Acthar in Dermatomyositis and Polymyositis Treatment Registry: An Interim Analysis

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INTRODUCTION

Approved Treatments

- Several different therapeutic agents are used to treat patients with dermatomyositis (DM) and polymyositis (PM)
- However, only corticosteroids (CS) and adrenocorticotropic hormone (ACTH) injection (H.P. Acthar® Gel, repository corticotropin injection; Questcor Pharmaceuticals, Inc., Hayward, CA) are FDA-approved for these diseases
  - Acthar Gel is specifically approved for an exacerbation or as maintenance therapy in selected cases of systemic DM/PM[1]

Corticosteroids

- Initial short-term, high-dose CS have been the mainstay of therapy for DM/PM
  - Dosing is typically 1 mg/kg/d for at least 4-6 weeks, followed by tapering, based on clinical response[2]
  - Long-term follow-up of corticosteroid-treated patients shows a high proportion of patients are unable to achieve a return to previous normal activities[3]
    - Functional disability associated with long-term CS therapy occurred in 48% (15/31) of patients, including steroid-induced myopathy, osteoporotic vertebral fracture, and avascular necrosis of the femoral head[3]
    - In our practice we also see long-term CS therapy associated with weight gain, diabetes exacerbation, mood changes, and gastrointestinal disturbances

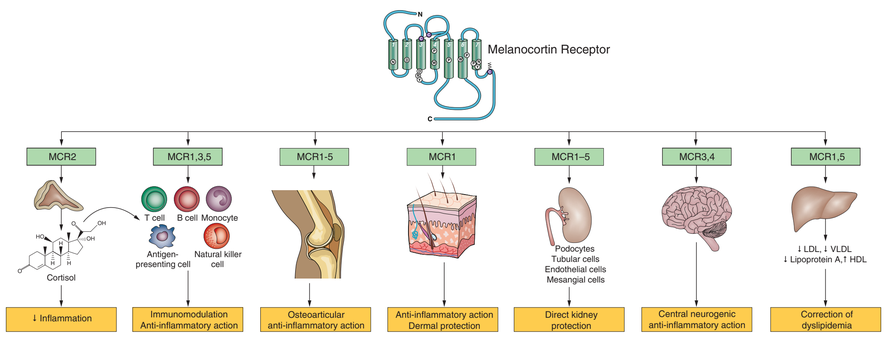
Acthar Gel

- A case series reported on 5 Acthar Gel-treated myositis patients (3 DM, 2 PM)[4] who had failed or were unable to tolerate previous therapy with CS, intravenous immunoglobulin (IVIG), or immunosuppressive therapy
  - Patients treated with Acthar Gel 80 IU SC twice weekly (4 patients) or once weekly (1 patient) showed improvement in muscle strength, as reflected by manual muscle testing (MMT) and functional studies
  - Three patients with impaired ambulation regained independent ambulation
  - All patients tolerated treatment for up to 3 months with no significant adverse events[4]

Acthar Gel Potential Mechanisms of Action

- Acthar Gel is a long-acting formulation of full-sequence ACTH ($ACTH_{1-39}$) that includes pro-opiomelanocortin peptides[5]
- In addition to known steroidogenic effects, ACTH also exhibits nonsteroidogenic effects through a system of melanocortin receptors (MCR) widely distributed throughout the immune system, skeletal muscle, endothelial cells, and other tissues **(Figure 1)**[5,6]
- ACTH is derived from pro-opiomelanocortin (POMC), a protein synthesized in the pituitary gland and cleaved into the melanocyte-stimulating hormones (MSH) β-MSH, γ-MSH, and ACTH, which in turn is cleaved into α-MSH[7]
- Melanocortin peptides and receptors play a role in steroidogenesis and activation of anti-inflammatory pathways[6]
- Acthar Gel is believed to have direct, steroid-independent, anti-inflammatory properties via melanocortin receptors 1, 3, 4 and 5, and indirect effects through the stimulation of cortisol release via melanocortin receptor 2[5]
- Steroids do not bind to any of the 5 melanocortin receptors

Figure 1. Potential Anti-Inflammatory Mechanism of Action of Melanocortins in the Treatment of DM/PM



HDL = high-density lipoprotein; LDL = low-density lipoprotein; MCR = melanocortin receptor; VLDL = very-low-density lipoprotein.

- Effects of the MC pathway on skeletal muscle are not well characterized[8]
  - The MC pathway is involved in regulation of energy homeostasis in skeletal muscle, which involves cyclic adenosine monophosphate (cAMP)-mediated AMP kinase activity that has been shown to increase glucose transport and fatty acid oxidation in striated muscle[8]
  - Experimental evidence shows that α-MSH increases fatty acid oxidation in skeletal muscle, in which MCR5 plays a major role[8]
  - The MC pathway may also play a role in somatic neuromuscular growth and regrowth and may act on the neuromuscular system to protect muscles from damage[9,10]

OBJECTIVES

- This study was undertaken to examine patient demographics, dosing, side effects, and efficacy of Acthar Gel in patients with DM/PM refractory to CS therapy

METHODS

Study Design

- Observational case study of DM/PM patients with a myositis treatment history refractory to CS and/or immunosuppressive therapy
  - Patients were enrolled in the ADAPT (Acthar in Dermatomyositis and Polymyositis Treatment) registry (Clinical Trials.gov NCT01637064)
- Diagnostic criteria for DM and PM were based on characteristic muscle biopsy results in all patients
- Demographics, laboratory data, strength measurements, and overall impression of change were collected at baseline and after 3, 6, 9, and 12 months of treatment when available

Patients

- Male or female patients 18-85 years old with clinical or pathologic diagnosis of DM or PM
  - Capable of providing informed consent
- Patients excluded
  - History of scleroderma, osteoporosis, systemic fungal infections, or ocular herpes simplex
  - Recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, or sensitivity to proteins of porcine origin
  - Any other comorbid condition that would make completion of the trial unlikely
  - Pregnant or breast-feeding, or, for women of childbearing age, unable/unwilling to use appropriate birth control

Study Drug

- The recommended starting Acthar Gel dose was 80 IU subcutaneously twice weekly
- Physicians started and adjusted dosing at their own discretion

Statistical Analyses

- Statistics are based on frequency distribution for all categorical variables and on mean (standard deviation), median, and range for continuous variables
- Exploratory analysis of categorical variables utilized chi-square statistic with continuity correction or Fisher's exact, as appropriate
- Categorical response to Acthar Gel: Yes (responders) or No (no response or no change) based on MMT and/or as determined by attending physician based on de-identified data from patient charts
- Nonparametric analysis of creatine phosphokinase (CPK) utilizing the Mann-Whitney U test
- Independent samples t-test for association of Acthar Gel with age and treatment duration
- All tests were 2-sided and level of statistical significance was <0.05

RESULTS

Patient Demographics

- A total of 28 patients were screened
- 24 patients were diagnosed with DM or PM (7 DM, 17 PM) and are included in this analysis
  - Two patients did not have myositis and 2 patients had inclusion-body myositis; these 4 patients were excluded from the analysis
- Patients had DM/PM refractory to previous therapy, having received an average of 3.4 medications over an average of 3.2 years before beginning treatment with Acthar Gel
- Most patients were female and ≥50 years of age; 70.8% had PM and 62.5% had evidence of disease activity at baseline (**Table 1**)

Table 1. Demographic and Clinical Characteristics at Baseline (N=24)

Characteristic	n (%)
Dermatomyositis	7 (29.2)
Polymyositis	17 (70.8)
Sex	
Female	18 (75)
Male	6 (25)
Age (years)	
Mean (SD)	55.4 (15.42)
Median	58.5
Range	26-77
<50	7 (29.2)
≥50	17 (70.8)
Autoantibodies present?	
No	11 (45.8)
Myositis-specific	6 (25)
Other (SS-A, ANA)	7 (29.2)
CPK (IU/L)	
Mean (SD)	423.5 (419.3)
Median	295.0
Range	53-1764
<200	11 (45.8)
≥200	13 (54.2)
Disease activity*	
Yes	15 (62.5)
No	9 (37.5)
Rash	
Yes	4 (16.7)
No	20 (83.3)

*Disease activity defined as elevated CPK or decline in MMT within 90 days before initiation of Acthar Gel.
ANA = antinuclear antibodies; CPK = creatine phosphokinase; SS-A = Sjögren's-syndrome-related antigen A.

Treatment & Concomitant Medications

- Acthar Gel was administered 80 IU twice weekly to 22 patients, 40 IU twice weekly to 1 patient, and 80 IU once weekly to 1 patient
- Median duration of treatment was 6 months (range 2-18 months)
- All but 2 patients (22/24) were concomitantly treated with other medications for myositis during treatment
  - 12 patients were receiving prednisone, 7 were receiving IVIG, and 16 were receiving immunosuppressive therapy (methotrexate, n=9; mycophenolate mofetil [MMF], n=5; azathioprine, n=1; cyclosporine, n=1)

Efficacy

- **Overall, 14/24 patients (58.3%; 57% of DM, 59% of PM) responded to treatment with Acthar Gel**
- Nine of the study variables assessed showed a significant association of response to treatment (**Table 2**)
- Variables not significantly associated with treatment response included: DM/PM diagnosis, sex, age, presence of autoantibodies at baseline, extramuscular symptoms (rash) at baseline, and administration of concomitant medications other than MMF (prednisone, methotrexate, IVIG, or any immunosuppressive)
- All 5 patients treated concurrently with MMF responded to combination therapy with Acthar Gel (100%) vs the 9 other patients treated with any other immunosuppressive medication (47.4%; *P*=0.053)
- Response to Acthar Gel occurred more frequently in patients with disease activity at baseline (*P*<0.0001)
- Longer duration of therapy correlated with a larger percent change in CPK levels from baseline (Spearman's rank-order correlation = −0.503; *P*=0.0123)
- Treatment duration also was a significant factor related to treatment response; responders were treated for a mean duration of 9.7 months and nonresponders were treated for a mean of 3.5 months (*P*<0.0001)

Table 2. Association of Study Variables With Response to Acthar Gel (N=24)

Study Variable	Response to Acthar? Yes	Response to Acthar? No	*P*-value
CPK at baseline, n (%)			
<200 IU/L	2 (18.2)	9 (81.8)	NS
≥200 IU/L	12 (92.3)	1 (7.7)	<0.001
CPK (IU/L) at baseline, median (range)	616 (84-1764)	105 (53-460)	0.0047
CPK at follow-up, n (%)			
<200 IU/L	5 (35.7)	9 (64.3)	NS
≥200 IU/L	9 (90.1)	1 (10.0)	0.0129
CPK (IU/L) at follow-up, median (range)	338 (34-870)	110 (34-420)	0.0461
Reduction of CPK from baseline ≥30%, n (%)			
Yes	8 (88.9)	1 (11.1)	0.0333
No	6 (40)	9 (60)	NS
% change in CPK from baseline, median (range)	-32.9 (-89.0, 2.4)	-9.0 (-35.9, 37.5)	0.0205
Disease activity at baseline*, n (%)			
Yes	13 (86.7)	2 (13.3)	<0.001
No	1 (11.1)	8 (88.9)	NS
Treatment duration, n (%)			
≤6 months	4 (28.6)	10 (71.4)	NS
>6 months	10 (100)	0 (0.0)	<0.001
Months of treatment, mean (SD)	9.7 (4.0)	3.5 (1.4)	<0.0001

*Disease activity defined as elevated CPK or decline in MMT within 90 days before initiation of Acthar Gel.
CPK = creatine phosphokinase; NS = variable not significantly associated with response to Acthar.

Safety

- Treatment with Acthar Gel was well tolerated (**Table 3**)
- 10 patients (41.7%) reported adverse events that were mild-to-moderate in severity; none discontinued treatment

Table 3. Adverse Events (N=24)

Adverse Event	n (%)
Any AE	10 (41.7)
Worsening of diabetes	3 (12.5)
Lower extremity edema	2 (8.3)
Edema	1 (4.2)
Gastric reflux	1 (4.2)
Headache	1 (4.2)
Increased blood pressure	1 (4.2)
Nausea	1 (4.2)
Vertigo	1 (4.2)
Weight gain	1 (4.2)

CONCLUSIONS

- 14 of 24 patients (58.3%) refractory to CS therapy responded to treatment with Acthar Gel administered at 80 IU twice weekly
- Acthar Gel was well tolerated in myositis patients during a treatment period of up to 18 months; adverse events were mild-to-moderate in severity
- This interim analysis suggests that clinical and enzymatic evidence of disease activity might be important considerations for predicting response to treatment with Acthar Gel
- The registry is designed to collect data in 100 patients, including prospectively treated patients; treatment of a larger population for a longer duration will provide further insight into potential factors for predicting both response and durability of response
- A prospective controlled study is needed to more clearly assess the effectiveness of treatment

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