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PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	A Single Center Clinical Trial to Evaluate the Effect of Sclerotherapy on Fistulas and Sinus Tracts in Adult Patients with Hidradenitis Suppurativa
Principal Investigator	**Dr. Martina Porter**

B1. PURPOSE OF PROTOCOL

The purpose of the protocol is to evaluate the effect of sclerotherapy on fistula and sinus tract evolvement using hypertonic saline injections in fistulas and sinus tracts in subjects with hidradenitis suppurativa

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Hidradenitis Suppurativa (HS) is a chronic suppurative disease characterized by firm, tender, inflammatory, red nodules that often evolve into fluctuant and malodorous painful abscesses, fistulas, and non-healing sores. Rupture of the lesion, suppuration, formation of sinus tracts and scarring frequently occurs. It has been estimated to affect up to 4% of the population, affecting women more commonly than men. A study performed in 2007[1] showed that the disease can cause significant morbidity, especially among patients who have an early onset of disease, long duration and continuous evolution. Proposed etiologic factors include follicular occlusion, bacterial infection, genetics[2-4], host defense defects, hormonal influences, cigarette smoking, and irritants. Although the current belief is that the primary defect is occlusion of the terminal parts of the follicular acroinfundibulum[5] and recent genetic information supports this hypothesis,[6,7] the apocrine milieu is likely to play a meaningful role in the disease because it primarily affects apocrine gland-containing regions such as the axillary, inguinal and perineal areas. Importantly, the disease also responds well to complete excision of these apocrine gland-containing sites. While this approach is substantially disfiguring, requiring large areas of excision, it also typically results in a cure in the region excised, while other areas will remain active.

In order to classify HS the Hurley classification and the Sartorius scoring system are used, both rely on clinical data, which may be inaccurate because of the difficulty in assessing the extensiveness of the lesions beneath the skin surface. This can lead to underestimation of severity.[8] Ultrasound has also been used as a low-invasive and safe method for evaluating the lesions of HS.

One persistent problem for many patients is the continued presence of draining fistulas and sinus

tracts lined with epithelium that can sometimes form "honeycomb network". Because the tracts are lined with epithelium, they are unlikely to close or fill in by themselves. A treatment approach that has evolved to manage this persistent problem is sometimes called "unroofing" or "deroofing" in which the surface the epithelial track is slit and laid open. As shown in appendix 1, the disadvantage of this treatment is the wide area of surgical exposure and morbidity that results.

Sclerotherapy is a well-known, safe and successful treatment for spider and varicose veins. A sclerosant is injected directly into the varicose vein and causes endothelial and vein wall damage, which leads to occlusion and ultimately results in fibrosis of the targeted vein. One of the sclerosants commonly used in clinical practice is hypertonic saline, which causes dehydration of endothelial cells and denaturation of cell surface protein and ultimately causes the vein to collapse and close. Hypertonic saline is one of the most popular agents because of lack of allergenicity, low cost and easy availability. A downside is that upon injection patients experience more pain, because of stinging, in comparison with other sclerosants but complication rates such as ulceration are low. Excision is the only reliable way to treat these semi-permanent HS lesions. The less-invasive sclerotherapy treatment might be an alternative for this since it can disrupt the epithelial lining and allow for wound healing from the inside of the tract to occur.

We have treated two patients with this as innovative therapy using 0.2-0.4 cc of hypertonic saline injected in to a tract. In patient one, we did 2 treatments about 1 month apart with substantial reduction in the lumen of the fistula. Patient 2 has been treated once and asked for a second treatment. Patient one had some erythema development near the site about 1 month after treatment, which resolved and appeared to be due to concomitant disease outside the treated fistula. Both patients, as expected, experienced mild to moderate stinging.

This project was first started at MGH through cede review and are now continuing it at Beth Israel Deaconess Medical Center, which will be the only study site.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study Design and plan:

The design of this study is a single center, single-blinded clinical research treatment study. This clinical study will be conducted at Beth Israel Deaconess Medical Center in Boston (the study was previously conducted at MGH and is currently being conducted at both institutions through Cede Review with MGH as the overseeing IRB and BIDMC). All subjects with a signed informed consent will be screened to ensure they meet all inclusion criteria and do not meet the exclusion criteria. After enrolment, the duration of the study is approximately 8 weeks, involving 3 or 4 visits. A schematic overview of the main procedures during each visit is illustrated in Appendix 2.

The clinical effect of the hypertonic saline treatment will be evaluated with Physician and patients Assessments at week 2 (t=2), week four (t=4) and week 8 (t=8) and compared with the first visit (baseline) (t=0). If necessary, subjects will be eligible to receive another hypertonic saline injected in week 2 and/or week 4, with a maximum of three injections. Simultaneously improvement will be assessed by ultrasound if possible, using the Philips Lumify Ultrasound Device, and by patients using HS Improvement Assessments. Pain and stinging during treatment sessions will be monitored using numeric rating scales (NRS). For monitoring quality of life the DLQI will be used.

Prior to performing any study related procedures, the investigator will discuss with each subject the nature of the study, its requirements and its restrictions. A written informed consent form will be obtained from each participant prior to any procedure. Each subject with a signed informed consent form will be screened at the first visit, to ensure all the inclusion criteria are met and none of the exclusion criteria. Medical history and demographic information will be taken. Patients will have their medication reviewed and undergo a full HS examination, including lesion counts, Hurley staging and target site assessment. Target HS area(s) will be digitally photographed and be imaged with ultrasound. The duration of the study is approximately 8 weeks, involving a minimum of 3 and a maximum of 4 visits. In case of an adverse event or disease progression, patients are instructed to call and/or visit the clinic. An overview of the exact procedures during each visit can be found in the chart

Study Table (Chart with Study Procedures)

Activity (timeline)	0 week (Baseline)	2 Week	4 Week	Week 8
Subject Information and Informed Consent	✓			
Eligibility Criteria	✓			
Medical History	✓			
Prior and concomitant therapy	✓			

Review and document pregnancy avoidance with females of child bearing age	✓			
23.4% Hypertonic Saline Injection	✓	✓	✓	
Urine Pregnancy Test (For all females of childbearing age)	✓	✓	✓	
Ultrasound (to locate the tracts)	✓			✓

B. Statistical Considerations

a. Sample Size Justification:

The total number of subjects to be studied is 20 and the number to be studied at BIDMC is 14.
A sample size calculation is not applicable, for this is an early feasibility and tolerability pilot study.

b. *Data Analysis:*

Primary study parameter(s)

The clinical efficacy will be measured by Physician and patients Assessments. These are continuous variables and depending on the date distribution a one way ANOVA, a Kruskal Wallis or a Wilcoxon rank sum test will be performed for analysis.

Secondary study parameter(s)

Hence the small patient group in this pilot study, no power is expected from statistical analysis.

Therefore all outcomes will be assessed by using descriptive statistics.

The clinical efficacy will also be measured using the following outcomes:

- Measuring the length and the lumen of the fistulas using ultrasound if possible. Since this variable is highly dependent on investigator and experience with ultrasound, descriptive statistics will be used to present this variable.

The patient reported outcomes:

- HS Improvement assessment: this is a continuous variable and depending on the date

distribution a one way ANOVA, a Kruskal Wallis or a Wilcoxon rank sum test will be performed for analysis.

- NRS to assess pain and stinging: continuous variable. Per individual a percentage improvement will be calculated as a main outcome.
- DLQI: continuous variable. this is a continuous variable and depending on the date distribution a one way ANOVA, a Kruskal Wallis or a Wilcoxon rank sum test will be performed for analysis.

C. Subject Selection

Patients potentially eligible for this study are at least 18 years of age and have active HS sites with fistula(s) or sinus tracts. A total of 20 subjects will be enrolled in the study. Potential patients will be assessed for eligibility to participate in this clinical study using the criteria for inclusion and exclusion listed below.

Inclusion Criteria:

A subject must meet all of the following criteria in order to be eligible to participate in this study:

1. Male or female subjects are at least 18 years of age or older
2. A confirmed diagnosis of HS disease
3. Presence of inflammatory HS lesion(s) and one or more fistula(s) or sinus tracts

Exclusion Criteria:

Eligible subjects will be excluded from participation if they meet any of the following criteria:

1. Receiving any other kind of treatment for fistulas including introduction of anti-inflammatory systemic therapy such as prednisone or adalimumab within the prior month.
2. Are currently pregnant or planning to get pregnant during the study.
3. Are participating in another study using an investigational agent or procedure during participation in this study.
4. Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study.

Urine Pregnancy Test

A urine pregnancy test will be performed locally for all females of childbearing potential at the Baseline Visit prior to the first dose of study drug and at minimum at monthly intervals (either at study visits or at home between scheduled study visits). The results of the monthly at home tests must be communicated to the site. More frequent pregnancy tests will be performed throughout the

study if required per local/country requirements.

- If the Baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin.
- If the Baseline or postbaseline urine pregnancy test performed at the site is positive, dosing with study drug must be withheld and a serum pregnancy test is required. The serum pregnancy test will be performed by the central laboratory. If the serum pregnancy test is negative, study drug may be started or resumed. If the serum pregnancy test is positive, study drug must be permanently discontinued. In the event a pregnancy test comes back borderline, a repeat test is required (≥ 3 days later). If the repeat serum pregnancy test is:
    - Positive, the subject must be discontinued;
    - Negative, the subject can continue in the trial;
    - Still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can continue in the study (unless prohibited locally) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

If time between visits is longer than 1 month, then collect the results of the monthly at home urine pregnancy test between scheduled visits.

If during the course of the study a female becomes surgically sterile or postmenopausal and complete documentation as described in Protocol Section 5.2 (Contraception Requirements for Females) is available, pregnancy testing is no longer required.

A pregnant or breastfeeding female will not be eligible to enter the study or be allowed to continue study drug.

B4. POSSIBLE BENEFITS

The potential benefits of this study are that the individual subject's Hidradenitis Suppurativa caused fistulas and sinus tracts might improve with the administration of sclerosants like hypertonic saline.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Hypertonic saline is as effective as other sclerosants with the advantage of lack of allergenicity and low costs. The most common adverse events or risks associated with sclerotherapy using hypertonic saline are hyperpigmentation, teleangiectic matting (neovascularization), pain, ulceration and tissue necrosis. Other reported less common adverse events include exacerbation of hypertension, necrosis of kidney cortex, hemolysis, hematuria, central nervous system disorders, hypernatremia and membranous fat necrosis.

When used to treat fistulas or sinus tracts, none of the systemic adverse events are expected to occur. The common adverse events can be minimized by adhering to meticulous technique.

Risks listed in ICF are as follows:

More Common: Stinging, pain in the injected area
Less Common: Skin Ulceration,
Rare: Infection

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Dermatologists from Beth Israel Deaconess Medical Center will be informed using IRB-approved recruitment letters of this study and asked to refer eligible patients to our research unit. These letters will explain the purpose of the research, including a brief description of the nature and extent of involvement, and the investigator's email and phone number will be included. A research study advertisement will also be posted in the dermatology clinic.

A list of potential subjects will be compiled from Dr. Kimball and Dr. Porter's patient population using ICD codes for HS. These identified patients will be sent recruitment letters informing them of the study and to contact one of the doctors if they are interested.

The study will also be placed on TrialX as well as skinstudies.com, craigslist, twitter and BU quickie jobs. TrialX will use clinicaltrials.gov information; skinstudies.com, craigslist, twitter and BU quickie jobs will use the recruitment flyer and language from the targeted provider email.

We will advertise the study on Twitter as well with the following posting: "Do you have Hidradenitis Suppurativa (HS)? You may be eligible to participate in a clinical trial. If you are interested visit our website skintudies.com, email us at clears@bidmc.harvard.edu or call at 617-667-5834."

Consent

Prior to entering the study, a licensed physician investigator will explain to the potential subject the nature of the study, its purpose, procedures, expected duration, and the benefits and risks involved in study participation. The licensed physician will explain the main study.

Subjects will be given the opportunity to ask questions and be informed of their right to study withdrawal. After this explanation and before any study-specific procedures have been performed, the potential subject may voluntarily sign and date the informed consent form for the main study, thereby giving permission for the subject to enter the study.

Prior to participation in the study, the subject will receive a copy of the signed and dated written informed consent form and any other written information provided to the subject. If, for any reason, the subject desires more time to consider the decision, the subject will be given a copy of the unsigned consent form for reference and instructed to call the office if they decide to participate in the study.

Subject Protection

In order to address the issue of patients feeling pressured to participate, a standard approach was developed and implemented years ago. This gives the patient the opportunity to actively demonstrate their interest before enrolling in the study. If a discussion about the study presents itself during a clinical encounter, the patient is offered to take the consent home and read and then asked to follow up with the clinic if they are interested. It is also attempted to have a physician who is not involved in their clinical care go over their consent form in order to provide further separation.

B7. STUDY LOCATION

Privacy

Subject visits will be conducted in the CRC at BIDMC or, rarely, in private patient exam rooms in the dermatology clinic if the CRC is not available at the time of subject visits. Both locations should ensure adequate privacy for patients. Patients will complete all study related procedures in these private settings, including questionnaires. Questionnaires will be in written form and returned directly to the investigators or study staff.

Pre-screening telephone calls and subject visits will be limited only to the minimum amount of data necessary to accomplish the research purposes. No sensitive questions will be discussed by telephone

Physical Setting

Subject visits will be conducted in the CRC at BIDMC or, rarely, in private patient exam rooms in the dermatology clinic if the CRC is not available at the time of subject visits. Both locations should ensure adequate privacy for patients. Patients will complete all study related procedures in these private settings, including questionnaires.

B8. DATA SECURITY

All subjects will be assigned a subject number at their screening visit. Only investigators and study staff at BIDMC will have access to the subject's identifiable health information. To ensure appropriate privacy and confidentiality, any paper source documentation and questionnaires will be stored in a locked cabinet. Only the PI, sub-investigator, and study staff will have access to this locked cabinet. This documentation will all be coded. Subject's identifiable health information will be kept separate from coded documentation. Any electronic data containing PHI will be stored on a password protected computer in a locked office and on a secure server behind the BIDMC firewall. The Investigator will maintain adequate records for the study, including resultssource documentation, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, adverse events, and other pertinent data. All essential documents will retained by the Investigators for at least 2 years in a long-term storage facility as arranged through the CTO.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☒ No

Is the BIDMC PI the lead investigator of the multi-site study? ☒ Yes ☐ No

B10 Dissemination of Research Results

Subjects will be thanked for their participation in the study immediately following their last visit. Because we are not able to anticipate the final completion date of the study, which may take years, and because we are not primarily responsible for analyzing and publishing the data, it will not be feasible for investigators to provide results to individual subjects. Subjects may contact the PI following their completion of the study to inquire about the final findings of the study, if available to the investigators, at that time.

Planned dissemination of research results may include abstract presentations at dermatology conferences and submission of data for publication in academic journals as an original research article.