Acthar in Dermatomyositis and Polymyositis Treatment Registry: An Interim Analysis

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 select cases of systemic DM/PM.

Corticosteroids
- Initial short-term, high-dose CS have been the mainstream of therapy for DM/PM - Dosing is usually 1-2 mg/kg for at least 4-6 weeks, followed by tapering, based on clinical response
- Long-term follow-up of corticosteroid-treated patients shows a high proportion of patients who die or require a wheelchair.
- Functional disability associated with long-term CS therapy occurred in 48% (35/73) of patients, including steroid-induced myopathy, osteoporotic vertebral fracture, and avascular necrosis of the femoral head.
- 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) who had previously failed to tolerate previous therapy with CS, intravenous immunoglobulin (IVIG), or immunosuppressive therapies.
- Patients treated with Acthar Gel 80 IU/sqtwc and 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.

Acthar Gel Potential Mechanisms of Action
- Acthar Gel is a long-acting formulation of full-sequence ACTH (ACTH-41) that includes pro-opiomelanocortin peptides.
- In addition to CS-like corticosteroid effects, ACTH also exhibits noncorticosteroid effects through a system of melanocortin receptors (MCR) widely distributed throughout the immune system, skeletal muscle, endothelial cells, and other tissues

- Effects of the MC pathway on skeletal muscle are not well characterized:
  - 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.
  - Experimental evidence shows that MSH increases fatty acid oxidation in skeletal muscle, in which MCR5 plays a major role.
  - The MC pathway may also play a role in somatic muscular growth and regeneration and may act as the neuropeptide system to protect muscles from damage.

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) Clinical Trial (Trial ID NCT01313706A).
- Diagnostic criteria for DM and PM were based on characteristic muscle biopsy results in all patients.
- Diagnostic, 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, osteosclerosis, systemic fungal infections, or bacterial or viral infections.
  - Recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, or sensitivity to propofol injection.
- Any other comorbid condition that would make completion of the trial unlikely.
- Pregnant or breastfeeding, 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.
- Exploration of categorical variables utilized chi-square statistic with continuity correction or Fisher's exact, as appropriate.
- Categorical response to Acthar Gel was defined as 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 change in intact pro-opiomelanocortin (MC) peptide levels was done using Wilcoxon rank-sum test.

RESULTS
Patient Demographics
- A total of 28 patients were screened.
- 24 patients were diagnosed with DM/PM (7 DM, 17 PM) and are included in this analysis.
- Two patients did not have myositis and 2 patients were lost to follow-up.

Treatment Parameters
- Only 1 patient was receiving IVIG, and 16 were receiving other immunosuppressive therapy (methotrexate, azathioprine, cyclosporine, mycophenolate mofetil).

Adverse Events
- Any adverse event was recorded in 59% of patients.
- Nausea was the most frequently reported adverse event (88.9% of patients).
- Adverse event data were collected at baseline and after 3, 6, 9, and 12 months of treatment.

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Yes n (%)</th>
<th>No n (%)</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>10 (41.7)</td>
<td>14 (58.3)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median 50</td>
<td>Range 35-74</td>
</tr>
<tr>
<td>Race</td>
<td>16 (66.7)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Autoantibodies present</td>
<td>Yes 17 (70.8)</td>
<td>No 7 (29.2)</td>
</tr>
<tr>
<td>Disease activity at baseline</td>
<td>Yes 7 (29.2)</td>
<td>No 17 (70.8)</td>
</tr>
<tr>
<td>Rash</td>
<td>Yes 9 (37.5)</td>
<td>No 15 (62.5)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Yes 4 (16.7)</td>
<td>No 20 (83.3)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>15 (62.5)</td>
<td>0.0047</td>
</tr>
<tr>
<td>Weight gain</td>
<td>10 (41.7)</td>
<td>0.0018</td>
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CONCLUSIONS
- 14 of 24 patients (58.3%) refractory to CS therapy responded to treatment with Acthar Gel, with 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 non-responders, to further assess the effectiveness of Acthar Gel in a larger population.

REFERENCES
5. Getting SJ. Pharm Ther 2006;111;1-25.

Table 3. Adverse Events (N=24)

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Table 4. Disease Activity at Baseline (n=24)

<table>
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<th>Disease Activity</th>
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</tr>
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