Study Title

Use of Acthar in Rheumatoid Arthritis Flares

NCT# NCT02541955

Questcor/Mallinckrodt Study Drug
H.P. Acthar® Gel

Investigator
Veena K. Ranganath MD, MS

Sub-Investigators
David Elashoff, PhD

Study Type
Open-label Randomized Pilot Study

Research Setting
Single Site at UCLA
Department of Medicine
Division of Rheumatology

Country of Primary Site
USA

Version 7: July 30, 2024

1. Hypothesis

Use of Acthar in Rheumatoid Arthritis (RA) flare does the following:

1) Decreases evidence ultrasound measured synovitis (PDUS and GSUS)

2) Increases the duration of efficacy of biologics and/or DMARDs, without need for switching RA treatment regimen.

---

2. Rationale for the study

Rheumatoid arthritis (RA) is an autoimmune destructive arthritic disease that waxes and wanes in disease activity without cause. The current recommendations to the rheumatologist are to switch the RA therapeutic regimen every 3 months till patients obtain good response to therapy and/or remission, according to treat to target (T2T) guidelines. Although 70% of patients on biologics or combination DMARDs can obtain a good response to therapy, many times patients experience flares of disease and/or a loss of efficacy. It is sometimes difficult to ascertain whether the increase in disease activity is due to a RA flare or if the clinician should change therapy.

Comprehension of the definition of RA flare is critical and this is an active area of scientific investigation. Recently, a RCT of 30 RA patients diagnosed with flare was randomized to treatment with dexamethasone (IV 120mg qd x3d) and methylprednisolone (IV 1gm qd x3d) (PMID 24400920). DAS28 was evaluated at day 4 and 30 after treatment, with decrease of DAS28 by 2.4 in both treatment arms at day 4 and was maintained at day 30. Another study of the BRASS database, demonstrated that 57% of all RA patients reported at least one flare and 30% of patients in remission develop flares. Approximately 40-56% of patients who flared reported medication changes at the time of their flare. Of these patients 20-33% used prednisone to treat their flare, while 23-32% of patients either started a new DMARD/biologic or increased the dose.

Musculoskeletal ultrasound (MSUS) use in rheumatoid arthritis is another area of active research interest. It allows for a dynamic, safe, method for evaluating synovitis of the joints in RA patients. There are several studies demonstrating that evidence of PDUS and GSUS predicts future erosions. In addition, there are few studies that have evaluated utility of US to predict flares. One study by Saleem et al. of 93 RA patients in remission, demonstrated that the presence of PDUS activity was an accurate determinant of RA flare.

There is sparse data to aid rheumatologists in dosing Acthar for RA flare. The investigator brochure provides dosing recommendations for infantile spasms (75u/m2 SQ bid for 2wks and then tapered), multiple sclerosis flares (80-120units SQ x2-3wks, then tapered). However, for other disorders and diseases, “dosing will need to be individualized depending on the disease under treatment and the medical condition of the patient”.

Thus, we propose an open label pilot randomized controlled study to evaluate the efficacy of Acthar, to decrease evidence of MSUS synovitis and disease activity

measures, as well as its ability to prevent the necessity to change the patient's RA treatment regimen.

---

3. **Patient population and estimated sample size**

We anticipate enrolling 40 RA patients in current flare from the UCLA Rheumatology clinics and randomizing patients 1:1 to use of Acthar 40units q week vs 80units 2x a week for up to 4 weeks. Flare would be defined as meeting at least one of the following criteria: 1) patient believes that he/she is having an RA flare, 2) physician believes that the patient is having an RA flare, or 3) increase in CDAI (change of at least 5) or increase in DAS (change of 0.6) since their last visit. Patients would be given flare questionnaire (English translation of the French 'Flare' instrument—this is currently worked on by our research group, and the OMERACT Flare Questionnaire) prior to enrollment and during the course of the study. MSUS of joints, DAS28, CDAI, RAPID3, and HAQ-DI would be performed at the screening/baseline, week-2, week-4 and at week-12. The ultrasonographer will not be blinded to the randomization groups at the time of acquisition of the images. However, blinded scoring of still images will be performed, randomized to visit date and patient.

We also like to include the JIA (Juvenile Idiopathic Arthritis) population in this study because patients who are diagnosed with JIA (<16 years of age) are persons who meet the ACR 2010 Classification Criteria for RA. We would expect that disease flares would respond similarly to Acthar or any steroid taper. In addition, we do not believe that the inclusion of adults diagnosed with polyarticular JIA would generate heterogeneity in their therapeutic response to Acthar.

The screening/baseline visit, in most cases, will occur on the same day. If there are no safety concerns, then we will randomize the patient on the same day as screening and initiate treatment. If there are safety concerns (active mild infections etc.) or entry criteria that the patient may meet in the near future (<1mos on DMARDs), we will consider that visit a screening visit and baseline the patient at a later time point. In clinical practice, patients who present with RA flare are treated the same day with Depomedrol 60-80mg IM x1 or a Medrol dose pack, without obtaining safety labs first. Thus, if the patient had a screening/baseline visit on the same day and safety labs demonstrated a concern (i.e. positive MTB, hepatitis C positive, etc.), we would withdraw the patient from the study. In addition, we will collect urine specimen for future biomarker assays (ie, cortisol). This will be explained in the consent form.

If patients are still experiencing RA flare at week-4, then rescue medications or other rescue methods can be instituted: steroids, NSAIDs, physical therapy, occupational therapy, change in DMARDs/biologics, etc. This will be per primary rheumatologist and patient discussion. If the patient requires rescue medications, he/she will continue to return for visits as scheduled.

US assessments will be performed using the 34-joint US score. To date, no single US scoring system has been yet determined as the prevailing method. However, several US scoring systems have demonstrated that power Doppler synovitis and B-mode synovial hypertrophy scores are sensitive to change. For this proposal, selection of

the specific 34 joints was based on maximizing precision, reliability, and feasibility for ultrasonography. Most US scoring systems weigh heavily on the hands and wrists. Some studies demonstrate the presence of normal amounts of fluid at the metarsophalangeal (MTP) joints and frequent presence of deformities such as hammer toes. Thus, these joints were excluded. Grey-scale synovial hypertrophy and power Doppler will be assessed for bilateral wrists (dorsal), MCPs 2-5 (dorsal and volar), and PIPs 2-5 (volar). All the above areas will be examined with B-Mode and power Doppler mode sonography. Standard OMERACT definitions will be used for effusion and synovial hypertrophy.

ACTH influences the activity of immune cells, including T cells (which occupy an undisputed central place in immunology because of their primary and/or contributing role in the orchestration of different types of immune responses).

T cells can be divided into several subsets according to their phenotypic features that associate with distinct functions. T regulatory cells (TReg) inhibit the proinflammatory activities of T effector cells (TEff), which typically augment and/or sustain inflammation.

At the baseline/screen visit and the 2-week visit, we will draw blood to monitor by flow cytometry the numbers of TReg and TEff (Th1, Th2 and Th17 cell subsets, each with specific roles in infection, allergy and autoimmunity) in ACTH-treated individuals (high 80u 2x a week and 40u every week) over time.

Secretion of cytokines (IFN-alpha, IL-4, IL-6, IL-17) will be measured in parallel. Realtime PCR on magnetic-bead sorted cells will measure the transcription factors that regulate the TEff subsets (T-bet for Th1 and GATA3 for Th2, ROR-gamma-t for Th17) or Foxp3 expression for TReg.

In parallel, cell proliferation will be analyzed together with a phenotypic evaluation by flow cytometry. Specifically, we will study the different T cell subsets for T cell markers associated with function (memory, activation, etc.: CD44, CD62L, CD25, CD69, CD127). We have a SORP BD LSRII flow cytometer (Becton Dickinson) with a 17 color capability for these multi-staining studies. This will allow concomitant studies of intracellular phosphorylation of ERK1/2, AKT and mTOR also by flow cytometry on sorted cells in the ACTH-treated individuals before and after treatment (baseline to 2wks) together with the transcription factors specific for each cell subset. Confirmatory western blots studies will validate the results. The information from these studies proposed in this application will advance significantly the mechanistic understanding of the therapeutic effects of ACTH on the immune response at the cellullar and molecular levels, facilitating a rational use of the drug, and improved dosing and posology.

Adverse events will be monitored at all visits. CBC, CMP and HbA1C will be evaluated at the screening/baseline visit.

Inclusion

1) Patients must meet 1987 ACR classification criteria OR patients diagnosed with Juvenile Idiopathic Arthritis (JIA) must meet 2010 ACR classification criteria
2) DAS > 3.2
2) Age ≥ 18 years of age
3) Meet one of the above RA flare requirements
4) Stable concomitant DMARDs and/or biologics for at least 1 month (if on no background DMARDs/biologics must be stable for 1 month).
5) FLARE questionnaire score of greater than or equal to 4
6) PDUS sum score of greater than 0

Exclusion

1) Prior treatment with Acthar in the last 2mos
2) Active known infection (active infection with HIV, hepatitis B/C, or tuberculosis).
3) Subjects who have received live or live attenuated vaccines (or the zoster vaccine) within 6 weeks prior to the first dose of study drug
4) Active gastritis or history of prior GI bleed, congestive heart failure Class III/IV, uncontrolled hypertension
5) History of scleroderma or active lupus patients
6) Allergies to porcine proteins
7) >10mg of prednisone or equivalent methylprednisolone dose use within the last 4 weeks or more

---

4. Study design

This would be a small randomized controlled trial (RCT) of 40 RA patients experiencing flare randomized to Acthar 40 Units QWK versus 80 Units BIW for up to 4 weeks.

Arm A (n=20)	Arm B (n=20)
40 U QWK x4WK	80 U BIW x4WK

Patients who have a power Doppler score of 0 (of the 34 joint ultrasound protocol) will stop Acthar (Arm A or Arm B) at the week 2 visit. These subjects will still proceed with all other procedures in the study. After 4 weeks of drug therapy patients will be monitored for an additional 8 weeks for total study duration of 12 weeks.

Patients will be contacted after study completion for safety follow up evaluation.

---

5. Payment

Each participant will receive $100 for each completed visit for a total of $400 for all completed visits. If a chest x-ray is required, the participant will receive a parking pass for the examination. The study will reimburse patients for the ride share service that they use to come to clinic for their study visits.

Participants can be paid via check or cash.

6. **Primary end-point**

Change in Ultrasound Power Doppler Score of joints (baseline to 2 weeks)

7. **Secondary end-points**

Change in DAS28ESR-4 (baseline to 2 weeks and baseline to 4weeks)

Change in Ultrasound Power Doppler Score (baseline to 4 weeks)

Change in Ultrasound GSUS Score of joints (baseline to 2 weeks and baseline to 4 weeks)

Change in HAQ-DI (baseline to 4 weeks)

% Patients maintaining original RA treatment plan at week-12 (this is exploratory)

Change in cytokines (baseline to 2wks)

Change in flow cytometry of TReg and TEff (baseline to 2wks)

---

8. **Estimated time line** (including IRB approval, study initiation, enrolment, study completion and submission of publication):

IRB Approval 2wks-2 months

Contract Negotiation (can occur concurrently with IRB) 2-3months

Enrollment: 18 months

---

8. Patient Withdrawal:
Patients have the right to withdraw from the study at any time for any reason. There should be an attempt to have all patients complete the withdrawal visits or safety follow-ups as detailed in the Schedule of Assessments. If the patient decides to prematurely discontinue study treatment ("refuses treatment"), he/she should be asked if he/she can still be contacted for further information. If the reason for removal of a patient from the study is an adverse event, the specific event will be recorded on the CRF. The study team will attempt to follow the patient until the event has resolved or stabilized.

The investigator may withdraw patients from the study in the event of inter-current illness, adverse events, treatment failure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), or any reason where it is felt by the investigator that it is in the best interest of the patient to be terminated from the study. The reason(s) for withdrawal must be documented and explained to the patient.

9. Sample Size Justification:

The initial hypotheses will assess whether both groups combined can reduce disease activity outcomes (PDUS, GSUS, DAS28ESR-4, HAQ-DI) from the baseline to the week

2 time point. The overall sample size of 40 will have 80% power to detect effect sizes of at least 0.454 using a paired t-test with a 0.05 two-sided significance level.

Next, we will compare the change scores for the disease activity outcomes between the two study arms. The sample size of 20 in each group will have 80% power to detect effect sizes of least 0.91 using a two group t-test with a 0.050 two-sided significance level.

Finally, the sample size of 40 will provide a level of precision on our estimates of change in disease activity measures of +/- 0.31 standard deviation units for the disease activity measures. This is based on the width of the 95% confidence interval for the change in each disease activity outcome.

10. Statistical Analysis:

The initial analysis will use paired t-tests to compare disease activity outcomes between the baseline and 2-week time point combining both arms together. Next, two-sample t-tests will be used to compare the disease activity outcomes between study arms. To incorporate all the observation time points in the analysis we will construct a mixed effects model separately for each outcome. The dependent variable in these models will be the disease outcome measure at each time point. The fixed effects in the models will be study arm (40 vs 80), time, and the arm by time interaction effect. Exploratory models for the clinical outcomes (DAS28, HAQ) will also include terms for MSUS measures (PDUS and GSUS) to allow for the examination of correlation between MSUS and clinical outcome measures. Finally, we will also include a term in the model for switching of original RA therapy. Fisher's exact tests will be used to compare the % of each study arm that maintain original RA treatment plan. Log-rank tests will be used to compare the time of maintenance of original RA treatment between arms. We will construct 95% confidence intervals for the differences between treatment response between the arms as well as for overall changes in response to therapy.

Study Procedures Matrix

Procedure**	**Visit 1 (Screening/ Baseline)**	**Visit 2 (Week-2)**	**Visit 3 (Week-4)**	**Safety Follow up**	**Visit 4 (Week-12)**	**Safety Follow up**
Visit Time Window		+/- 1 week	+/-1 week	-4/+2 weeks	+/- 2 weeks	
Eligibility Assessments	X					
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Medical History	X					
QuantiFERON	X[1]					
Physical Examination	X					
Targeted Physical Examination		X	X		X	
Vital Signs	X	X	X		X	
Concomitant Medication	X	X	X	X	X	X
Assessment of Signs and Symptoms		X	X		X	
Adverse Events Assessment		X	X	X	X	X
Chest X-ray	X[2]					
CBC and Chem Panel Tests	X[3]	X	X		X	
Hemoglobin A1C	X[4]				X	
HIV, Hepatitis B and C Serologies	X[5]					
Rheumatoid Factor and CCP	X[7]					
hsCRP	X	X	X		X	
ESR	X	X	X		X	
Urine Specimen	X	X	X		X	
Biomarker test	X	X	X		X	
Urine Pregnancy Test	X	X	X		X	
Joint Assessment	X	X	X		X	
MD Global Patient Global	X	X	X		X	
CDAI	X	X	X		X	
DAS28	X	X	X		X	
HAQ-DI and other questionnaires	X	X	X		X	
Ultrasound Acquisition	X	X	X		X	
Ultrasound Scoring	X	X	X		X	
Dispensing of Study Medication	X	X[6]				

1. QuantiFERON/PPD does not have to be done if previously done within 12 months
2. Chest x-ray does not have to be done if they were done within the past 12 months
3. CBC and Chem panel laboratory tests do not have to be done if they were done within the past 8 weeks.
4. Hemoglobin A1C does not have to be done if done within the past 12 months

5. Hepatitis B and C serologies do not have to be done if they were done within the past 12 months.
6. Will dispense medication if patients have PDUS>0.
7. 7. Will not perform CCP/RF if done in past.

** Study procedures may be repeated per PI discretion.