy and Procedures.
- The plan for subject safety and minimizing risks of the research is as follows: Inspection of the treatment site at each visit. Adverse effects of topical lovastatin/cholesterol will be specifically assessed at each research visit by the investigator, per outlined procedures. Participants are encouraged to reach out to the study coordinator if they think they are experiencing any adverse events. Other expected adverse effects deemed intolerable by the patient will prompt reduction in the patient's dose and treatment if indicated. Any condition necessitating cessation of the study drug will be followed to resolution.
- However, the side effect profile associated with both topical cholesterol and lovastatin is extremely small. We do not anticipate there being any complications associated with treatment other than minor, local irritation. The rare chance of developing stain induced myopathy and its associated signs and symptoms will be addressed during enrollment and each individual visit.

14.0 Potential Benefits to Subjects or Others

Patients will may benefit from the intervention. Researchers hope that the treatment will help clear active DSAP lesions, but all benefits are hypothetical currently.

15.0 Sharing of Results with Subjects

Results may be shared with subjects at the end of the study per verbal request.

16.0 Drugs or Devices

5. Drugs will be compounded by Tidewater Pharmacy or Chemistry Rx prior to the patients week 0 visit. They will be stored at this pharmacy until the subject is able to pick it up or have it delivered to their home address.

6. Investigators will be in charge to handle dermoscope and will be responsible to upload the images to the secured folder. The Dermatoscope is device used SOC for analysis of DSAP lesions.

7. An investigational drug exemption support document has been submitted to the eIRB.

References

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