Open-label Prospective Randomized Study to Determine the Efficacy and Safety of Two Dosing Regimens of ACTHar in the Treatment of Proliferative Lupus Nephritis

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Study Title **ACTHar in the treatment of Lupus Nephritis**

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A. SPECIFIC AIM

Start with a concise summary of the overall project (a few sentences). Please include hypotheses for each endpoint (see Section C) and provide rationale in Section B.

Open-label prospective randomized study to determine the efficacy and safety of two dosing regimens of ACTHar in the treatment of proliferative lupus nephritis. The treatment of lupus nephritis (LN) has remained mostly unchanged for many decades: High doses of steroids are still the cornerstone of LN therapy despite their devastating side effects. It is only recently that attempts at changing the requirements regarding steroid use have been made. The current proposal will evaluate the role of ACTH in the form of ACTHar gel in the treatment of proliferative LN. While we expect that a part of the therapeutic effects of ACTHar in LN will be mediated through the endogenous production of steroids, we hypothesize that a larger portion of the ACTH benefit may be due to the direct anti-inflammatory and reno-protective effect of ACTH dependent on the activation of the melanocortin receptors, rather than steroid production.

Accordingly, we propose that this study will evaluate the most effective dose of ACTHar gel in proliferative LN (Class III and IV) that produces the least steroid-like side effects, comparing two doses of ACTHar in conjunction with Mycophenolate Mofetil (MMF); MMF, in conjunction with Prednisone, is considered the current standard of care for LN. The dose of ACTHar was inferred based on the positive results of a study of membranous nephropathy. The primary outcome is renal response. Secondary outcomes are overall lupus activity and steroid side effects.

B. BACKGROUND AND CLINICAL SIGNIFICANCE

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology that mainly affects females of childbearing age. The disease is characterized by immune activation and the development of autoantibodies—particularly to double stranded DNA (dsDNA)—which are thought to be involved in tissue damage [1, 2]. Additionally, about 50% of SLE patients experience inflammation of the kidneys. LN is a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). Treatment of lupus nephritis is traditionally considered in two phases, induction and maintenance. Induction is aimed at reversing the immune-mediated inflammatory processes with high doses of immunosuppressives or cytotoxics in conjunction with high dose glucocorticoids (1mg/kg). Maintenance therapy is intended to assure durability of response and prevent recurrences using lower and presumably safer levels of immunosuppressive medications. Despite this aggressive therapy, 50% of patients do not achieve remission within 6 months [3]. Even if treatment is continued for 24 months, approximately one-third of SLE patients have an inadequate response [1, 3, 4]. Moreover, serious adverse events (SAEs) are common, especially with long-duration therapy. Complications of high-dose corticosteroid therapy in SLE patients include osteoporosis, aseptic necrosis, hypertension, diabetes, opportunistic infection, and cataracts. MMF therapy for lupus nephritis also causes serious adverse effects, including opportunistic infection and cancer. Clearly, safer and more effective therapies are needed for SLE.

The SLEDAI-2K (SLE Disease Activity Instrument) defines significant proteinuria as more than 500 mg of urinary protein excretion over 24 hours and the BILAG-2004 (British Isles Lupus Assessment Group), as either newly documented proteinuria over 1 gram or significant increase from baseline [1, 2]. In clinical practice and for the current study, significant proteinuria is defined as a protein-creatinine ratio of over 1 on a 24 hour collection.

Renal biopsies provide information regarding the pathology and establish activity and chronicity indices. They are classified according to the 2003 International Society of Nephrology Renal Pathology Society (ISN/RPS) system. Class I, minimal mesangial lupus nephritis, has normal glomeruli under the light microscope with minimal mesangial immune deposits on immunofluorescence. Class II, mesangial proliferative lupus nephritis, shows mesangial hypercellularity and mesangial immune deposits. Class III is defined as focal proliferative glomerulonephritis where less than 50% of all glomeruli are affected. Involved glomeruli usually display segmental endocapillary proliferative lesions or inactive

glomerular scars and typically contain focal subendothelial deposits identifiable by light microscopy. Class IV is defined as diffuse segmental or global glomerulonephritis where more than 50% of the glomeruli are affected with diffuse subendothelial deposits. The affected glomeruli in Class IV can be segmental (involving less than 50% of the glomerular tuft) or global (involving more than 50% of the glomerular tuft). Class V, membranous lupus nephritis, shows global or segmental subepithelial immune deposits and can also have mesangial alterations. Class V can occur in combination with Class III or IV. Class VI is advanced sclerosing lupus nephritis indicated by over 90% global glomerulosclerosis with no evidence of active disease [3]. Class I and II nephritis typically only require nonimmunodulatory therapy [5] and are not included in this proposal. Patients with isolated membranous lupus nephritis will also be excluded from the current study.

Induction therapy.

Rationale for choosing MMF as background therapy

While IV Cytoxan (CYC) administration per NIH protocol was the standard of care for the treatment of renal disease in SLE, the serious side effects led to a continued search for new approaches. Studies have shown that Mycophenolate Mofetil (MMF) provides comparable efficacy to IV CYC for both induction and maintenance with fewer side effects [13-17, 20]. MMF is an immunosuppressive agent that suppresses *de novo* purine synthesis by selectively inhibiting inosine-5'-monophosphate dehydrogenase. Unlike other cell types, lymphocytes are heavily dependent upon this mechanism for proliferation. As a result, MMF is capable of decreasing the proliferation of lymphocytes and the production of autoantibodies without the cytotoxic or mutagenic effects of CYC [18, 19]. Clinical trials comparing these two medications are discordant in their response rates but uniformly show them to be equivalent in efficacy. In the study conducted by Chan *et al.*, 95% of patients achieved clinical response (both complete and partial) with MMF (32 patients) and 90% with CYC (30 patients) [14]. In contrast, in the study by Ginzler *et al.*, only 52% responded to MMF (71 patients) and 30% to CYC (69 patients) [16]. The disparity observed between the Chan and Ginzler studies may be attributed to inherent differences in design and patient population. However, 90% response rates have never been reported in any of the LN studies. ASPREVA, in their clinical trial results, showed a 56% response rate with MMF and 53% with CYC. Each of the 370 LN patients was randomized to either a target MMF dose of 3 g/day or an IV CYC dose of 0.5 to 1 g/m^2 monthly for a 24 week induction period. The primary outcome was a specified decrease in urine protein-creatinine ratio and stabilization or improvement of serum creatinine [20]. The current standard of care treatment for SLE patients with Class III and Class IV glomerulonephritis consists of high doses of corticosteroids, accompanied by MMF. A summary of all these clinical trials is presented in Table 1.

For the current study background, induction therapy is suggested to be MMF with a target dose of 3g/day for 6 months. Based on the data from the published clinical trials summarized in Table 1, the expected complete response rate is predicted to be 20%. Clinical response (both complete and partial) is expected to be 50%.

Rationale for ACTHar

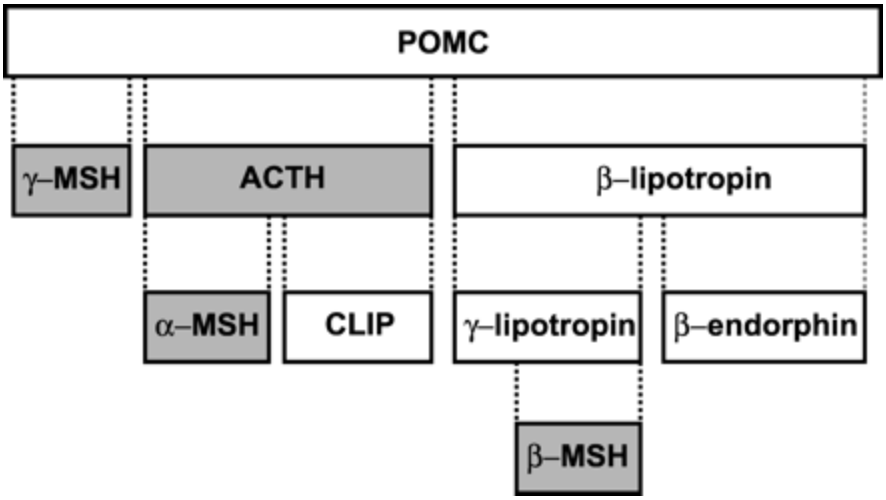
Although corticosteroid treatment has shown great ability in managing the manifestations of lupus, its potential for a variety of side effects motivates clinical trials in which steroid regimens are replaced. The suppression of the immune system can increase the risk of infections. However, it is the metabolic effects such as diabetes, significant weight gain, Cushingoid habitus (moon face, buffalo hump, truncal obesity), striae, increased blood pressure, and fluid retention, which are most concerning to both patients and doctors. Long term steroid use can lead to other serious consequences such as osteoporosis and fractures, avascular necrosis, high blood sugar, and cataracts.

Alternate approaches to steroid dosing
The MyLupus study group proposed a lower steroid dosing regimen for the treatment of LN, in combination with immunosuppressives, in an exploratory, multi-center, open label study that enrolled 81 patients who were randomized to a standard prednisone dose (SD) of 1 mg/kg/day or a reduced prednisone dose (RD) of 0.5mg/kg/day, both in combination with enteric-coated mycophenolate sodium. After 24 weeks, 19% of SD patients compared to the 18% of RD patients achieved a complete response; however, non-inferiority was not demonstrated. SD patients had a higher percentage of partial responders than the RD group (48% vs. 33%) [25]. While there may be select patients with low grade proteinuria or minimal disease where the RD regimen may be appropriate, the differences in partial responders between the groups are concerning. 1 mg/kg of prednisone remains the standard dosing for LN treatment.

Another ongoing attempt to replacing steroids in the treatment of LN is the RITUXILUP study proposed by Liz Lightstone. RITUXILUP is an open labeled, randomized, controlled, multicentre trial aimed at demonstrating that the addition of Rituximab to MMF therapy is beneficial in treating a flare of lupus nephritis and has both immediate and long lasting steroid-sparing effects [33].

This proposal, however, focuses on an alternative different from both RITUXILUP and high doses of steroids used for induction therapy. H.P. Acthar Gel is an adrenocorticotropic hormone (ACTH) analogue, a 39 amino acid peptide. Acthar is a highly purified sterile preparation of the adrenocorticotropic hormone in 16% gelatin that provides a prolonged release after intramuscular or subcutaneous injection.

Adrenocorticotropic hormone (ACTH) and α-, β-, and γ-melanocyte-stimulating (α-, β-, γ-MSH) hormones derive from post-translational processing of the precursor molecule proopiomelanocortin (POMC). These POMC products are collectively called melanocortin peptides or melanocortins [32].



The melanocortin peptides bind several melanocortin receptors that belong to the class A of G protein-coupled seven transmembrane receptors. Ligand affinity, tissue distribution, and functions of each receptor subtype are reported in Table 2.

TABLE 2 *Affinity, distribution, and functions of MCR subtypes*

MCR Subtype	Ligand Affinity	Prevalent Tissue Expression	Functions
MC1R	α-MSH ≥ ACTH ≫ γ-MSH	Melanocytes	Pigmentary effects
		Immune/inflammatory cells; keratinocytes; endothelial cells; glial cells	Antipyretic/Anti-inflammatory
MC2R	ACTH	Adrenal cortex	Steroidogenesis
MC3R	γ-MSH = ACTH ≥ α-MSH	CNS (Central Nervous System)	Autonomic functions
		Macrophages	Anti-inflammatory
MC4R	α-MSH = ACTH ≫ γ-MSH	CNS	Control of feeding and energy homeostasis; erectile activity
MC5R	α-MSH ≥ ACTH > γ-MSH	Exocrine glands, lymphocytes	Regulation of exocrine secretions, immunoregulatory functions

There is still uncertainty regarding which melanocortin receptor subtypes are involved in the anti-inflammatory effects. MC1R, which is the receptor with the greatest affinity for α-MSH, is expressed by virtually all the cells and seems responsible for the anti-inflammatory effect of melanocortins. Below is a summary of the anti-inflammatory effects of melanocortins:

Mechanism of the anti-inflammatory effect of melanocortins

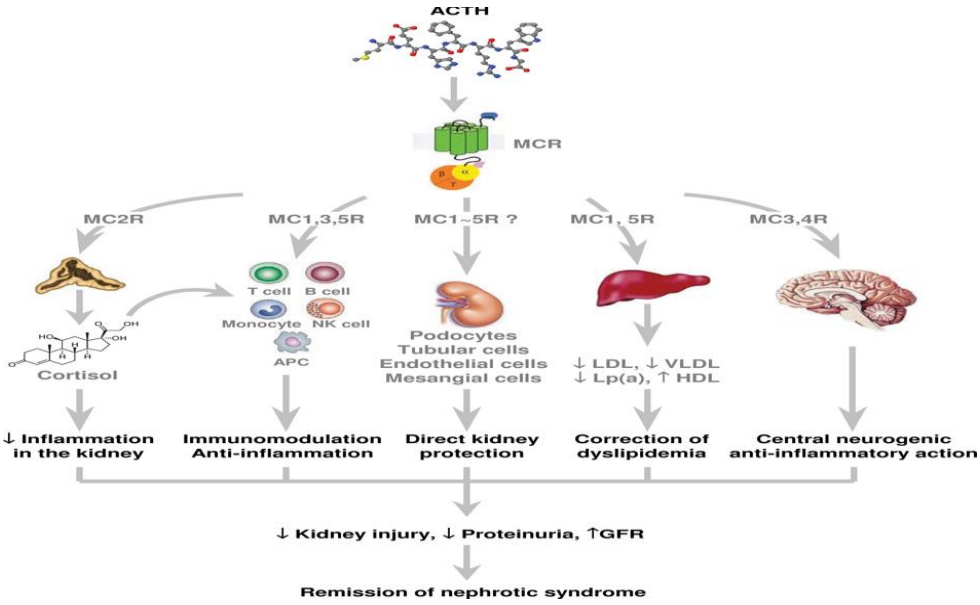
Effect	Target Cell, Tissue, or Organ
Reduced of production/expression of Proinflammatory cytokines and chemokines	Macrophages, endothelial cells, keratinocytes, fibroblasts, whole blood, liver
Nitric oxide (NO)	Macrophages, microglia, melanocytes, keratinocytes
Oxygen peroxide	Keratinocytes, melanocytes
Adhesion molecules (ICAM, VCAM)	Endothelial cells, kidney, liver, heart
Inhibition of white cell migration	Skin, lung, heart, kidney, liver, joints

The idea that MC1R activation contributes to the anti-inflammatory effects of melanocortins is supported by both immunoneutralization studies and experiments using MC1R-selective synthetic analogs. These MC1R-selective agonists "down-regulated expression and secretion of endothelial cell selectin (E-selectin), vascular cell adhesion molecule (VCAM), and intercellular adhesion molecule (ICAM), in human dermal vascular endothelial cells treated with tumor necrosis factor α (TNF-α)" through activation of NF-κB [32].

ACTH was widely used in the 1950s as an effective therapy for childhood nephrotic syndrome, but has since been replaced by synthetic glucocorticoid analogues. Clinical and experimental evidence now suggests that ACTH has antiproteinuric, lipid-lowering, and renoprotective properties, which are not fully explained by its steroidogenic effects. ACTH therapy is effective in inducing remission of nephrotic syndrome in patients with a variety of proteinuric nephropathies, even those resistant to steroids and other immunosuppressants [29].

A recent review by Gong discusses the kidney-specific MCR expression, stating that MC5R and MC2R are expressed in human kidney-specific cDNA. Furthermore, MC1R and MC4R expression were detected by RT-PCR in the kidney and in cultured podocytes, glomerular endothelial cells, and tubular epithelial cells. It is likely that the antiproteinuric effect of ACTH is justified by the direct protective effect of several MCRs on glomerular structures. Regardless of the types of MCRs expressed in the kidney, however, evidence supports the idea that the kidney might be a direct effector organ of ACTH and other melanocortin peptides. ACTH, furthermore, may directly activate MCRs in other cell types and trigger downstream renoprotective effects [29].

Further understanding of the role of ACTH in kidney disease is provided by a recent study by Bomback in patients with refractory nephrotic syndrome despite appropriate immunosuppression. ACTH was effective in inducing remission. Twenty-one patients with nephrotic syndrome were treated with ACTH 80 mg SQ twice a week: 11 with idiopathic membranous nephropathy, 4 with membranoproliferative glomerulonephritis, 1 with focal segmental glomerulosclerosis, 1 with minimal change disease, 1 with immunoglobulin A (IgA) nephropathy, 1 with Class V systemic lupus erythematosus (SLE) glomerulonephritis, 1 with monoclonal diffuse proliferative glomerulonephritis, and 1 with unbiopsied nephrotic syndrome. Eleven out of 21 patients (52%) achieved a complete or partial remission, with 4 (19%) in complete remission. Five patients reported steroid-like adverse effects (2 weight gain, 2 hyperglycemia, 1 bone demineralization), but there were no severe infections [30].



The mechanism of action of Acthar in the treatment of SLE is currently being investigated. H.P. Acthar Gel and endogenous ACTH stimulate the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a number of weakly androgenic substances by binding to MC2R. The trophic effects of endogenous ACTH on the adrenal cortex are not well understood beyond the fact that they appear to be mediated by cAMP. Prolonged administration of large doses of Acthar induces hyperplasia and hypertrophy of the adrenal cortex. The release of endogenous ACTH is under the influence of the nervous system via the regulatory hormone released from the hypothalamus and by a negative corticosteroid feedback mechanism. Elevated plasma cortisol suppresses pituitary ACTH release. Acthar binding to melanocortin receptors in a variety of cell types, including immune cells is likely responsible for some of the beneficial effects.

Recent data from Multiple Sclerosis (MS) suggests the ACTHar gel (80 IU X3 daily doses) is superior to 1000 mg of IV Medrol given monthly for 12 months in the treatment of MS exacerbations [31], raising the possibility of improved outcomes in LN with ACTHar in a manner similar to that described by Gourley: the addition of Medrol to the standard of care for LN improved outcomes [8].

Urinary Biomarkers

Urinary cytokines, including soluble ICAM-1 (s-ICAM-1), VCAM-1, P-Selectin, soluble TNFR-1 (s-TNFR-1), and CXC Chemokine Ligand 16 (CXCL16), have potential diagnostic significance in lupus nephritis. In addition to elevated levels in renal parenchyma and serum, urinary levels of these molecules (VCAM-1 and CXCL16, in particular) were demonstrated in SLE patients with lupus nephritis, but not in normal controls or SLE patients without nephritis. Given the fact that these molecules are present in the urine of lupus patients, particularly in those with severe nephritis and track disease activity, it has been proposed that these molecules can be used as biomarkers of active disease, and they

seem to be involved in the pathogenesis of LN. These molecules could be viewed as possible therapeutic targets in our approach to treating lupus nephritis [34]. We propose that monitoring these molecules will provide further insight into the mechanism of action of ACTH in LN.

Skin Biopsies

Membrane endothelial protein C receptor (mEPCR), and ICAM-1 are highly expressed in peritubular capillaries of kidneys from patients with lupus but also in skin biopsies from uninvolved skin (buttocks). In a recent study by our collaborator Dr Izmirly skin biopsy sections were stained with specific antibodies reactive with mEPCR, ICAM-1. There was a significant increase in the prevalence of blood vessels that stained for mEPCR and ICAM-1 in patients compared to controls [94% vs 59% ($p = 0.045$) and 81% vs 67% ($p = 0.037$), respectively]. Dermal staining for mEPCR was greater in patients with proliferative glomerulonephritis than in those with membranous disease (96% vs 60%; $p = 0.029$). A composite of poor prognostic renal markers and death was significantly associated with greater expression of mEPCR staining. These data are consistent with the notion that in patients with LN, activation of the microvasculature extends beyond the clinically targeted organ [Izmirly –quote 36]. Furthermore, in a separate study also looking at non-lesional skin biopsy samples from 21 SLE patients and 11 healthy controls endothelial cell expression of iNOS in SLE patients (mean +/- SEM score 1.5 +/- 0.2) was significantly greater compared with controls (0.6 +/- 0.2; $P < 0.01$), and higher in patients with active disease compared with those with inactive SLE (1.7 +/- 0.2 versus 1.2 +/- 0.2; $P < 0.01$), there were no differences between patients with active SLE, inactive SLE, and normal controls in cNOS. [Belmonts quote -37] We also plan on doing skin biopsies on all the patients at screening and at 6 months. These data suggest that skin from SLE patients provides a window into renal and systemic inflammation and track therapeutic responses, and as a consequence response to ACTHar. We plan to evaluate the presence of MCR in the kidney and skin biopsy samples. Skin biopsies will be obtained at screening and the week 24 visit, and mEPCR, ICAM-1, VCAM-1 will be evaluated in all biopsies.

Maintenance therapies

Recurrent renal flares cause renal damage leading to glomerulosclerosis and irreversible deterioration of renal function [9]. Safe and effective maintenance therapies are needed to prevent renal relapses, reduce progression to ESRD, and reduce the chance of adverse events. Clinical trials focusing on maintenance therapies by Contreras *et al.* [13], ALMS (Aspreva Lupus Management Study) [26] and Houssiau *et al.* (MAINTAIN) [27] suggest that MMF is at least equivalent to AZA for maintenance therapy. A summary of the maintenance trials is presented in **Table 3**. The current study patients will be maintained on MMF for total treatment duration of 2 years.

Non-immunomodulatory treatments are also used in the treatment of LN patients. These include ACE inhibitors, ARBs, and statins and are not restricted in this study.

C. RESEARCH DESIGN AND METHODS

Study Design

The study is a randomized, controlled phase IV, single center trial of ACTHar plus CellCept (Mycophenolate Mofetil), as defined by the ASPREVA Nephritis Trial (MMF 3000 mg daily) in the treatment of lupus nephritis. The primary outcome will be assessed at 6 months. Thereafter, subsequent therapy will be with CellCept maintenance 2000 mg daily.

Study Duration

Follow-ups for each patient will be conducted for a total of 24 months.

Primary Outcome

The proportion of participants who achieve a complete response at 6 months.

1. Complete response (CR) is defined as *all* of the following criteria having been achieved:
    a. Stabilization of estimated glomerular filtration rate (i.e., a 6-month eGFR level ± 10% of baseline) or improvement if the screening value is changed from patient's baseline
    b. Inactive urinary sediment (red blood cells per high-power field [RBCs/HPF] <5-10, not due to gyn bleeding)
    c. Urine protein/creatinine ratio <0.5

Secondary Outcomes

1. Frequency of responders = CR + Partial Responders (PR). PR = improvement from baseline of at least ≥50% in all abnormal renal parameters (proteinuria and serum creatinine) without deterioration of any measurements at 6 months
2. Frequency of extra-renal flares as defined by the SELENA-SLEDAI Flare Index. Extra-renal disease activity measured by SELENA-SLEDAI and BILAG
3. Steroid -like side effects: increased in BP by 20 mmHg for both SBP and DBP, increased blood sugar with a fasting plasma glucose level ≥ 126 mg/dl, weight gain ≥ 10% of the initial weight, infections
4. Side effects

Inclusion Criteria

1. Diagnosis of systemic lupus erythematosus (SLE) by American College of Rheumatology (ACR)/SLICC criteria
2. Age ≥ 16 years
3. Active lupus nephritis defined by:
    a. Kidney biopsy documentation of International Society of Nephrology/Renal Pathology Society (ISN/RPS) Class III or Class IV proliferative nephritis (including Class V occurring in combination with Class III or IV) within 12 months, and a urine protein/creatinine ratio >1 at time of entry to study
4. Ability to provide informed consent

Exclusion Criteria

1. Moderately severe anemia (Hgb < 8 mg/dL)
2. Neutropenia (< 1,000/mm3)
3. Thrombocytopenia (platelets < 50,000/mm3)
4. Positive purified protein derivative (PPD) test confirmed by positive Quantiferon TB gold.
5. Pulmonary fibrotic changes on chest radiograph consistent with prior healed tuberculosis
6. Active infections that in the opinion of the investigator increase the risks to the subject.
7. Known human immunodeficiency virus (HIV) and hepatitis B or C
8. End-stage renal disease (estimated GFR clearance < 20 mL/min/1.73 m2)
9. History of cancer, except carcinoma in situ and treated basal and squamous cell carcinomas
10. Pregnancy
11. Lactation
12. Unwillingness to use a medically acceptable form of birth control (including but not limited to a diaphragm, an intrauterine device, progesterone implants or injections, oral contraceptives, the double-barrier method, or a condom)
13. Previous failure to respond to MMF
14. Use of rituximab within the past year
15. Use of experimental therapeutic agents within the past 60 days
16. Greater than or equal to 5 times the upper limit of normal of liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], or alkaline phosphatase)
17. Severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, cardiac, or neurological disease (or, in the investigator's opinion, any other concomitant medical condition that places the participant at risk by participating in this study) with the exception of diseases or conditions related to active SLE
18. Current substance abuse

Treatment Description

Dose finding study of patients with a recent flare of LN, and biopsy proven LN (Class III, IV) treated with CellCept 3 grams daily and ACTHar gel 80 U biw or Acthar gel 80 U qod. The dose of 80 U biw was chosen based on the published literature in MN. However, in an attempt to improve outcomes we also suggest a higher dose of 80 U qod to be used for one month of "induction". Patients in the 80 U qod arm will be tapered to 80 biw after the first month of therapy. In all groups, patients can be on a prednisone dose of ≤ 20 mg prior to initiating therapy with CellCept or ACTHar. Based on the investigator's judgment, patients will be switched to oral prednisone for worsening lupus nephritis or extra-renal lupus. Patients will be maintained on ACTHar for a total of 3 months. Patients with partial response will be offered the option to continue ACTHar 80 U biw for a total of 6 months. Each dosing arm will include 10 patients.

Biomarkers

Patients whose renal biopsies are available (we expect that 80% of patients will have a biopsy done within 1 month of the screening visit) will have frozen sections stained for MCR using anti-MCR antibodies in the manner described by Gong [35]. Similarly, skin biopsy samples obtained at D 0 and week 24 will be stained for MCR. The readout of MCR activation by ACTH in the skin will be ICAM-1, VCAM1, mEPCR. Also, levels of ICAM-1, VCAM-1, and E-selectin will be evaluated in urine samples collected at D 0, weeks 4, 12 and 24. Our center has extensive expertise in the measurement of these cytokines. Our collaborator Dr. Robert Clancy will supervise the work of examining all biomarkers. We hypothesize that dermal and urinary biomarkers are likely to decrease faster in response to treatment with ACTHar as a consequence of the direct activation of the MCR.

Treatment Overview

Screening protocol –as per attached schedule of assessments

CONCOMITANT MEDICATIONS

Participants may receive all required and non-prohibited concomitant medications as clinically indicated. Prednisone in a dose of ≤20 mg daily is allowed at study entry, but should be tapered to below 10 mg daily as tolerated by week 24.

Prophylactic Medications

All participants may receive *Pneumocystis carinii* pneumonia (PCP) prophylaxis using Mepron 75 mg bid. All participants not already on either an ACE inhibitor (ACEI) or an angiotensin receptor blocker (ARB) will be encouraged to start such agents during the screening period unless contraindicated. Doses should be adjusted in an attempt to achieve a targeted systolic blood pressure less than 120 mm/Hg. A

combination of medications such as an ARB, calcium channel blocker, or beta-blocker may also be used if the ACEI does not control systolic blood pressure adequately or the participant is intolerant to the ACEI. Measures to prevent and to treat osteoporosis are strongly encouraged. These measures may include any or all of the following: calcium carbonate or citrate (1500 mg/day), vitamin D (400 IU/day), and bisphosphonates. During treatment with MMF, proton pump inhibitors may be used as prophylaxis against gastro-intestinal toxicity. At the discretion of the investigator, participants may be treated with a cholesterol-lowering agent such as a statin.

Permitted Medications

Nonsteroidal Anti-inflammatory Drugs

The use of NSAIDs and/or other symptomatic medications that are either prescribed or available over the counter should be recorded at each visit. Participants will be asked whether these medications were used for SLE-related symptoms or for symptoms not attributed to lupus. Although NSAID use is allowed during the trial, it is recommended that these agents not be initiated during the trial due to the possible adverse effects on renal function. Participants using an NSAID before study entry will be instructed to maintain stable use during the trial unless side effects develop requiring dose reduction or discontinuation.

Prohibited Medications

Participants may not use immunosuppressive agents other than the baseline prednisone and/or anti-malarial agents, except as prescribed by the protocol. Specifically, the prohibited immunosuppressants include Cytoxan preparations, methotrexate, and cyclosporine. Participants should have immunosuppressants, other than prednisone/prednisolone or anti-malarials, discontinued before commencement of the study. The use of any investigational drug or treatment other than the treatments under study is prohibited during participation in this study. It is suggested that the participant refrain from using any herbal remedies without consulting the investigators.

DRUG ACCOUNTABILITY

The investigator will maintain adequate records of the disposition of the investigational agent, including the date and quantity of drug that was received, the participants to whom the drug was dispensed (participant by participant accounting), and an account of any drug accidentally or deliberately destroyed. Records for receipt, storage, use, and disposition of the study drug will be maintained on site. A drug-dispensing log will be kept current for each participant and will contain the identification of each participant and the date and quantity of drug dispensed. All records regarding disposition of the investigational product will be available for inspection by Questcor.

ASSESSMENT OF COMPLIANCE WITH STUDY MEDICATION

ACTH and MMF compliance will be checked at each visit.

Dosage and Administration of Acthar *Daily /weekly dose, administration, frequency*

Patients will be treated with CellCept 3 grams daily and randomly assigned to ACTHar gel 80 U biw or Acthar gel 80 U qod.

The dose of 80 U biw was chosen based on the published literature in MN [30].

In an attempt to improve outcomes, we also suggest a higher dose of 80 U qod to be used for one month of “induction”. Patients in the 80 U qod will be tapered to 80 biw after the first month of therapy.

Patients will be maintained on ACTHar for a total of 3 months.

Patients that do not achieve complete response at week 12 will be offered the option to continue ACTHar 80 U biw for a total of 6 months, or 24 weeks.

Laboratory Testing and Study Schedule --see schedule of events

Patient Monitoring and Evaluation *Contingencies for patients not responding (i.e. dose adjustment, schedule change)*

Glucocorticoids may be increased during the study for worsening renal and extra-renal manifestations of SLE. The dose may be increased as required by the clinical manifestations up to 1 mg/kg/d. ACTHar will be discontinued and patients will be considered non-responders. Renal relapses, as defined by increase in proteinuria at two consecutive visits will require discontinuation of the study regimen and treatment based on investigator preference.

The major short-term side-effects of ACTH are salt and water retention, hypertension, hyperglycemia, central nervous system stimulation, peptic ulceration and immunosuppression. While such effects are reversible, if the use is prolonged, additional adverse effects including osteoporosis, cataracts, skin fragility, myopathy, Cushingoid facies, hirsutism, alopecia, fat re-distribution, and striae may occur, as well as infections which can be life-threatening.

Potential Pitfalls and Contingencies *Describe plans to address possible problems*

Study Drug Discontinuation

1. SLE Extra-renal Flare—severe BILAG A or SLEDAI flares
2. Renal Flare – increase proteinuria by 30% and/or increased in creatinine by 25% over the baseline visit 0, confirmed by repeat analysis. Proteinuria needs to be confirmed by a 24 hour urine P/C ratio.
3. ACTHar related steroid-like side effects – HTN, DM, hypoK refractory to optimal management
4. Severe life-threatening infections

Study drug can be decreased for ACTHar related AE, as described above. Patients will be closely monitored to document maintained efficacy. We propose the following taper regimen, 80 mg qod, decreased to 80 mg biw for one week if AE continues, decrease to 60 biw for one week, then 40 biw, and finally 20 biw.

If the study drug is discontinued for SLE related increased activity, the patients will be treated with the appropriate dose of prednisone and continued to be followed up until resolution of the symptoms. At the end of the 3 month treatment period, ACTH will be discontinued. In the event of adrenal insufficiency upon discontinuing the drug either for side effects or end of therapy, the previous dose of ACTH will be restarted and the above taper regimen will be followed.

Data Processing and Analysis

Statistical /Analytical Plan *Include data management and quality assurance*

Clinical response data will be evaluated every 3 months and reported as overall percent responders and complete and partial responders in each dosing arm. Also, side effects (including steroid-like side effects) will be evaluated every 3 months and reported to the IRB and Questcor. The observed response rates in this study will be compared to the historical expected complete response rate in LN of 20%, and total renal responses of 50%. A two-sided chi-square test will be used to compare the proportion of subjects with complete response and total responses between the treatment arms and these expected values. Differences in the baseline characteristic between the two treatment groups will be evaluated using descriptive statistics, the two-sample t-test for continuous variables and the chi-square test for categorical variables. Times to event for the endpoints of partial and complete remission will be analyzed with the use of the Cox proportional-hazards model. The proportion of SAEs in the study regimen will be compared with the expected SAEs from other lupus nephritis studies using a two-sided chi-square test at the 0.05 level of significance without using continuity correction.

The research will be conducted as per CUMC's strict guidelines, thus preventing unauthorized collection, use, and/or disclosure of data. Strict physical, technical, and administrative safeguards to protect data from unauthorized access and/or tampering will be in place. Appropriate measures to ensure confidentiality will be employed. The aggregate data will be entered in a database. The data will be kept in locked facilities that can only be accessed by study investigators or a member of the research team. This will be for a period of up to 10 years, after which the data collection forms and database from this study will be destroyed.

Sample Size Justification *Include power analyses or justification for enrollment plan*

N=10 patients per dosing arm.

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