A multicenter study assessing the efficacy and safety of Acthar in patients with rheumatoid arthritis: preliminary interim data from the open-label treatment period

Roy Fleischmann, Daniel E. Furst, Richard Brasington, Erin Connolly-Strong, Jingyu Liu, Matthew E. Barton

Presented at the American College of Rheumatology and Association of Rheumatology Health Professionals (ACR/ARHP) 2018
Chicago, Illinois • October 19–24, 2018

INDICATION

H.P. Acthar® Gel (repository corticotropin injection) is an adrenocorticotropic hormone (ACTH) analogue used for adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in rheumatoid arthritis (selected cases may require low-dose maintenance therapy).

SELECT IMPORTANT SAFETY INFORMATION

Contraindications

• Acthar should never be administered intravenously
• Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar
• Acthar is contraindicated where congenital infections are suspected in infants
• Acthar is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origins

DISCLOSURE STATEMENT

Funding to support the preparation of this content was provided by Mallinckrodt Pharmaceuticals.

STUDY LIMITATIONS

• Data reported here are from a pre-planned 50% data review of the open-label phase of an ongoing study. This is an interim analysis of 116 patients in a larger 2-part study with no comparator arm in Part 1. The trial is now fully enrolled with 232 patients. Because this is an interim report, significance tests were not conducted, and therefore $P$ values are not reported. Full results of this study may vary from the interim analysis$^{1,2}$
• Sample bias may exist since this was an open-label phase of an ongoing study, and patients were aware that they were receiving Acthar$^1$
• Examiner bias may also exist as the patient had to reach low disease activity in order to enter the second phase of the study$^1$
• The results cannot be solely attributed to Acthar since patients were on different medications at the start of the trial and no washout periods were undertaken. Acthar has not been formally studied in combination with other treatments$^1$

Please see additional Important Safety Information throughout and on back cover.
Please see accompanying full Prescribing Information.
ACTHAR WAS ASSESSED IN AN OPEN-LABEL PHASE OF AN ONGOING STUDY OF 116 PATIENTS

OBJECTIVE
- To evaluate the efficacy and safety of Acthar in patients with persistently active rheumatoid arthritis (RA) despite receiving 1 to 2 DMARDs and corticosteroids

STUDY DESIGN
Ongoing Multicenter, 2-Part Study

Part 1: 12-week open-label treatment phase
- Patients who did not achieve LDA at Week 12 or who experienced an RA flare were discontinued from the study
- Patients received either Acthar 80 U SC twice a week or placebo (1 mL) SC twice a week
- Patients received Acthar 80 U SC twice a week for the entire 12-week period

Part 2: Double-blind randomized phase
- Examiner bias may also exist as the patient had to reach low disease activity in order to enter the second phase of the study
- Sample bias may exist since this was an open-label phase of an ongoing study, and patients were aware that they were receiving Acthar

INTERIM STUDY ASSESSMENTS
Efficacy was evaluated at baseline and Weeks 4, 8, and 12
- Primary endpoint: Proportion of patients who achieved LDA at Week 12 defined as DAS28-ESR ≤3.2
- Secondary endpoints:
  - DAS28-ESR scores over time, including:
    - Tender and swollen joint count
    - General health VAS
    - Erythrocyte Sedimentation Rate (ESR)
  - ACR response criteria with improvements of 20%, 50%, or 70%
  - CDAS change from baseline over time
  - Patient-Reported Outcomes (PROs) change from baseline over time
    - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
    - Health Assessment Questionnaire-Disability Index (HAQ-DI)
    - Work Productivity and Activity Impairment (WPAI) questionnaire
    - Patient assessment of pain (ACR criteria)
    - Patient global assessment of disease activity (ACR criteria)
- AEs were monitored and recorded throughout the study

STUDY LIMITATIONS
- Data reported here are from a pre-planned 50% data review of the open-label phase of an ongoing study. This is an interim analysis of 116 patients in a larger 2-part study with no comparator arm in Part 1. The trial is now fully enrolled with 232 patients. Because this is an interim report, significance tests were not conducted, and therefore P values are not reported. Full results of this study may vary from the interim analysis
- Sample bias may exist since this was an open-label phase of an ongoing study, and patients were aware that they were receiving Acthar
- Examiner bias may also exist as the patient had to reach low disease activity in order to enter the second phase of the study
- The results cannot be solely attributed to Acthar since patients were on different medications at the start of the trial and no washout periods were undertaken. Acthar has not been formally studied in combination with other treatments

SELECT IMPORTANT SAFETY INFORMATION
Warnings and Precautions
- The adverse effects of Acthar are related primarily to its steroidogenic effects
- Acthar may increase susceptibility to new infection or reactivation of latent infections
**ACTHAR IN AN OPEN-LABEL PHASE OF AN ONGOING STUDY: PATIENT OVERVIEW**

### Key Inclusion Criteria

- Age 218 years
- Meet the criteria for RA as defined by the 2010 ACR/EULAR classification
- Have persistently active RA defined as a DAS28-ESR >3.2 despite treatment with required biologic/nonbiologic DMARD(s) and a corticosteroid
- Currently taking a corticosteroid in the 12 weeks prior to the screening visit and on a stable dose of 5–10 mg of prednisone (or prednisone equivalent) for 4 weeks prior to the screening visit
- Have been on at least 1 of the following for at least 12 weeks prior to the screening visit and must remain on same doses throughout the study:
  - Methotrexate ≤20 mg per week and 1 additional allowed biologic or nonbiologic DMARD
  - One allowed biologic DMARD

### Key Exclusion Criteria

- Had taken any investigational treatment for RA or biologic investigational agent within 24 weeks or any nonbiologic investigational agent within 6 weeks prior to the first dose of study drug
- History of use of Acthar for treatment of RA or sensitivity to Acthar
- Currently has other rheumatic autoimmune or inflammatory joint disease
- Used intra-articular corticosteroids within 14 days prior to screening visit
- Used B-cell-mediated therapies (e.g., rituximab) within 24 weeks prior to screening visit
- Have known contraindications to Acthar

### SELECT IMPORTANT SAFETY INFORMATION

**Warnings and Precautions (cont’d)**

- Suppression of the hypothalamic-pituitary-axis (HPA) may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Adrenal insufficiency may be minimized by tapering of the dose when discontinuing treatment. During recovery of the adrenal gland patients should be protected from the stress (e.g., trauma or surgery) by the use of corticosteroids. Monitor patients for effects of HPA suppression after stopping treatment.
- Cushing’s syndrome may occur during therapy but generally resolves after therapy is stopped. Monitor patients for signs and symptoms.
- Acthar can cause elevation of blood pressure, salt and water retention, and hypokalemia. Blood pressure, sodium and potassium levels may need to be monitored.
- Acthar often acts by masking symptoms of other diseases/disorders. Monitor patients carefully during and for a period following discontinuation of therapy.

### DMARDs Permitted During the Study

<table>
<thead>
<tr>
<th>Nonbiologic DMARDs</th>
<th>Biologic DMARDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>Infliximab</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Adalimumab</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Etanercept</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Certolizumab</td>
</tr>
<tr>
<td></td>
<td>Golimumab</td>
</tr>
<tr>
<td></td>
<td>Abatacept</td>
</tr>
<tr>
<td></td>
<td>Tofacitinib*</td>
</tr>
</tbody>
</table>

### PATIENT DEMOGRAPHICS AND CHARACTERISTICS

- As of May 10, 2018, 100 patients out of the 116 patients enrolled in the study had completed the 12-week open-label treatment phase (Part 1).
- 14 patients had discontinued due to:
  - Withdrawal by the patient (n=9)
  - Met withdrawal criteria (n=1)
  - Other reasons (n=4)
- 2 patients had not completed Part 1 of the study

### Patients Who Completed the 12-Week Open-Label Treatment Phase (n=100)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>54.2 (11.53)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>84 (84.0)</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>72.0 (14.51)</td>
</tr>
<tr>
<td>DAS28-ESR score, mean (SD)</td>
<td>6.3 (1.04)</td>
</tr>
<tr>
<td>Tender joint count, mean (SD)</td>
<td>14.8 (7.60)</td>
</tr>
<tr>
<td>Swollen joint count, mean (SD)</td>
<td>11.1 (5.31)</td>
</tr>
<tr>
<td>CDAI, mean (SD)</td>
<td>38.4 (12.93)</td>
</tr>
</tbody>
</table>

EULAR=European League Against Rheumatism; SD=standard deviation.
*Targeted synthetic DMARD (tsDMARD).
SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont’d)

• Acthar can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Monitor for signs of bleeding

• Acthar may be associated with central nervous system effects ranging from euphoria, insomnia, irritability, mood swings, personality changes, and severe depression, and psychosis. Existing conditions may be aggravated

• Patients with comorbid disease may have that disease worsened. Caution should be used when prescribing Acthar in patients with diabetes and myasthenia gravis

Please see additional Important Safety Information throughout and on back cover. Please see accompanying full Prescribing Information.
**SELECT IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions (cont’d)**

- Prolonged use of Acthar may produce cataracts, glaucoma and secondary ocular infections. Monitor for signs and symptoms.
- Acthar is immunogenic and prolonged administration of Acthar may increase the risk of hypersensitivity reactions. Neutralizing antibodies with chronic administration may lead to loss of endogenous ACTH activity.

Please see additional Important Safety Information throughout and on back cover. Please see accompanying full Prescribing Information.

---

**INTERIM DATA SUMMARY**

- The 12-week open-label phase of this ongoing trial in patients with persistently active RA after being treated previously with corticosteroids and biologic/nonbiologic DMARDs showed:
  - A decrease in DAS28-ESR scores in patients treated with Acthar was observed over time through Week 12
  - 61% of Acthar-treated patients had achieved LDA (DAS28-ESR ≤3.2) at Week 12
  - ACR 20/50/70 response was achieved by 85%, 66%, and 34% of patients, respectively, assessed at Week 12
  - Mean HAQ-DI scores decreased over the study period through Week 12

- AEIs observed were consistent with those in previous Acthar trials, and no new safety signals were reported:
  - Most common AEs were infections, infestations, general disorders, administration site conditions, and headaches
  - Two SAEs were reported by 1 patient each:
    - One patient had chest pain radiating to the left arm, shortness of breath, dizziness, and weakness that the investigator deemed as unrelated to Acthar; the SAE resolved, and the patient remained in the study
    - Another patient reported an SAE of pneumonia that the investigator assessed as “possibly related” to Acthar; the patient withdrew from the study

**STUDY LIMITATIONS**

- Data reported here are from a pre-planned 50% data review of the open-label phase of an ongoing study. This is an interim analysis of 116 patients in a larger 2-part study with no comparator arm in Part 1. The trial is now fully enrolled with 23Z patients. Because this is an interim report, significance tests were not conducted, and therefore P values are not reported. Full results of this study may vary from the interim analysis.
- Sample bias may exist since this was an open-label phase of an ongoing study, and patients were aware that they were receiving Acthar.
- Examiner bias may also exist as the patient had to reach low disease activity in order to enter the second phase of the study.
- The results cannot be solely attributed to Acthar since patients were on different medications at the start of the trial and no washout periods were undertaken. Acthar has not been formally studied in combination with other treatments.

---

**INTERIM RESULTS—KEY SECONDARY ENDPOINTS**

**ACR 20/50/70 Response Was Achieved by 85%, 66%, and 34% of Patients, Respectively, Assessed at Week 12**

Mean PRO Scores Improved From Week 4 Through Week 12 During Treatment With Acthar

<table>
<thead>
<tr>
<th>PRO Assessment</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Minimum Clinically Important Difference (MCID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional Assessment of Chronic Illness Therapy Fatigue (PACIT-F)</td>
<td>22.6 (8.69)</td>
<td>17.2 (8.08)</td>
<td>16.1 (8.24)</td>
<td>13.8 (7.36)</td>
<td>3–4*</td>
</tr>
<tr>
<td>Health Assessment Questionnaire-Disability Index (HAQ-DI)</td>
<td>1.6 (0.54)</td>
<td>1.1 (0.64)</td>
<td>0.9 (0.66)</td>
<td>0.7 (0.60)</td>
<td>0.22*</td>
</tr>
</tbody>
</table>

**Work Productivity and Activity Impairment (WPAI)**

- Percent time worked due to RA: 17.1 (22.77) 16.6 (25.55) 13.1 (16.88) 8.8 (13.76) ND
- Percent impairment while working due to RA: 46.2 (26.39) 30.7 (25.95) 25.6 (18.88) 20.4 (20.09) ND
- Percent overall work impairment due to RA: 52.8 (27.55) 39.0 (30.68) 34.6 (23.71) 26.6 (23.62) ND
- Percent activity impairment due to RA: 62.0 (22.96) 45.9 (26.75) 36.1 (22.69) 28.2 (23.88) ND
- Patient assessment of pain: 64.8 (19.55) 47.0 (22.94) 34.8 (21.00) 24.4 (21.55) 11†
- Patient global assessment of disease activity: 60.8 (19.58) 45.9 (19.93) 35.3 (21.66) 24.4 (20.47) 15% (absolute)/20% (relative improvement)††

---

**REFERENCES**

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Acthar should never be administered intravenously
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar
- Acthar is contraindicated where congenital infections are suspected in infants
- Acthar is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origins

WARNINGS AND PRECAUTIONS

- The adverse effects of Acthar are related primarily to its steroidogenic effects
- Acthar may increase susceptibility to new infection or reactivation of latent infections
- Suppression of the hypothalamic-pituitary-axis (HPA) may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Adrenal insufficiency may be minimized by tapering of the dose when discontinuing treatment. During recovery of the adrenal gland patients should be protected from the stress (e.g. trauma or surgery) by the use of corticosteroids. Monitor patients for effects of HPA suppression after stopping treatment
- Cushing’s syndrome may occur during therapy but generally resolves after therapy is stopped. Monitor patients for signs and symptoms
- Acthar can cause elevation of blood pressure, salt and water retention, and hypokalemia. Blood pressure, sodium and potassium levels may need to be monitored
- Acthar often acts by masking symptoms of other diseases/disorders. Monitor patients carefully during and for a period following discontinuation of therapy
- Acthar can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Monitor for signs of bleeding
- Acthar may be associated with central nervous system effects ranging from euphoria, insomnia, irritability, mood swings, personality changes, and severe depression, and psychosis. Existing conditions may be aggravated

- Patients with comorbid disease may have that disease worsened. Caution should be used when prescribing Acthar in patients with diabetes and myasthenia gravis
- Prolonged use of Acthar may produce cataracts, glaucoma and secondary ocular infections. Monitor for signs and symptoms
- Acthar is immunogenic and prolonged administration of Acthar may increase the risk of hypersensitivity reactions. Neutralizing antibodies with chronic administration may lead to loss of endogenous ACTH activity
- There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver
- Long-term use may have negative effects on growth and physical development in children. Monitor pediatric patients
- Decrease in bone density may occur. Bone density should be monitored for patients on long-term therapy
- Pregnancy Class C: Acthar has been shown to have an embryocidal effect and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

ADVERSE REACTIONS

- Common adverse reactions for Acthar are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain
- Specific adverse reactions reported in IS clinical trials in infants and children under 2 years of age included: infection, hypertension, irritability, Cushingoid symptoms, constipation, diarrhea, vomiting, pyrexia, weight gain, increased appetite, decreased appetite, nasal congestion, acne, rash, and cardiac hypertrophy. Convulsions were also reported, but these may actually be occurring because some IS patients progress to other forms of seizures and IS sometimes mask other seizures, which become visible once the clinical spasms from IS resolve

Other adverse events reported are included in the full Prescribing Information. Please see accompanying full Prescribing Information.