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Research Article

Six Months' Treatment of Moderately to Severely Active Systemic Lupus Erythematosus with Repository Corticotropin Injection: An Extension of a Single-Site, Open-Label Trial

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Abstract

Background: Patients with systemic lupus erythematosus (SLE) are frequently inadequately controlled with or intolerant to traditional treatments, necessitating alternative therapeutic options. This trial assessed the efficacy and safety of repository corticotropin injection (H.P. Acthar® Gel, Mallinckrodt ARD, Inc., Hazelwood, MO, USA) for six months.

Methods: This 6-month extension of a 28-day trial published in 2014 includes 5 individuals (all women, mean 51.0 years of age, mean duration of SLE 9.4 years), who received 1 mL (80 U/mL) of Acthar Gel by subcutaneous injection twice weekly. The primary outcome measure was Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K), and secondary outcomes were British Isles Lupus Assessment Group Index (BILAG) 2004, blood pressure, and Swollen, Tender, and Total Joint Counts.

Results: Subjects experienced significant improvements in SLE DAI-2K from Day 0 to Month 3 ($P = 0.040$) and Day 0 to Month 6 ($P = 0.0007$). Tender Joint Count was significantly improved from Day 0 to Month 3 ($P = 0.0057$) and Month 6 ($P = 0.0020$), as was Swollen Joint Count (Month 3, $P = 0.020$; Month 6, $P = 0.0041$) and Total Joint Count (Month 3, $P = 0.0073$; Month 6, $P = 0.0021$).As measured by BILAG 2004, mean mild and moderate arthritis scores were 2.4 at Day 0, 0.4 at Month 3, and 0.0 at Month 6. Blood pressure values were unchanged from start to finish.

Conclusions: This 6-month extension not only demonstrated improvements in SLEDAI-2K but also revealed Acthar Gel could produce significant, longer-term improvements in Swollen, Tender, and Total Joint Counts, as well as BILAG 2004.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex, chronic autoimmune disease that impacts multiple organs, including kidneys, brain, and heart; in addition, SLE manifests in a variety of tissue types, such as cutaneous. [1] (Table 1). The disease is also characterized by a range of clinical signs, symptoms, and disease severities, along with disease flares that are often unpredictable [1].

The outcomes of SLE flares include clinically significant and measurable increases in disease activity in at least 1 organ system; such changes are the result of either new or worsening clinical signs and symptoms and/or abnormal laboratory measurements, [2] (Table 2) and such effects indicate that a change in treatment should be considered [2]. It is therefore critical to effectively manage disease activity and disease flare in order to reduce the risk of accumulated organ and tissue damage over time, decrease

Table 1: Duration of disease, and previous and concomitant medications.

Subject[aa]	Years, Disease Duration, Lupus Criteria	Current medications	Dose	Schedule	Reason for restarting Acthar Gel 80 U/mL SC twice weekly	Date Acthar Gel was stopped, restarted
10	8, +ANA, arthritis, neuro disorder, malar and discoid rash	Belimumab [Benlysta]	960 mg IV	q 4 weeks	Increasing SLE symptoms	3/17/2013, 5/14/2013
		Hydroxychloroquine sulfate [Plaquenil]	200 mg	PO BID		
		Diclofenac	Cream 5%	BID		
5	4, +ANA, arthritis, malar rash, mucosal ulcers	Hydroxychloroquine sulfate [Plaquenil]	200 mg	2 tabs PO QD	Disease progression, patient request	11/30/2012, 2/18/2013
		Meloxicam [Mobic]	15 mg	1 tab PO QD		
		Belimumab [Benlysta]	1040 mg	IV q 4 wks		
9	10, +ANA +Sm Ab, arthritis, mucosal ulcers, malar rash, photosensitivity	Belimumab [Benlysta]	620 mg	IV q 4 wks	Patient request due to worsening fatigue and joint pain	1/19/2013, 2/28/2013
		Hydroxychloroquine sulfate [Plaquenil]	200 mg	2 tabs PO QD		
		Methotrexate	12.5 mg	PO once weekly		
		Hydrocortisone	10 mg	1 tab PO am		
		Hydrocortisone	5 mg	1 tab PO pm		
		Folic acid	1 mg	PO QD		
		Diclofenac sodium	75 mg	PO BID		
7	7, +ANA, arthritis, malar rash, mucosal ulcers, photosensitivity	Belimumab [Benlysta]	840 mg	IVq 4 weeks	Flare and rash in joints	12/13/12, 1/07/13
		Celecoxib [Celebrex]	200 mg	PO BID		
6	3, +ANA, arthritis, photosensitivity malar rash, pleurisy, mucosal ulcers	Belimumab [Benlysta]	1160 mg	IVq 4 weeks	Worsening SLE flare	12/01/12, 1/09/13
		Methotrexate	20 mg	PO once weekly		
		Meloxicam [Mobic]	7.5 mg	PO BID		
		Folic acid	400 mcg	PO BID		

[a]Each of these subject numbers matches the identification code utilized in the previous 28-day study [12]

Table 2: SLEDAI-2K and Joint Count.

Subject[a]	SLEDAI-2K			Joint Count		
	Day 0	Month 3	Month 6	Day 0	Month 3	Month 6
10	Arthritis = 4	Arthritis = 0	Arthritis = 0	Tender = 17	Tender = 2	Tender = 2
	Hematuria = 4	Hematuria = 0	Hematuria = 0	Swollen = 7	Swollen = 1	Swollen = 1
5	Arthritis = 4	Arthritis = 0	Arthritis = 0	Tender = 16	Tender = 2	Tender = 3
	Hematuria = 4	Hematuria = 0	Hematuria = 0	Swollen = 8	Swollen = 0	Swollen = 0
9	Arthritis = 4	Arthritis = 4	Arthritis = 0	Tender = 8	Tender = 3	Tender = 2
	Alopecia = 2	Alopecia = 2	Alopecia = 2	Swollen = 3	Swollen = 2	Swollen = 0
7	Arthritis = 4	Arthritis = 4	Arthritis = 0	Tender = 13	Tender = 6	Tender = 2
	Rash = 2	Rash = 0	Rash = 0	Swollen = 8	Swollen = 3	Swollen = 0
6	Arthritis = 4	Arthritis = 0	Arthritis = 0	Tender = 16	Tender = 4	Tender = 1
	Rash = 2	Rash = 0	Rash = 0	Swollen = 11	Swollen = 0	Swollen = 1

[a]Each of these subject numbers matches the identification code utilized in the previous 28-day study [12].

the morbidity and mortality associated with end - stage organ damage, and lower the economic burden of SLE on individuals and improve their quality of life (QoL) [1,3-6].

Although multiple immune suppressants, including azathioprine, mycophenolate mofetil, and methotrexate, have been used to reduce disease severity and/or decrease the use of steroids, there remains a substantial unmet need for flare management and active disease control among those with SLE, as approximately one - third of them still experience flaring after remission [6]. There are few medications currently approved by the US FDA for treatment of SLE, and they include prednisone, hydroxychloroquine, belimumab, and H.P. Acthar® Gel (repository corticotropin injection, Mallinckrodt ARD, Inc., Hazelwood, MO, USA). Acthar Gel is a long-acting formulation containing the full sequence of ACTH $_{(1–39)}$ that also may include other proopiomelanocortin peptides [7,8]. The steroidogenic effect of melanocortin (MC) signaling is a result of activation of the MC_2 receptor which can be induced by ACTH on the adrenal gland, and after multiple downstream steps, there is induction of cortisol; cortisol signals through the glucocorticoid receptor on multiple cell types [8-10].

Acthar Gel was initially approved by the FDA in 1952 [8]. Several updates have been made to its prescribing information since then, and SLE is one of the indications currently listed. However, many physicians treating SLE are unaware that Acthar Gel is an approved treatment option, and there have been very few clinical trials or publications that address the efficacy or safety of Acthar Gel for the treatment of SLE. Acthar Gel has been included in very few animal or clinical trials for SLE, only 1 of which lasted more than 12 weeks but studied mouse strains (New Zealand Black and New Zealand White strains; NZB/W F1), rather than human subjects [11]. However, the current study is a continuation of a 28-day trial that we published in *Lupus* in 2014 in which 10 subjects with moderately to severely active SLE who did not respond adequately to at least 1 previous treatment received Acthar Gel 80 U/mL SC daily for 10 days [12]. The 10 participants in that previous study had significant improvements from baseline at Days 14 and 28 in the primary endpoint (Systemic Lupus Erythematosus Disease Activity Index-2000 [SLEDAI-2K]) as well as in the majority of the secondary outcome measures (Physician Global Assessment, Patient Global Assessment, erythrocyte sedimentation rate [ESR], and Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue) [12]. Only Lupus QoL and C-reactive protein (CRP) were not significantly different at both intervals. The goal of the current study is to determine if the benefits obtained during the previous short - term trial [12] can be sustained for an entire 6 months. To that end, both the SLEDAI-2K and British Isles Lupus Assessment Group (BILAG) 2004 index [13-15] which require more time than many of the outcome measures utilized in the initial study, have been utilized.

METHODS

Study population

Men and women (18-75 yrs old) were eligible to participate in the initial 28-day study [12] if they met American College of Rheumatology (ACR) criteria for SLE and presented with chronic, moderately to severely active disease, along with disease flare, while receiving standard treatments. All participants provided written informed consent, were free to discontinue treatment at any point, and were recruited from a single site in Lansing, MI, USA. The initial study [12] protocol was approved by an Investigational Research Board/Independent Human Research Ethics Committee and carried out in accordance with Good Clinical Practice guidelines, and the study was conducted in accordance with the Declaration of Helsinki 1975, revised Hong Kong 1989.

Study design

This was a single-site, open-label extension of a previously reported study [12]. Participants received 1 mL (80 U/mL) of Acthar Gel by subcutaneous injection twice weekly for 6 months following the original 28-day trial (see Table (1)). The first dose of the previous study was given at the investigator site, during which subjects were educated on aseptic subcutaneous injection technique in order to administer all remaining injections at home. Subjects were instructed to report all adverse events (AEs) that occurred at any time during the study.

Inclusion/exclusion criteria

In order to meet the eligibility requirements of the initial 28-day study [12] participants had to match ACR criteria for SLE and lupus flare and had to fulfill at least 4 of the 11 ACR classification criteria for SLE, including a history of antinuclear antibody (ANA) positivity. Participants also had to have a diagnosis of SLE with chronic disease activity that required ongoing treatment and/or observation ≥ 8 weeks prior to screening of the previous study [12]. They must have received a stable dose (or equivalent) of prednisone ≤ 20 mg/day for ≥ 4 weeks prior to granting informed consent, and at the time of screening and Day 0 of the previous study, subjects met SLE flare criteria, including a SLEDAI-2K score ≥ 6 points, and at least 1 on the BILAG 2004 A organ system score or 2 B organ system scores. Female individuals of childbearing age were required to employ birth control from screening until 90 days after the final Acthar Gel dose.

The exclusion criteria prohibited concurrent enrollment in any other clinical trial within 4 weeks of Day 0 of the initial study [12] if it employed an investigational product, or within 5 half - lives of the investigational product used in that clinical study. Any participant who received any new oral prednisone therapy or underwent any change in the dosing of his or her current one during the 4 weeks prior to the signing of the consent form was excluded from this trial. Additional exclusion criteria have been reported in the previous publication [12].

Outcome measures

The primary outcome measures of this study were changes in SLEDAI-2K from Day 0 to Month 3 and to Month 6. Secondary outcome measures included BILAG 2004 scores and blood pressure, as well as Swollen, Tender, and Total Joint Counts. (Both SLEDAI-2K and BILAG 2004 are well-established measurements in the field of SLE) [13-15].

Data analysis

Paired t-tests were used to assess the changes from Day 0 to Month 3 and to Month 6 for each of the dependent variables, with

Table 3: Individual BILAG 2004 results at Day 0, Month 3, and Month 6.

Subject[a]	BILAG 2004	BILAG 2004 Score		
		Day 0	Month 3	Month 6
10	#6 (skin)	4	0	0
	#41 (moderate arthritis)	2	0	0
	#42 (mild arthritis)	2	0	0
5	#6 (skin)	4	0	0
	#41 (moderate arthritis)	2	0	0
	#42 (mild arthritis)	2	0	0
	#88 (active urinary sedimentation)[b]	-	-	-
9	#16 (mild alopecia)	2	2	2
	#41 (moderate arthritis)	2	1	0
	#42 (mild arthritis)	2	1	0
7	#6 (skin)	4	0	0
	#41 (moderate arthritis)	3	1	0
	#42 (mild arthritis)	3	1	0
6	#6 (skin)	3	0	0
	#41 (moderate arthritis)	3	0	0
	#42 (mild arthritis)	3	0	0

[a]Each of these subject numbers matches the identification code utilized in the previous 28-day study [12]. [b]Active Urinary Sedimentation is not scored numerical

Table 4: Changes in prednisone doses.

Subject[a]	Prednisone dose		
	Day 0	Month 3	Month 6
10	10 mg	0 mg	0 mg
5	10 mg	0 mg	0 mg
9	15 mg	5 mg	0 mg
7	10 mg	0 mg	0 mg
6	0 mg	0 mg	0 mg

[a]Each of these subject numbers matches the identification code utilized in the previous 28-day study [12].

the exception of BILAG 2004, which is a qualitative measurement. A positive response was defined as a greater than 4 point reduction from Day 0 in SLEDAI-2K score and no new BILAG A organ domain scores or no more than 1 new BILAG B organ domain scores compared with Day 0.

RESULTS

Five women (4 White and 1 African American mean 51.0 years of age, mean duration of SLE9.4 years) who completed the initial 28-day trial [12] participated in this 6-month extension study. (The remaining 5 patients from the original 30 day trial chose not to participate in the longer trial for various reasons, including financial and logistical, but not due to side - effects). The dates of initiation and doses of concomitant medications, as well as the reasons the subjects participated in the 6-month extension, are presented in Table (1).

All 5 of the participants experienced improvements in SLEDAI-2K (Table 2), and the changes from Day 0 to Month 3 were significant (P = 0.040), as were the improvements from Day 0 to Month 6 (P = 0.0007). Tender Joint Count was also significantly improved from Day 0 to Month 3 (P = 0.0057) and Month 6 (P = 0.0020), as was Swollen Joint Count (Month 3, P = 0.020; Month 6, P = 0.0041) (Table 2). When Tender and Swollen Joint Counts were combined, the Total Joint Counts were also significantly improved at Month 3 (P = 0.0073) and Month 6 (P = 0.0021). Two individuals were noted to have hematuria and one of those two had active urinary sediment at the onset of the study. Those findings resolved at the next time of evaluation and neither patient had renal insufficiency on blood testing.

The BILAG 2004 Index measurements improved among all of the subjects (Table 3). Four of the 5 individuals achieved scores of 0 on at least 1 measurement by Month 3, and all of them did by Month 6. Only 1 participant had no improvement on only 1 measure (mild alopecia), and that score remained the same from Day 0 to Month 3 and to Month 6. All other measures among all 5 participants reached scores of 0 by Month 6.

Four of the 5 individuals were receiving prednisone at Day 0 but only 1 of them still required it at Month 3, and none did by Month 6 (Table 4). There was very little change in mean systolic blood pressure from Day 0 to Month 6 (118.8 to 118.2) and a

slight decrease in diastolic blood pressure during that time (74.0 to 70.8) No other minor or major adverse events occurred during the six month trial.

DISCUSSION

Although the US FDA has approved Acthar Gel for the treatment of SLE, very few efficacy and safety studies have been conducted to evaluate its potential benefits and risks, and none of the trials have been for duration greater than 12 weeks. The original 28-day study published by these authors [12] demonstrated significant improvements following treatment with Acthar Gel in Physician Global Assessment, Patient Global Assessment, FACIT-Fatigue scale, ESR, and SLEDAI-2K, and this 6-month extension study not only confirmed those benefits in SLEDAI-2K, it also revealed that Acthar Gel could produce significant improvements in swollen and tender joints, as well as Total Joint Counts. Although BILAG-2004 is a qualitative scale, the improvements in this outcome measure do indicate substantial reduction in disease activity [15].

With the exception of mild alopecia that afflicted only 1 subject in this study, all of the other BILAG 2004 measurements reached the ideal score of 0 by Month 6.

There are several factors that contribute to the complexity of treating SLE [16]. Among those factors are insufficient responses by some patients to first - line therapies, as well as the large number of relapses that occur after initial clinical remissions. Second - line treatments are often prescribed for individuals who experience remission, according to the clinical judgments of physicians, obviating any standardized evaluation of results. The therapeutic armamentarium has expanded substantially in the past decade, and this expansion is expected to continue.

CONCLUSION

This 6-month extension study demonstrated that Acthar Gel can be a safe and effective long - term treatment for SLE. The results not only confirmed the improvements in SLEDAI-2K that were obtained in the original 28-day trial, they also revealed significant and continued improvements in Swollen, Tender, and Total Joint Counts, as well as BILAG 2004.

Clear limitations of this study include the limited number of patients involved and the lack of a placebo controlled cohort. Possible toxicities such as bone loss and other possible long-term steroid related problems could not be evaluated in the course of only six months.

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CONFLICT OF INTEREST STATEMENT

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