TITLE: A Phase I Study of Low Dose Radiotherapy for Advanced Hidradenitis Suppurativa

Contents

1.0 OBJECTIVES

1.1 Primary Objective

- To establish the safety of radiotherapy in the treatment of advanced hidradenitis suppurativa

1.2 Secondary Objectives

- To examine the efficacy of radiotherapy in improving quality of life for patients with advanced hidradenitis suppurativa
- To explore histologic changes following radiotherapy for advanced hidradenitis suppurativa
- To explore changes in ultrasound findings following radiotherapy for advanced hidradenitis suppurativa
- To determinepossible changes in assessment of cutaneous discharge from HS lesions

2.0 BACKGROUND

2.1 Hidradenitis Suppurativa

Hidradenitits Suppurative (HS) is a chronic inflammatory skin disease characterized by recurrent, painful abscesses, sinus tracts, and scarring. The majority of HS lesions are found in apocrine bearing skin, which includes the axilla, groin, and inframammary regions. The etiology of HS is still unclear, but it is hypothesized that the lesions develop due to follicular occlusion where the aprocine gland meets the hair follicle. This follicular blockage leads to cyst formation. The colonization of the cyst by skin flora leads to an exuberant immune reaction to cyst contents that results in painful inflammation and abscess formation. The abscesses may heal over the following 1-2 weeks, leaving a scar. Even with treatment, inflammation can continue and lead to the formation of skin tracts that burrow in the dermis. Over time, the HS inflammation persists, and painful suppurating and connecting dermal tracts are found in the whole region, such as the axilla and groin. The impact of HS on quality of life can be devastating. Patients often report extreme embarrassment from the disfiguring lesions and their associated foul, odiferous discharge.

2.2 Current Treatment Options

There are only a few options for effective treatment of HS, and no definitive cure exists. Treatment depends on severity and clinical staging. The mainstay of treatment of mild disease involves antibacterial washes and topical antibiotics, and acute flares may be managed by intralesional corticosteroids and/or minor surgical procedures. Oral therapies include 3-6 months of broad-spectrum antibiotics, oral anti-androgens may be helpful in women, and systemic retinoids (isotretinoin or acitretin) may be beneficial in a subset of patients. Laser hair removal with 1064nm Nd:Yag laser has shown promise, but many patients

cannot afford this treatment. The only FDA approved treatment for HS is adalimumab (Humira), an antibody against tumor necrosis factor α (TNF-α)[1].

Patients who fail medical management or who are ineligible for TNF-α inhibitors are left with few options for salvage treatment. In this situation, patients will often resort to extensive surgical resection of the affected area with or without graft placement. Unfortunately, the recurrence rate of HS lesions in this area is high, with recurrence rates up to 50% of patients who have surgery. The use of a more "conservative" surgical approach, such as the CO2 laser to excise all apocrine bearing tissue, has shown potential for improved surgical results, but it's not widely available. In addition, recurrence of HS lesions still occurs in a number of patients who have undergone this laser procedure

2.3 Radiotherapy for HS

Given the current understanding of the etiology of HS and the mixed success rates of existing treatments, it is imperative to continue the search for more effective treatments. Radiotherapy is a good option on which to focus our efforts. Low to intermediate dose radiotherapy has been used to provide effective control for a number of benign cutaneous conditions, including inflammatory and proliferative disorders, as well as benign and malignant tumors [2]. The rationale for using radiotherapy to treat inflammatory disorders stems from the ability to directly target infiltrating and localized white blood cells. The proposed mechanisms of action of radiotherapy include apoptosis of infiltrating leukocytes, prevention of diapedesis of leukocytes into tissues, and prevention of macrophage production of toxic mediators [3]. Overall, this leads to normalization of the inflammatory cytokine milieu, which helps to dampen the inflammation leading to resolution of associated debilitating physical symptoms.

Only a few reports using radiotherapy for HS treatment have been published. In one case report, radiotherapy was given to a 53 year-old female with a history of HS for 5-6 years, who had failed previous medical management and surgery. External beam radiotherapy was directed to HS sites utilizing 6 MeV electrons prescribed to the 90 percent focus of the electron curve. A 5 mm tissue equivalent bolus was added to the skin surface and 1.0 cm margins around the visible disease was added to the Planning Treatment Volume. Over the course of five months she received multiple courses of radiotherapy with multiple dosing and fractionation schedules (1.5 – 2.5Gy per fraction with total doses of 4.5Gy to 7.5Gy). She tolerated the procedures well without any acute side effects. Over the course of treatment, the patient presented with two episodes of recurrent lesions (at 3 weeks and again at 3 months following initial treatment) and one new foci of disease (at 3 months after initial treatment). Recurrent and new foci of disease were treated with higher fracture schedules of higher fraction size. The patient remained lesion free for the following 1.5 years, until the time of publication [4].

As reviewed in above case report, a center in Germany treated 231 HS patients over 20 years who failed other treatment options. These patients received multiple fraction schedules with multiple fraction sizes (0.5 Gy – 1.5 Gy per fraction up to a total dose of 3.0 Gy to 8.0 Gy in one series). Chronic

recurrences were treated with 2 or more series with a total dose of greater than 10.0 Gy. No acute side effects were observed in this study. Complete symptomatic relief was documented in 38% (89/231) patients by the end of therapy and 40% (92 / 231) of patients reported an overall improvement in symptomatology. Only two patients had no response.

3.0 PATIENT ELIGIBILITY

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study.

3.1 Inclusion Criteria

- The subject must be diagnosed with HS at Montefiore HS Treatment Center, with Hurley Stage 2-3 (Recurrent abscesses or boils with diffuse or broad involvement, multiple interconnected sinus tracts in the whole area) [5].See Appendix A for photos.
- Subject must have failed maximal medical therapy for HS or be ineligible for “standard” medical therapy or surgery
- Age > 20 years old
- Women of childbearing potential must:
    - Have a negative serum or urine pregnancy test within 72 hours prior to the start of study therapy
    - Agree to utilize an adequate method of contraception throughout treatment and for at least 4 weeks after study therapy is completed. Adequate methods of contraception include hormonal methods (i.e. birth control pills, patches, injections, vaginal ring, or implants), barrier methods (i.e. condom or diaphragm), intrauterine device, or abstinence.
    - Be advised of the importance of avoiding pregnancy during trial participation and the potential risks of an unintentional pregnancy
- All patients must sign study specific informed consent prior to study entry.

4.0 STUDY DESIGN

4.1 General Design

- This phase I clinical trial will use a Simon two-stage design. In the first stage, 6 patients will be enrolled, if the patients in the study do not meet the termination criteria then the study will extend to a second stage and we will enroll a maximum of 20 patients. Patients will be treated with skin-directed radiotherapy, using a total prescription dose of 7.5 Gy in five fractions of 1.5 Gy over one week. Neither patient nor insurance will be billed for the radiotherapy procedures. If any subject experiences Grade > 3 toxicities, the study will be stopped and the IRB will be informed immediately so the study can be reevaluated.

- *Interim Analysis.*
  Once the first 6 patients are recruited, the study recruitment will be temporarily suspended and the patients will be followed for 3 months to monitor any toxicity issues. At the end of 3 months follow-up of the 6 patients, the results will be sent to the DSMB for further evaluation. The trial will be terminated if grade 3 or more toxicity is observed in more than 2 patients or at least one showing grade 4 level toxicity. Otherwise, upon approval from the DSMB, the second phase of recruiting will be initiated.

4.2 Study Calendar

	Pre-treatment	Week 1	Week 5*	Week 9*	Week 13*	Week 25 & 49#
History and Physical Examination	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X
Questionnaires: DLQI, PROMIS	X	X	X	X	X	X
Photos	X	X	X	X	X	X
Ultrasound	X		X	X	X	X
Blood Tests: CBC, CRP, ESR	X	-	-	-	X	X
Serum or Urine Pregnancy Test	X	-	-	-	-	-
Skin Biopsy, Discharge Measurement	X	-	-	-	X	X
Radiotherapy	-	XXXXX	-	-	-	-

*+/- 1 week
Optional

4.3 Study Endpoints

The primary endpoint of this study is safety, defined as the absence of any treatment-related Grade ≥3 adverse events during radiotherapy or within 3 months of radiotherapy completion, scored using CTCAE version 4.0.[6] Secondary study endpoints include:

- Quality of Life
    - Improvement in NIH Patient-Reported Outcomes Measurement Information System (PROMIS) measures, including pain interference and physical functioning at 3 months (and optionally at 6 months and 12 months) after treatment[7, 8]
        - A one point change, either positive (improvement) or negative (decline), will be considered to be clinically meaningful[9]

- Inflammation as measured by ultrasound.
    - Noninvasive imaging, such as ultrasound (US), allows for an objective assessment of subclinical disease activity.
    - Anechoic area will be measured in the dermis before and after treatment, as well as other sonographic criteria of HS [10](See Appendix for Sonographic Scoring and Diagnosis of HS)
    - As there are no validated ultrasound criteria to measure clinical improvement, reduction in anechoic areas and sonographic criteria will be calculated. It is estimated that the treatment will induce a 50% reduction in the anechoic area.
    - Anechoic areas and other sonographic criteria will be correlated with PROMIS scores and Hurley Staging.

- Evaluation of cutaneous discharge
    - Swabs will be collected from discharge and sent for fluid count, which will include evaluation of infiltrating leukocytes from the discharge.

- Immunohistochemical Evaluation of HS Tissue Biopsies
    - Tissue biopsies will be collected before and after treatment. Tissue sections will be evaluated by H&E as well as immunohistochemistry for infiltrating leukocytes and other cells, such as T cells, B cells, plasma cells, dendritic cells, macrophages, and keratin. Image J will be used to quantify cells in a standard manner for comparison before and after treatment.

4.4 Radiotherapy

4.4.1Immobilization, Simulation, and Localization

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient will be avoided to prevent uncontrolled movement during treatments. A variety of immobilization systems may be used, including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients' external contours) referenced to the stereotactic coordinate system. Patient immobilization will be reliable enough to ensure that

the gross target volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV) with any significant probability (i.e., < 5%).

4.4.2 Target Volumes and Treatment Planning

While patients with hidradenitis suppurativa may have multiple sites of symptomatic disease, subjects on this protocol will only receive radiotherapy directed at one region. This will generally be the region that is most bothersome to the patient.

Computed tomography will be the primary image platform for targeting and treatment planning. Radio-opaque markers may be placed on the patient at the time of simulation to aid with target delineation. Target volumes will be drawn on simulation CT imaging, using appropriate window levels. The general intent will be to include any grossly abnormal areas, based on clinical examination and CT findings, in the GTV. In selected cases of extensive disease, the GTV may be limited to the most problematic area of disease.

The GTV will be expanded to form a PTV. PTV expansions will generally be 10 mm in all directions but may be between 5 and 15 mm depending on the perceived setup uncertainty in each individual case. Nonuniform expansions are permitted, at the discretion of the treating physicians.

Treatment planning will be performed using standard software packages utilized in the Department of Radiation Oncology. Treatment may be delivered using external beam radiotherapy (EBRT) with either photons or electrons, or with high dose rate (HDR) brachytherapy, at the discretion of the treating physicians. The modality that is expected to provide the most complete coverage of the target volumes while minimizing irradiation of uninvolved tissues will generally be selected. The prescription isodose surface should encompass at least 95% of the PTV, and the minimum PTV dose must not fall below 90% of the prescription dose.

Patients in this study will receive a total radiotherapy dose of **7.5 Gy in five daily fractions of 1.5 Gy**.

4.4.3 Critical Structures

The radiotherapy dose used in this protocol is so low that standard dose limits for internal organs will not be exceeded. Nevertheless, careful planning will be utilized to minimize the exposure of all internal organs to radiotherapy. The “as low as reasonably achievable” (ALARA) principle will be employed.

5.0 STATISTICAL CONSIDERATIONS

A maximum of 20 patients will be enrolled into the study. The accrual rate is expected to be 1-2 patients per month based on the volume of patients with stage 2-3 HS treated within the Montefiore Hidradenitis Suppurativa Treatment Center. An early stopping rule for safety will be implemented as follows based on Simon’s optimal two-stage design. After the first 6 patients have been enrolled, accrual will be temporarily suspended while these patients are monitored for occurrence of treatment-related grade ≥ 3 toxicity for 3 months. At the end of 3

months, results will be sent to the DSMB for further evaluation. The trial will be terminated early if more than 1 patient experiences grade ≥ 3 treatment related toxicity or any patient experiences grade 4 toxicity. Otherwise, upon approval from the DSMB, the second phase of recruiting will be initiated. If 1 or fewer grade ≥ 3 toxicities and 0 grade 4 toxicities are observed, the trial will continue until a total of 20 patients have been evaluated. At the end of the trial, the treatment will be considered safe and worthy of further study if no more than 3 patients experience grade ≥ 3 treatment related toxicity and none experience grade 4 treatment related toxicity.

The target Grade ≥ 3 toxicity rates is no more than 10%, and a toxicity rate greater than 30% is considered clinically unacceptable. The design specified above has the following operating characteristics. The probability of accepting the treatment for further study if the toxicity rate is unacceptably high (> 30%) is at most 10%. In contrast, there is an 80% probability of accepting the treatment for further study if the toxicity rate is less than 10%. In addition, if 0 out of 20 patients experience Grade 4 toxicity at the end of the study, we will be able to conclude with 95% confidence that the true Grade 4 toxicity rate is not greater than 17%.

The proportion of patients who have treatment-related toxicity will be computed, along with exact 95% confidence intervals. Since the study is a phase I trial, we will NOT do any hypothesis testing or models, The study will present the descriptive summary statistics for each outcomes.Biomarker levels measured at different time points and other continuous variables will be summarized by computing means, medians, standard deviations and ranges.

PROMIS scores will be calculated using “PROMIS scoring manuals” found at http://www.healthmeasures.net/promis-scoring-manuals. The formula for scoring is: (Raw Sum of all questions answered X number of items on the short form) / Number of items that were actually answered. Using the provided score conversion table, the pro-rated raw score will be converted into a T-score for each participant.

Interpretation of PROMIS scores will be completed as explained at http://www.healthmeasures.net/score-and-interpret/interpret-scores/promis. T scores for each participant will be compared to calibrated scores of a validated reference population, where a score of 50 is the average for the United States general population with a standard deviation of 10.

6.0 REGULATORY CONSIDERATIONS

6.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to

participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

6.2 Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in this approved protocol. All revisions to the protocol must be provided to the PI. The PI should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

The investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the PI.

7.0 DATA HANDLING AND RECORD KEEPING

7.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.
- In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Confidentiality will be maintained by keeping records in secure areas in the clinic. Patient-identifiable materials, such as laboratory tests and specimens will be kept in secure areas, i.e. Nurse's station and/or freezer kept in lockable storage rooms. Computer files are accessible via password-protected computers that are kept in lockable rooms. All lab personnel that work with patient data or

samples have passed human subject protection courses, and certification of this is on file in the IRB office.

7.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Source documents will be stored as outline in "Confidentiality" in section 7.1 above.

7.3 Case Report Forms

The Montefiore Electronic Medical Record will be used as the primary data collection instrument for the study.

8.0 Data Safety and Monitoring Boards

A Data Safety Monitoring Committee is being convened by Dr. Barrett Katz. They will have the responsibility for ensuring data and safety monitoring along with the PI who is ultimately responsible for the ongoing monitoring and safety of clinical protocols. The primary functions of this DSMC are as follows:

1. To review and ensure protocol compliance with dose escalation in phase I trials
2. To review/assure protocol compliance for all trials that have two-stage phase II designs,
3. Reviewing all internal and external serious adverse reports, investigator alerts, action letters, and other safety reports for trials being performed at AECC-affiliated institutions and;
4. To implement and to determine the adequacy of DSM plans of all approved protocols.

The committee will meet quarterly or more frequently as needed. This committee lead by Dr. Katz will review serious (grade 3 or higher) adverse events from this study. In the event that the DSMC decides that a revision is warranted, the committee will immediately notify the principal investigator of this study. The DSMC has the authority to close trials to patient accrual should the risk to patients be excessive or outweigh the potential benefits of the study. All study

suspensions and closures will be forwarded to the IRB/CCI and study sponsor from the DSMC.

9.0 ADVERSE EVENTS

9.1 Adverse Event Definitions

- AEs are defined as outlined by Albert Einstein College of Medicine's "Reportable Events Policy."[11]

9.2 Adverse Event Reporting

- AEs will be reported to the IRB as outlined by Albert Einstein College of Medicine's "Reportable Events Policy."

10.0 RISKS/BENEFITS

- Anticipated risks (medical, social, psychological, and/or legal)
    - This protocol is considered greater than minimal risk, due to radiation exposure and the skin biopsy procedure.
    - The initial risk of radiotherapy is temporary discomfort and inconvenience during the treatment period.
    - This dose of radiotherapy may cause temporary hair loss at the treatment site for a few months.
    - The risk of acute or chronic radiation-induced dermatitis is thought to be very low with the dose of radiotherapy being employed in this study.
    - A risk of low-intermediate dose radiation is Radiation Induced Cancer (RIC) such as skin cancer (BCC, SCC, melanoma)[2]. In patients treated for benign disease with intermediate dose radiotherapy (Range 3-50 Gy, mean approximately 20Gy), normal tissue side effects are rare or minimal. RIC risk is normally very small in adults (<1%) and decreases with increasing age.
    - Blood draw may cause discomfort, pain, and bruising.
    - Risks from skin biopsy may include temporary pain during the procedure, a small chance of infection, and the possibility that biopsy leaves a small scar.
    - A psychological risk is that the treatment will not have any clinical improvement.
    - Breach of confidentiality is a possible risk if data is lost or stolen.
- How anticipated risks will be minimized
    - To minimize RIC risks- careful body positioning during radiotherapy and shielding of tissues outside of the intended treatment field will be

employed in a customized fashion for each patient. In most cases, treatment with superficial forms of radiotherapy (electrons or surface brachytherapy) will be employed to minimize the volume of tissue irradiatied.
    - Lab tests and skin biopsy will be performed carefully, using standard safety measures.
    - Confidentiality will be maintained as described in Section 7.1.
- Potential benefits
    - Potential benefits include disease improvement and potential remission, along with improved quality of life

11.0 REFERENCES

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2. McKeown, S.R., et al., *Radiotherapy for benign disease; assessing the risk of radiation-induced cancer following exposure to intermediate dose radiation.* Br J Radiol, 2015. **88**(1056): p. 20150405.
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7. Cella, D., et al., *The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008.* J Clin Epidemiol, 2010. **63**(11): p. 1179-94.
8. Cook, K.F., et al., *PROMIS measures of pain, fatigue, negative affect, physical function, and social function demonstrated clinical validity across a range of chronic conditions.* J Clin Epidemiol, 2016. **73**: p. 89-102.
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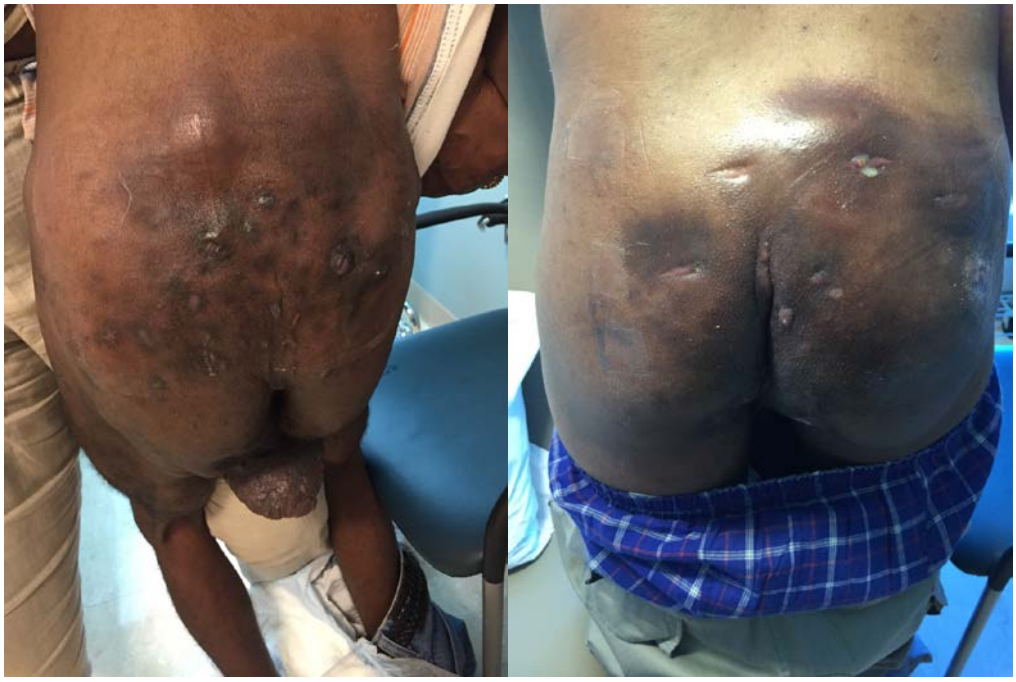
10. Wortsman, X., et al., *Ultrasound in-depth characterization and staging of hidradenitis suppurativa.* Dermatol Surg, 2013. **39**(12): p. 1835-42.
11. *Reportable Events Policy .pdf.*

12.0 APPENDICES

Appendix A: Photos



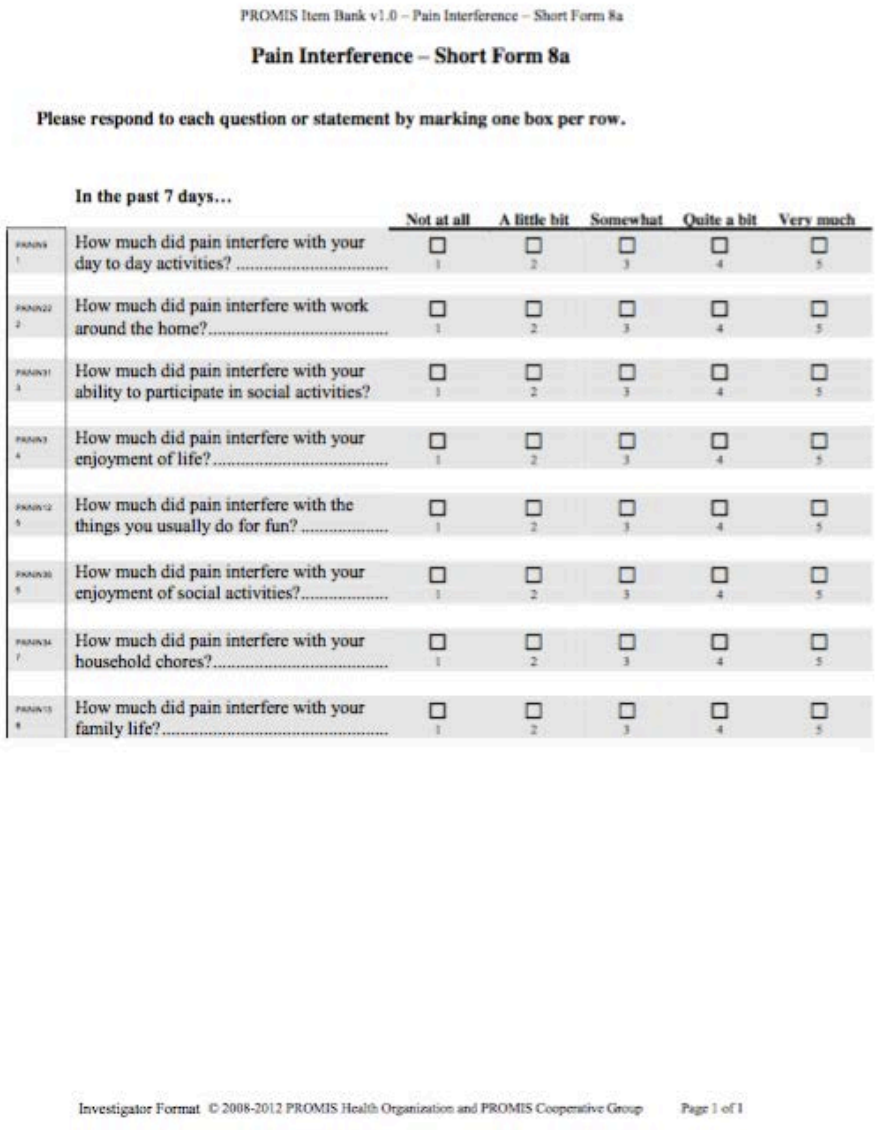
Persistent HS Hurley Stage 3 Lesions on the buttocks of two patients.

Appendix B: Relevant Skin and Subcutaneous Tissue CTCAE Items[6]

Skin and Subcutaneous Tissue Disorders					
	Grade				
Adverse Event	1	2	3	4	5
Bullous dermatitis	Asymptomatic; blisters covering	Blisters covering 10 - 30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Dry Skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL		
Pain of Skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain, limiting self care		
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated		
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA, no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial	-		

		impact			
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact			
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	

Appendix C: PROMIS – Pain Interference



PROMIS Item Bank v1.0 – Pain Interference – Short Form 8a

Pain Interference – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
PAIN65 1	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAIN22 2	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAIN31 3	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAIN3 4	How much did pain interfere with your enjoyment of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAIN12 5	How much did pain interfere with the things you usually do for fun?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAIN30 6	How much did pain interfere with your enjoyment of social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAIN34 7	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAIN13 8	How much did pain interfere with your family life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Appendix D: PROMIS- Physical Functioning

PROMIS SF v1.0 - Physical Function 12a

Physical Function – Short Form

Please respond to each item by marking one box per row.

The following questions ask about your ability to stand and move with and without support. "Support" means using items such as canes, walking sticks walkers and leg braces, or other people.		**Yes**	**No**
PF Screener 2	Can you walk 25 feet on a level surface (with or without support)?	☐	☐
		Yes→ Participant receives all items No→ Participant skips PFC6 to PFB5 and proceeds to PFA55	

		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFC6	Are you able to walk a block on flat ground?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC20	Are you able to walk up and down two steps?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA39	Are you able to run at a fast pace for two miles?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA25	Are you able to do yard work like raking leaves, weeding, or pushing a lawn mower?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFB7	Does your health now limit you in doing strenuous activities such as backpacking, skiing, playing tennis, bicycling or jogging?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB5	Does your health now limit you in hiking a couple of miles on uneven surfaces, including hills?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA55	Are you able to wash and dry your body?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC53	Are you able to get in and out of bed?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA9	Are you able to bend down and pick up clothing from the floor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS SF v1.0 - Physical Function 12a

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA12	Are you able to push open a heavy door?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PF_23	Are you able to reach and get down an object (such as a can of soup) from above your head?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFC35	Does your health now limit you in doing eight hours of physical labor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Appendix E: DLQI

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ❒ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	 Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒

Please check you have answered EVERY question. Thank you.

Appendix F: Ultrasound Criteria for Diagnosis & Staging Hidradenitis Suppurativa [10]

Box 1
Ultrasound criteria for diagnosing hidradenitis suppurativa

1. Widening of the hair follicles
2. Thickening and/or abnormal echogenicity of the dermis
3. Dermal pseudocystic nodules (ie, round or oval-shaped hypoechoic or anechoic nodular structures)
4. Fluid collections (ie, anechoic or hypoechoic fluid deposits in the dermis and/or hypodermis connected to the base of widened hair follicles)
5. Fistulous tracts (ie, anechoic or hypoechoic bandlike structures across skin layers in the dermis and/or hypodermis connected to the base of widened hair follicles)

The presence of ≥3 findings is the sonographic criteria for diagnosing HS.

From Wortsman X, Moreno C, Soto R, et al. Ultrasound in-depth characterization and staging of hidradenitis suppurativa. Dermatol Surg 2013;39:1837; with permission.

Box 2
Sonographic Scoring of Hidradenitis Suppurativa

Stage I Single fluid collection and/or dermal changes[a] affecting a single body segment (either one side or bilateral), without fistulous tracts

Stage II Two to four fluid collections and/or a single fistulous tract with dermal changes, affecting up to two body segments (either one side or bilateral)

Stage III Five or more fluid collections and/or two or more fistulous tracts with dermal changes, and/or involvement of three or more body segments (either one side or bilateral)

[a] Dermal changes include hypoechoic or anechoic pseudocystic nodules, widening of the hair follicles, and/or alterations in the dermal thickness or echogenicity.

From Wortsman X, Moreno C, Soto R, et al. Ultrasound in-depth characterization and staging of hidradenitis suppurativa. Dermatol Surg 2013;39:1837; with permission.