ACTH effects on myelination in MS patients

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1 Hypotheses and Rationale for the Study:

1.1 Hypothesis/Hypotheses:

Patients identified as having new enhancing lesions and treated with a course of ACTH at the time of initial MRI and then subsequently treated with monthly pulse doses of 3 days of ACTH treatment over one year will have a greater degree of remyelination as measured by myelin water fraction (MWF) as compared to those patients treated with one course of ACTH.

1.2 Rationale for the study:

MS is a chronic inflammatory disease of central nervous system characterized by focal T cell and macrophage infiltrates associated with demyelination. The primary innate immune cells in MS consist of infiltrating macrophages/monocytes and resident microglia. Cells of the innate immune system are effector cells that function to cause central nervous system (CNS) injury both through direct effects on neighboring cells, such as oligodendrocytes, and through generation of soluble proinflammatory mediators that have distant effects on cells, such as neurons. The innate immune inflammatory is thus sufficient to explain focal injury and diffuse injury. In the majority of patients, MS begins as a relapsing-remitting course but eventually evolves to a state of progressive decline in disability. Focal inflammatory demyelinating lesions are the predominant pathological findings in the patients with relapsing disease whereas diffuse axonal injury with microglial activation has been found to be the hallmark of progressive disease [1]. Microglial activation itself occurs either as a response to CNS injury for example as in Wallerian degeneration, or in response to signals from other inflammatory cells including macrophages and lymphocytes.

High dose corticosteroids (methylprednisolone) have been a mainstay of treatment for MS relapses and have been shown to shorten the time to recovery from relapses, presumably at least in part due to their anti-inflammatory effects. However, despite their anti-inflammatory properties, corticosteroids have been shown to impair and delay remyelination in animal models of MS [2, 3] and there is little clinical evidence of a longer-term beneficial effect. Adrenocorticotropic hormone (ACTH) gel, a long-acting formulation of the full sequence ACTH that includes other pro-opiomelanocortin (POMC) peptides, is considered an alternative to corticosteroids in the treatment of relapses (currently FDA approved for this indication). ACTH gel exerts direct anti-inflammatory and immune-modulating effects within the CNS, specifically on infiltrating macrophages and resident microglia [4, 5] as well as protecting mature oligodendrocytes from inflammation-related damage and excitotoxicity [6]. These effects are mediated not only via induction of endogenous corticosteroid production but also via effects on melanocortin receptors [7].

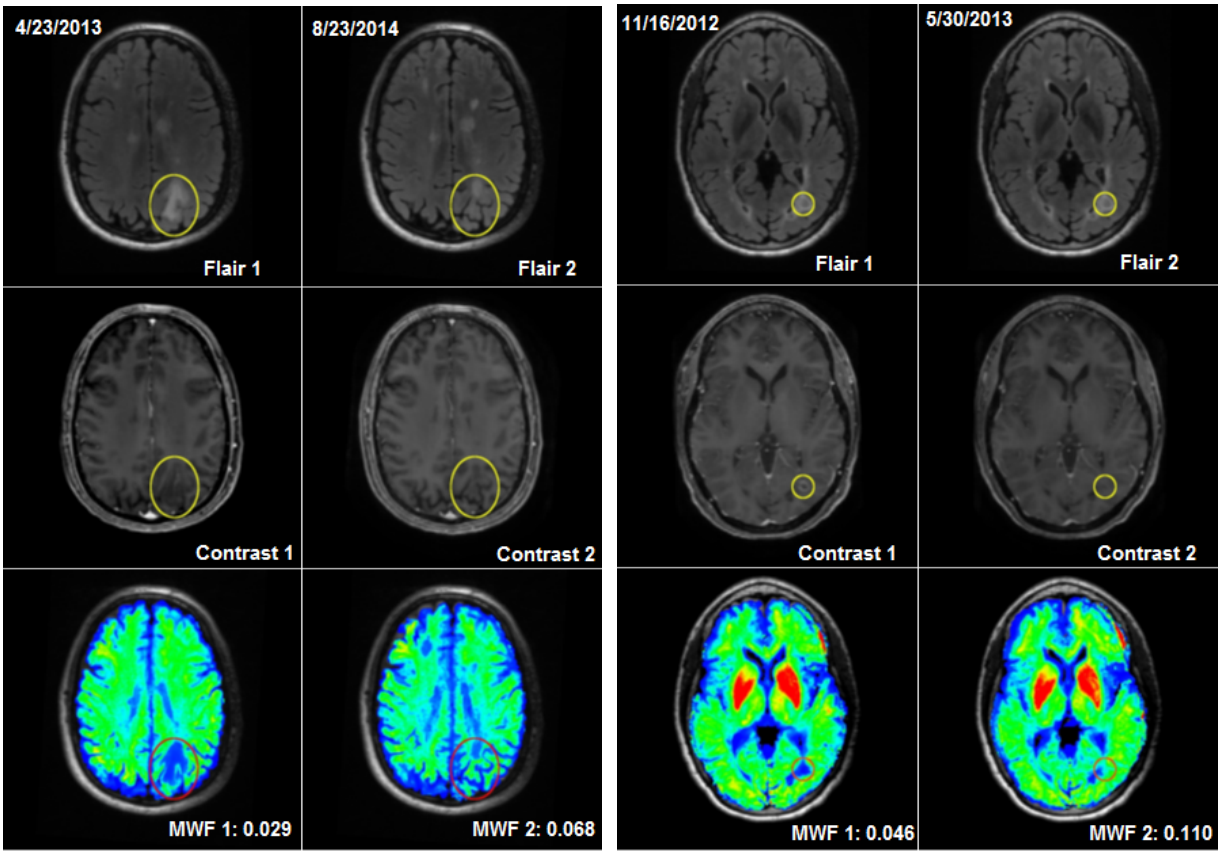
Chronic dosing of corticosteroids, specifically high dose methylprednisolone, (doses varying from once monthly to multiple doses every couple months) have been studied and found to be well-tolerated, safe and of a benefit on clinical as well as on conventional MRI measures of disease activity [8-10]. The rationale for these studies was based upon a potential benefit of chronic anti-inflammatory treatment to promote repair and neuroprotection. Following this same rationale, however instead implementing ACTH based upon it effect on the melancortin receptors, we propose to study the benefit of monthly pulses of ACTH in a cohort of MS patients. We are targeting patients with new enhancing lesions to determine if monthly exposure to ACTH will promote more robost endogenous remyelination in new lesions compared to a one-time treatment course. We hypothesize that continued exposure to the anti-inflammatory effects of ACTH on new lesions would be superior to promoting remyelination as compared to a one-time treatment course. Given that the majority of endogenous remyelination is felt to begin within months after lesion development [11] and likely to be most prominent in the few months following, a one year study is most likely sufficient to measure this process.

T2 relaxometry is a MR imaging technique in which a series of T2-weighted images at different echo times are obtained and the contribution of water associated with myelin and other tissue compartments can be differentiated using T2 decay curve analysis [12]. The relative contribution of the myelin water, represented as the myelin water fraction (MWF), has been shown to highly correlate with histological myelin measurement in animal models [13] and ex-vivo brain [14,15] and has been applied to MS patients [16]. The histological correlation of T2 relaxometry with myelin content makes it an excellent candidate as a biomarker for myelin content and it has been found to be reproducible and sensitive marker to change over time [17-20]. Through the application a multi-slice 2D T2prep spiral gradient echo (GRE) imaging, T2 data can be efficiently acquired [21,22] and we have further optimized a 3D T2prep GRE sequence at 3T for which full brain coverage can be achieved within 10 minutes [23]. One of the main advantages of using T2 relaxometry and MWF as a surrogate for myelin over other advanced MR modalities lies in the T2 spectrum (the T2 decay curve analysis). Both MWF and the extracellular T2 component (the intermediate peak) within the T2 spectrum) can increase with edema [24], thus once the extracellular pool stabilizes, we can ensure that any change in MWF is a true reflection of myelination.

To validate this concept, we performed a pilot study, which included 10 patients with either new contrast enhancing lesions or new non-contrast enhancing lesions. A total of 27 lesions were followed longitudinally, 15 of which demonstrated contrast enhancement on the initial MRI. Using a paired t-test we showed that the intra/extracellular water peak shifted in contrast enhancing

lesions (p=0.044). Resolving edema presumably caused this shift. As expected, no significant shift in the intra/extracellular water peak was shown in non-contrast enhancing lesions. We then used the longitudinal change in the T2 extracellular peak as a control for resolving edema in a random effects model aimed at calculating true myelin water fraction change. Based on our model we determined that true MWF change in lesions was anything above 0.045 (p=0.0139). 7 out of 15 contrast enhancing lesions showed true myelin water fraction change while no significant change was seen in non-contrast enhancing lesions.

Example A Example B



Example A is of a new contrast enhancing lesions in the left occipital region where there was a large shift in the extracellular peak and a large increase in MWF. Because of the relative resolution of the lesion seen on FLAIR, we presume this lesion is edematous. We saw a MWF increased of 137%, but the extracellular peak was also shifted by 11 ms. In this example, the large increase in MWF is likely due in part to edema.

Example B is a new contrast-enhancing lesion in the left periventricular region. This lesion demonstrated a 137% increase in MWF but no real shift in the EC peak. Therefore, the increase in MWF in this lesion likely represents true remyelination.

In conclusion, we were able to show that the extracellular water peak shifts in the face of edema, and the T2 spectrum can be used as a control for edema in early lesions. Using our model we were able to accurately detect myelin change.

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2 Specific Aims

Specific aim #1: The primary objective of this study is to determine if monthly pulse doses of a three-day course ACTH (H.P. Acthar®) is more effective at recovering myelin at 12 months, as measured by MWF, in new multiple sclerosis lesions as compared to one course of treatment.

Specific aim #2: The main secondary objective is to utilize every three-month MWF measurements to determine the peak time of remyelination in new multiple sclerosis lesions when followed over the course of 12 months.

3 Study design

3.1: Study Description

This pilot study proposal is designed to perform a chronological measurement of MWF in new contrast-enhancing lesions in patients treated with ACTH during an acute exacerbation of MS.

The treatment decision will be made by the patient's MS treating physician as part of standard of care for MS patients having an with acute exacerbation. After the patient's treating physician has recommended ACTH, the study will be offered to the patient and the consenting process will be initiated, as described in eIRB. If the patient agrees to participate and signs the consent and HIPAA forms, he/she will become a study subject and randomized to one of two treatment groups. The initial stage of the study is for all patients to receive the standard of care course of and ACTH and depending on the randomization, a patient may or may not receive additional monthly doses of ACTH. If the patient does not enroll into the study, ACTH will be prescribed as standard of care. Participation in this study will be offered to every eligible patient. Every physician in Judith Jaffe MS Center is an investigator for this study and will be discussing the study with their eligible patients.

The initial course of ACTH (H.P. Acthar®) will be administered as recommended in the package insert, a subcutaneous daily dose of 80-120 units daily for 2-3 weeks. However, as recommended in the package insert, the dosage may be individualized according to the medical condition of each

patient. Therefore, the frequency and dose of the drug may be determined by considering the severity of the disease and the initial response of the patient. The typical dosing for an MS exacerbation is 80units/day for 3-5 days and it is expected that this will be the initial dosing for the majority of the patients.

MS patients enrolled in this study will be randomized into:

Group A: 80units/day ACTH for 3-5 days (The dose could be adjusted based on the individual needs of the patients up to 80-120 units daily for 2-3 weeks.)

Group B: 80units/day ACTH for 3-5 days (The dose could be adjusted based on the individual needs of the patients up to 80-120 units daily for 2-3 weeks.), followed by monthly 80 units/day ACTH for 3 days for 12 months of treatment.

The Judith Jaffe Multiple Sclerosis Center currently has over 1000 patients in a clinical and MRI database. Patients who have signed consent for the database will have their standard of care MRI scans monitored for new enhancing lesions; this will only have to be repeated if initial scan is not completed at our MS center with our current clinical protocol. All RRMS patients with new enhancing lesions will be considered for the study and approached regarding participation Patients that are considered candidates and consent for the study, patients will then be randomized (1:1) to receive one course of ACTH followed by monthly pulses vs. receiving only one course of ACTH treatment. All patients will have follow-up MRI's are 3 months, 6 months and 12 months post lesion onset for a total of 3 additional scans. If a patient is identified as having an enhancing lesion from MRI scan not obtained through our database, an additional scan will be obtained through the study and serve as the baseline MRI. All patients will receive the first course of ACTH within 4 weeks of new lesion detection.

3.2: Study endpoints

The primary endpoint of this study will be change in MWF within new enhancing lesions over the course of 12 months. The absolute change in lesion MWF (over our test-retest variability) between baseline and one year MRI's will be calculated and compared between treatment groups.

The main secondary end-point will be longitudinal assessment of MWF (every 3 months) to determine the dynamics of myelin change over 12 months, specifically to determine the timing of remyelination. The advantage of T2 relaxometry is the ability to look at both the contribution of water within myelin bilayers (MWF) but also the water within the intra/extracellular compartment (the intermediate peak within the T2 spectrum). This second peak (extracellular peak) can increase with edema, thus once the extracellular pool stabilizes, we can ensure that any change in myelin water fraction (MWF) is a true reflection of myelination.

We will also explore a measurement called "absolute myelin content". Through this measurement, we can control for the increased edema associated with a new lesion, thus providing for a more accurate measure of true myelin change.

Additional secondary end points include measurement of the following clinical measurements: EDSS, and the following MRI measurements: change in T2 lesion volume, whole brain volume, and cortical volume.

If patients in either arm have an additional relapse during the study, they will be removed from the study. At that point patients are likely to change on-going treatment for their MS and based upon their treating physician, may require additional steroids (either ACTH or methylprednisolone)

3.3 Inclusion and Exclusion Criteria:

Inclusion criteria:
Patients with RRMS or SPMS with new contrast-enhancing lesions who will start as part of their standard of care ACTH.

Exclusion criteria:

- Patients having received oral or IV corticosteroids within one month prior to initial scan demonstrating contrast enhancing lesion
- Patients with known or new allergy to ACTH
- Patients being treated with Natalizumab, Rituximab, and Cyclophosphamide
- Patients unwilling to have serial MRI exams
- Patients unable to undergo MRI imaging because of having an artificial heart valve, metal plate, pin, or other metallic objects in their body or is unable to complete all the MRI scans required for this study
- Patients with acute or chronic renal disease in whom administration of gadolinium may pose risk of nephrogenic systemic fibrosis
- Patients that are pregnant
- Premenopausal woman not willing to use at least one form of contraception
- Patients with a known history of diabetes mellitus
- Progressive neurological disorder other than RRMS or SPMS
- Clinically significant cardiovascular disease, including myocardial infarct within last 6 months, unstable ischemic heart disease, congestive heart failure, or angina
- Subjects on chronic steroid therapy for treatment of MS or other systematic disease
- Subject currently has a significant medical condition (other than MS) including the following: neurological, psychiatric, metabolic, hepatic, renal, hematological, pulmonary, cardiovascular (including uncontrolled hypertension), gastrointestinal, urological disorder, or central nervous system (CNS) infection that would pose a risk to the subject if they were to participate in the study or that might confound the results of the study
    - Note: Active medical conditions that are minor or well-controlled are not exclusionary if, in the judgment of the Primary Investigator, they do not affect risk or the subject or the study results.

- Subject is unable to cooperate with any study procedures, unlikely to adhere to the study procedures and keep appointments, in the opinion of the Investigator, or was planning to relocate during the study

3.4 Randomization procedure:

Given this is a small pilot study and a chance that simple randomization would course all patients to fall within one treatment group we will randomize patients *in permuted blocks*. This randomization scheme consists of a sequence of blocks such that each block contains a pre-specified number of treatment assignments in random order. The purpose of this is so that the randomization scheme is balanced at the completion of each block. Patients will be randomized after the consent is signed.

3.5 Sample Size:

We are proposing a pilot to study fifteen patients per study arm (for a total of 30 patients, includint ~ 10 screen failures) with new enhancing lesions over a 12 month time period. The longitudinal dynamics of MWF have only been studied in a handful of patients and the effect of any specific steroid treatment has not been studied, thus we are unable to propose a proper calculated sample size. However, from our preliminary longitudinal MWF lesion data, we are able to determine that at least 50% of new enhancing lesions show some signs of remyelination after initial acute treatment (methylprednisolone or ACTH). If we were to perform a sample size based upon an assumption that repeated course of ACTH will show a 25% greater proportion of lesions showing signs of improvement, we would require approximately 53 lesions per arm. In order to achieve that goal, we would have to screen and enroll at least 50 patients per arm. Therefore we are proposing a small pilot study to gain more information regarding the potential benefit of repeated courses of ACTH to allow for a more accurate design of a larger clinical trial. In addition, we will focus our efforts toward patients with more than one lesion in an attempt to reach a goal of at least 25 lesions per arm. We expect that repeated course of ACTH may profoundly affect the remyelination and hope to a much higher proportion of lesions showing repair. Again, we are hopeful that information gained from this pilot study can help to accurately calculate sample sizes for larger clinical trials as well as gain insight into the potential benefit of ACTH on remyelination.

3.6 Clinical visit schedule:

Screening visits: Patients will be screened during standard of care clinical visits for multiple sclerosis. If a patient had MRI within 2 weeks of visit and had new enhancing lesions, the patient will be asked to participate in the study.

Baseline visit: Baseline EDSS (if not obtained during screening visit), *consent signed*, schedule repeat MRI with and without contrast if screening MRI not completed as part of the Weill Cornell Multiple Sclerosis Center Clinical Protocol. Initiation of ACTH (H.P. Acthar®) course of therapy following visit (patient will do home therapy) after randomization.

Visit 1: EDSS, safety evaluations, and initiation of monthly course of ACTH (H.P. Acthar®) in patients randomized to this arm.

Visit 2: EDSS, safety evaluations.

Visits 3, 4, 5: EDSS, safety evaluations, MRI with and without contrast

Visit 6 (last visit): EDSS, safety evaluations, MRI with and without contrast.

3.7 Study schema:

Tests and Evaluations	Time point: screening /Baseline -	Visit 1 (1 month)	Visit 2 (2 months)	Visit 3 (3 months)	Visit 4 (6 months)	Visit 5 (9 months)	Visit 6 (12 months- end of study)
Consent obtained	**X**						
MS history and EDSS, safety evaluations	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Randomization to treatment arm	**X**						
MRI	**X**			**X**	**X**	**X**	**X**

4 Assessment and documentation of adverse events

An AE is any physical or clinical worsening in symptoms or disease experienced by the patient at any time during the course of the study, whether or not it is considered related to study participation

or procedures. Multiple sclerosis symptoms that worsen during the course of the trial will be treated as AEs. AEs may also include complications that occur as a result of protocol-mandated procedures.

ACTH Safety Background

ACTH has been approved by the US Food and Drug Administration for treatment of MS relapses, however, we are proposing to use this drug on a monthly pulsed dosing (80mg for three days per month) schedule for one year. A few trials have evaluated the longer-term clinical benefit and safety profile of ACTH pulse therapy in idiopathic glomerular diseases, such as nephrotic syndrome and focal segmental glomerulosclerosis (FSGS), as well as one pilot study in MS. These studies had varying dosing schedules, some of which included a higher per month drug exposure as compared to our proposed study [26-30]. None of the studies reported severe-events related to ACTH and the adverse events were consistent with the expected common side effect profile listed on approved label. Based upon these studies, the adverse events between the two groups of patients proposed in this study should be similar.

The studies are summarized below.

- In an investigation of twenty-four patients with nephrotic syndrome from idiopathic FSGS, patients were treated with a median dose of 80 units injected subcutaneously twice weekly for up to 24 weeks [26]. ACTH gel provided a favorable safety profile with adverse events reported in 21 of 24 patients, most of which were mild and transient [26]. There were 52 typical steroid-related events (ranging from weight gain, mild elevation of BP, mood alteration) and no serious infections.
- In an investigation of 15 subjects with resistant glomerular diseases treated with 80 units of subcutaneous ACTH twice weekly for 6 months, no moderate to serious events or significant infections were reported with three of the 15 subjects reporting typical steroid-like adverse events (worsening glycemic control, weight gain, insomnia, mild elevation of BP and mild skin pigmentation changes) [28]. Importantly, no severe infections were reported.
- An investigation of twenty-one patients with nephrotic syndrome treated with ACTH gel twice weekly for up to 12 months reported five patients with steroid-like adverse events (impaired blood glucose control, weight gain, and 1 patient showed evidence of accelerated bone loss on bone densitometry not observed prior to ACTH gel therapy) but no severe infections [27].
- In a study of 23 nephrotic patients treated with an average of 25mg/week for a range of 5-11 months reported only similar steroid-related adverse events, all of which were mild [29].

In a pilot study in multiple sclerosis, monthly ACTH was compared to monthly IV methylprednisone (corticosteroid). Twelve subjects tolerated a regimen of 80 units of ACTH injected subcutaneously for three consecutive days once a month for 12 month [30]. The ACTH pulse therapy proved to have a favorable relapse and psychiatric side effect profile when compared to IV methylprednisolone as well as a lower number of adverse events. The study reported no

moderate to severe events. Psychiatric episodes only occurred in the IV methylprednisolone group and the ACTH group had a significantly stronger improvement in Mental Health Inventory. The ACTH treatment group had a lower number of infection incidence rate. When the two treatment groups were compared, they reported a similar amount of disease-related significant adverse events.

Adverse events

1. Common adverse reactions for H.P. Acthar Gel 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.

2. Severe and non-common adverse reactions: The adverse events of H.P. Acthar Gel are related primarily to its steroidogenic effects. Not all of the adverse events described below have been seen after treatment with H.P. Acthar Gel, but might be expected to occur.

H.P. Acthar Gel may increase susceptibility to new infection and increase risk of exacerbation, dissemination, or reactivation of latent infections. Signs and symptoms of infection may be masked.

Treatment with H.P. Acthar Gel can cause hypothalamic-pituitary-axis (HPA) suppression and Cushing's syndrome. Suppression of the HPA may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Signs or symptoms of Cushing's syndrome may occur during therapy but generally resolve after therapy is stopped.

H.P. Acthar Gel can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium and calcium.

Live or attenuated vaccine to patients on immunosuppressive doses should not be administered. Killed or inactivated vaccines may be administered; however, the response to such vaccines can not be predicted. Other immunization procedures should be undertaken with caution in patients who are receiving H.P. Acthar Gel, especially when high doses are administered, because of the possible hazards of neurological complications and lack of antibody response.

H.P. Acthar Gel often acts by masking symptoms of other diseases/disorders without altering the course of the other disease/disorder (monitor patients for signs of infection, abnormal cardiac function, hypertension, hyperglycemia, change in body weight, and fecal blood loss. Monitor patients for signs of other underlying disease/disorders that may be masked).

H.P. Acthar Gel can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Signs of gastrointestinal perforation, such as peritoneal irritation, may be masked by the therapy.

Use of H.P. Acthar Gel may be associated with central nervous system effects ranging from euphoria, insomnia, irritability, mood swings, personality changed, severe depression and psychosis. Existing emotional instability or psychotic tendencies may be aggravated.

Patients with a comorbid disease may have that disease worsened. Symptoms of diabetes and myasthenia gravis may be worsened with treatment.

Prolonged use of H.P. Acthar Gel may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi and viruses.

H.P. Acthar Gel is immunogenic. Prolonged administration of H.P. Acthar Gel may increase the risk of hypersensitivity reactions. Neutralizing antibodies with chronic administration may lead to a loss of endogenous ACTH activity.

There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver.

Decrease in bone formation and an increase in bone resorption both through an effect on calcium regulation and inhibition of osteoblast function may occur. These, together with a decrease in the protein matrix of the bone (secondary to an increase in protein catabolism) and reduced sex hormone production, may lead to the development of osteoporosis. Bone density should be monitored in patients on long term therapy.

H.P. Acthar Gel has been shown to have an embryocidal effect. Women of child-bearing potential should use approved methods of birth-control while administering the drug.

3. **Adverse Reactions after Additional Postmarketing Experience**

A. The following adverse reactions associated with the use of H.P. Acthar Gel have been identified from the postmarketing experience with H.P. Acthar Gel.

Allergic responses have presented as dizziness, nausea and shock.

Necrotizing angitis and congestive heart failure.

Skin thinning, facial erythema and increased sweating.

Pancreatitis, abdominal distention and ulcerative esophagitis.

Headache, vertigo, subdural hematoma, intracranial hemorrhage.

The adverse event collection period for this study begins at the baseline visit and will end after the last day of study medication. Patients discontinued from the study will be followed for at least 14 days after the last day of the study medication. At each visit patients will be specifically asked for adverse events using the table below.

All AEs, the onset and resolution dates, relationship to study drug, severity and seriousness will be documented. Based on the available information, the physician investigator will use the following guidelines to determine the relationship of any adverse event to the use of the study drug:

Unrelated: No temporal association, or the cause has been identified, or study medication cannot be implicated

Possible: Temporal association, but other etiologies are likely to be the cause; however, involvement of study mediation cannot be excluded

Probable: Temporal association, other etiologies are possible, but unlikely.

The severity of adverse events experienced during the course of the study will be assessed using a grading system:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life-threatening AE; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care acitivies of daily living.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE

Reference: Common Terminology Criteria for Adverse Events (NIH):
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Adverse events that occur during the study (from enrollment through the final visit), regardless of treatment group or relationship to the research, will be reported according to the policy of WCMC's Office of Research Integrity and Assurance and Data Safety Monitoring Board.

As per WCMC IRB reporting policy, only AE Grades 3, 4, and 5 will be reported to the IRB and DSMB.
(http://weill.cornell.edu/research/rea_com/irb_adv.html

All safety data will be reported to the WCMC DSMB. No efficacy interim analysis will be performed. Safety review will be done by the DSMB after the six-month visit of the first patient and then yearly. More frequent meetings or meetings ad-hoc could be organized if needed or

requested by the DSMB. The study does not have preset rules for discontinuation. Upon review of the data, the DSMB can recommend stopping the study at any time if appropriate.

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