Efficacy and Safety of H.P. Acthar gel for the treatment of refractory cutaneous manifestations of dermatomyositis

Principal Investigator: Anthony Fernandez, MD, PhD

Introduction

Adult and juvenile dermatomyositis (DM) are systemic immune-mediated inflammatory diseases most commonly affecting the skin and musculoskeletal system. Amyopathic dermatomyositis is a subtype of dermatomyositis that affects only the skin and lacks the characteristic muscle involvement. Treatment of these conditions, in particular the cutaneous manifestations, is challenging and currently no universally effective single treatment exists. Many patients have cutaneous manifestations that are refractory to numerous medications (**1, 2**).

Background and Significance

H.P. Acthar gel (adrenocorticotropic hormone gel) received FDA approval for treatment of a variety of diseases, including dermatomyositis, in 1952. Despite this there is a paucity of clinical data concerning the efficacy of H.P. Acthar gel for treating dermatomyositis. Recently a small, retrospective case series describing significant improvement in both cutaneous and musculoskeletal symptoms in 5 patients with refractory dermatomyositis treated with H.P. Acthar gel was reported and has resulted in renewed interest in use of this medication in dermatomyositis patients (**3**). The proposed efficacy of H.P. Acthar gel has been attributed to its unique ability to induce production of endogenous cortisol, corticosterone, aldosterone, and to bind melanocortin receptors on lymphocytes and other cells to modulate immunologic responses. Our hypothesis is that H.P. Acthar gel will be safe and effective for treating the cutaneous manifestations of dermatomyositis in patients with refractory classic dermatomyositis, juvenile dermatomyositis, and amyopathic dermatomyositis.

Study Design

Methods

Prospective, Open-label study

Sample

Our sample will include approximately 10-15 patients with refractory cutaneous symptoms related to either classic dermatomyositis, juvenile dermatomyositis, or amyopathic dermatomyositis. This sample size was chosen to ensure adequate power to detect 50% decreases in the mean total and activity scores of the modified CDASI, and 75% decreases in the mean damage scores. This is not affected by the baseline modified CDASI score (though the % change and coefficient of variation will change based on this level).

Our inclusion/exclusion criteria are as follows:

Inclusion Criteria:

- Patients ≥ 18 years old with refractory cutaneous symptoms related to either classic dermatomyositis (CD), juvenile dermatomyositis (JD), or amyopathic dermatomyositis(AD). Diagnosis will be based on either Bohan and Peter criteria (CD and JD) or Sontheimer's criteria (AD) (**4-7**).

- Patients must have had a skin biopsy with histologic features consistent with dermatomyositis and current cutaneous manifestations consistent with dermatomyositis.

- Although not mandatory, patients with evidence of current or previous active myositis will be eligible for enrollment. Patients will be considered to have refractory disease if cutaneous manifestations exist despite treatment with steroids at least one steroid-sparing systemic treatment commonly found to be useful in patients with dermatomyositis. These may include azathioprine, cyclosporine, mycophenolate mofetil, IVIG, methotrexate, cyclophosphamide, chlorambucil, sirolimus, adalimumab, infliximab and rituximab.

- Use of topical medications and sunscreen currently and in past will be noted but not weighed for assessment of refractory cutaneous disease.

Exclusion criteria:

- Patients with dermatomyositis who have minimal-to-no active cutaneous features (focal involvement with less than 1% total body surface area involved).

- Patients whose cutaneous findings are not consistent with dermatomyositis and/or have previous biopsy results suggestive of an alternative diagnosis
- Patients with inflammatory myositis other than dermatomyositis, such as polymyositis or inclusion body myositis.
- Patients with malignancy-associated dermatomyositis
- Patients with clear features of an overlap myositis
- Patients younger than 18 years old
- Patients with acutely active or chronic infections.
- Patients with uncontrolled diabetes, hypertension, cardiovascular, hepatic, or renal disease
- Pregnant or lactating females.
- Patients with any medical condition that is felt by the primary investigator to place the patient at unreasonable risk for adverse effects during treatment with H.P. Acthar.
- Hypersensitivity to H.P. Acthar, any of its components (allergy to pig-derived proteins)
- Patients with osteoporosis
- Patients who have had surgery within 8 weeks of screening
- Patients with a history of or current gastric ulcers
- Patients taking daily doses of systemic corticosteroids greater than the equivalent of 40mg prednisone.

Research Procedures

1) Upon enrollment patients will undergo a thorough history (including assessing time of diagnosis), review of systems, and a complete physical examination.

2) A detailed examination of the skin and mucous membranes will be performed, noting for presence/absence of the following: scalp erythema and atrophy, heliotrope rash, typical erythema and atrophy of sun-exposed areas on the neck, upper chest and upper back (shawl sign), erythema +/- scaling of the elbows and/or knees (Gottron's sign), gottron's papules, periungual erythema, ragged cuticles, proximal nailfold capillary loops, palmar scaling and hyperkeratosis (mechanic's hands), a rash involving the hips (holster sign), oral ulcerations, cutaneous ulcerations, purpura.

3) Objective cutaneous dermatomyositis scoring by the primary investigator using the **modified Cutaneous Dermatomyositis Disease Area and Severity Index** (CDASI) score and **Abbreviated Cutaneous Assessment Tool** (aCAT) will be performed at each visit (**8-13**).

4) Objective general cutaneous disease scoring by the primary investigator using the **Physician Global Activity** for (a) **overall skin** (b) **skin activity** (c) **skin damage** will be performed at each visit (each assessed using both VAS-0-10 visual analog scale and Likert scale- 0-4 for each) (**9**).

5) Objective scoring tools to be completed by the patient at each visit will include: **Patient Global Assessment (Skin) Score** (0-10 visual analog scale), **Patient Global (Itch) Score** (0-10 visual analog scale), and the **Dermatology Life Quality Index** (validated quality of life assessment) (**8-12**).

6) Photographs of all cutaneous lesions will be performed at baseline and at each follow-up visit.

7) Evaluation for current presence of myositis will be performed using the **Manual Muscle Testing 8 (MMT-8)** scoring tool by the primary investigator, as well as with serologic studies below (**11, 12**).

8) Completion of the **Myositis Disease Activity Assessment Tool** (MDAAT) by the primary investigator to assess disease activity of extramuscular organ systems (**12**).

9) Serologic studies at baseline will include an AM cortisol level, CBC w/ diff, CMP, CK, aldolase, LDH, comprehensive myositis panel (ARUP labs), C3, C4, and HbA1c. The above serologic studies (except for the comprehensive myositis panel) will be repeated at the final visit.

10) Patients may continue their current immunosuppressive treatment regimens at the time of starting H.P. Acthar. If it is felt that patients should taper off of medications they will require a washout period:

- corticosteroids- 2weeks
- methotrexate/azathioprine/mycophenolate/cyclosporine/sirolimus- 4 weeks
- adalimumab/infliximab/IVIG/chlorambucil/cyclophosphamide- 8 weeks
- rituximab- 6 months.

They will be instructed to continue topical medications, moisturizers, and sunscreen based on their current practice, which will be recorded at baseline and during subsequent visits.

11) All patients will receive 80 U (1 mL) of H.P. Acthar gel via subcutaneous injection twice weekly for 24 weeks (approximately 6 months).

12) Patients will require **follow-up visits in person at 1mo (+/- 5 days), 3mo (+/- 5 days), and 6mo (+/- 5 days**) after initiation of the H.P. Acthar, at which time examinations and clinical scoring tool assessments will be repeated.

13) If corticosteroids are continued in patients receiving H.P. Acthar gel they will be tapered at the primary investigator's discretion based on clinical evaluation at follow-up appointments.

14) H.P. Acthar will be discontinued in any given patient at the primary investigator's discretion if deemed necessary for the patient's overall health and well-being at any point during the study.

Serologic Studies	**Baseline**	**6mo**
CBC w/ diff	X	X
CMP	X	X
AM cortisol level	X	X
Creatine Kinase	X	X
Aldolase	X	X
LDH	X	X
C3	X	X
C4	X	X
HbA1c	X	X
Comprehensive myositis panel (ARUP labs)	X	

Length of above tests is that of a typical phlebotomy blood draw.

Clinical Assessments	Baseline	1 mo +/- 5d	3mo +/- 5d	6mo +/- 5d
Modified CDASI	X	X	X	X
aCAT	X	X	X	X
PGA (VAS scoring)	X	X	X	X
PGA (Likert scoring)	X	X	X	X
Global Patient Score (by pt)	X	X	X	X
Global Itch Score (by pt)	X	X	X	X
DLQI	X	X	X	X
MMT-8	X	X	X	X
MDAAT	X	X	X	X

Length of each test/procedure:
Modified CDASI: 5 min
aCAT: 5-10 min
PGA (VAS scoring): < 1 minute
PGA (Likert scoring): < 1 minute
Global Patient Score: < 1 min
Global Itch Score: < 1 min
DLQI: 5 min
MMT-8: 5 min
MDAAT: 15-30 min (depending on severity of disease)

**see references above associated with each individual test for details concerning validity and reliability

Study End Points

1. **Primary end-points**:

   Statistically significant improvement in cutaneous manifestations of dermatomyositis based on changes in **modified CDASI** score, **CAT** score, and **Physican's Global Assessment (overall, activity, damage)** scores at end of study vs. baseline.

2. **Secondary end-points**:

a) Statistically significant change in **MDAAT** Score and **MMT-8** score

b) Statistically significant change in **Global Patient Score**, **Global Itch Score**, and/or the **Dermatology Life Quality Index scores** between baseline and 6 months.

c) Safety and tolerability of H.P. Acthar gel based on frequency and types of adverse effects.

d) median/mean change in glucocorticoid dose from initiation to completion of study.

e) median/mean change in dose of systemic steroid-sparing immunosuppressive agents from initiation to completion of study.

f) median/mean change in HbA1c

Data Analysis

Access to Data will be limited to the P.I., research coordinator, and research nurse. Approval from the IRB to allow access to data will be sought via an IRB amendment application if any additional research personnel are added to the study.

Confidentiality of patients will be protected by assigning numbers to patients and avoiding use of PHI. Results of the study will be reported in aggregate and anonymously

Statistical analyses will be conducted by the section of Biostatistics in the Quantitative Health Sciences department at the Cleveland Clinic using the methods described below:

Statistical Methods

Patient and disease characteristics will be summarized using means, standard deviations, medians and other percentiles of interest for continuous measures and frequencies and percentages for categorical factors. Changes in scoring tool measures from baseline to six months will be calculated and compared using paired t-tests. If necessary, transformations of the data will be performed prior to analysis to meet distributional assumptions. If proper transformations cannot be found, then nonparametric Wilcoxon

signed rank tests will be performed. To assess trends scores over time, linear mixed effect models will be fit and estimates of the average change per month will be calculated. Analysis will be performed using SAS software (The SAS Institute; Cary, NC). A significance level of 0.05 will be assumed for all tests.

Sample Size Considerations

The primary assessment tool will be the CDASI. Scores for the modified CDASI range from 0 to 100 for activity, 0 to 32 for damage, and 0 to132 for the total score. In the paper by Yassaee (2010), investigators found a mean (SD) activity score of 17.83 (10.14), a mean (SD) damage score of 2.27 (2.73), and a mean (SD) total score of 20.10 (10.25). Given the apparent skewed distributions for these scores, a log-normal distribution for the scores was assumed. In these distributions, a coefficient of variation (CV = SD/Mean) of 0.6 appears appropriate for activity and total scores, while a CV of 1.25 was assumed for comparisons of total score. The required sample size for each scale to achieve 80% power to detect 25%, 50%, and 75% decreases in CDASI scores, based on the assumptions above, and assuming use of two-sided paired t-tests on log-transformed values. These calculations further assume that a small positive correlation (r=0.25) between baseline and 6-month scores within person, and use of a 0.05 significance level. Note that since Activity and Total CDASI scores assume the same CV, sample size requirements are identical. Under these assumptions, 10 patients are need to detect a 50% decrease in the mean CDASI activity score or CDASI total score with 80% power. This sample size would allow adequate power to detect decreases of at least 70% in the mean damage score. Eight patients would be required to detect a 75% decrease in the mean damage score.

Adverse Events and Data Monitoring Committee(DMC)

- Patients will be instructed to call immediately with any adverse events. All adverse events will be recorded during the administration of H.P. Acthar. Any serious adverse events will be reported immediately to the appropriate contact person at Questcor, as well as to the IRB in accordance with their policy.

    - A DMC will not be used because H.P. Acthar is an approved drug for treatment of dermatomyositis.

- A DRC is not planned given that Acthar is currently used in clinical medicine to treat multiple sclerosis and has a well-known adverse effect profile with low risk of significant adverse events.

- An interim analysis is not planned.

Consent

Consent will be obtained in a clinical setting by a member of the study team at the time of planned enrollment. Children under the age of 18 and non-English speaking subjects will not be enrolled in this clinical study.

References

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