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Repository corticotropin injection (H.P. Acthar gel) for the treatment of sarcoidosis-induced hypercalciuria and vitamin D dysregulation: a pilot, open label study

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Abstract. *Background:* Vitamin D dysregulation may occur in sarcoidosis patients and result in hypercalciuria, hypercalcemia, nephrolithiasis, and renal impairment. We performed an open label pilot study of highly purified (H.P.) Acthar® Gel (repository corticotropin injection) (RCI) on patients with sarcoidosis-induced vitamin D dysregulation and hypercalciuria. *Methods:* Nine patients with sarcoidosis-induced vitamin D dysregulation and hypercalciuria on stable maintenance anti-sarcoidosis therapy received 80 units of RCI subcutaneously twice weekly for 12 weeks. 24-hour urinary calcium excretion was measured at baseline and at 12 weeks. Other parameters measured over 16 weeks (including 4 weeks post the last RCI dose) included the following serum values: calcium, 25-OH vitamin D, 1,25- diOH vitamin D and serum parathyroid hormone (PTH). In addition, the Sarcoidosis Health Questionnaire (SHQ) and Short Form-36 (SF-36) as well as a urinary symptom score were measured in all subjects. *Results:* There was no significant change in the 24-hour urinary calcium excretion over 12 weeks of the study. However, there was evidence that RCI improved sarcoidosis-induced vitamin D dysregulation in that the serum 1,25- diOH vitamin D level significantly declined over 12 weeks. There was also improvement in most of the domains of the quality of life measures, although only a few of them reached statistical significance. There was also a trend toward improvement in urinary symptoms over the study period. The was evidence of the development corticosteroid side effects in the cohort, in that weight significantly increased over the study period. *Conclusions:* In this small pilot open label trial, 12 weeks of RCI did not significantly improve sarcoidosis-induced hypercalciuria. However, some statistically significant changes in serum vitamin D and PTH levels were demonstrated that were consistent with some amelioration of sarcoidosis-induced vitamin D dysregulation. Several corticosteroid-related side effects were demonstrated in this cohort. *(Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 192-197)*

Key words: sarcoidosis, treatment, vitamin D, hypercalciuria, corticotropin

Introduction

In the 1950's, several case reports suggested that corticotrophin was effective for the treatment of sarcoidosis (1, 2). During that decade, corticotrophin was approved for the treatment of sarcoidosis by the Food and Drug Administration (FDA), although no prospective, randomized, placebo-control or blinded studies had been performed. The FDA subsequently approved hydrocortisone and prednisone for the treatment of sarcoidosis, which resulted in decreased use of corticotrophin treatment because of cost, inconvenience of using an injected drug route of delivery, concern about the drug's efficacy and incomplete dosing information (3).

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Recently, a retrospective analysis of 47 sarcoidosis patients treated with corticotrophin in the form of H.P. Acthar® Gel (repository corticotropin injection) (RCI) was published demonstrating a benefit in approximately one-third of patients (3). Prior to RCI therapy, all these patients had been classified as having an incomplete response to their current anti-sarcoidosis regimen because of progressive symptomatic disease despite immunosuppressive therapy and/or excessive toxicity with current treatment. Another recent single-blind prospective trial of 16 patients with chronic pulmonary sarcoidosis showed that RCI improved some pulmonary function parameters, quality of life measures, and decreased lung inflammation on the basis of positron emission tomography scanning (4).

Vitamin D dysregulation in sarcoidosis results from increased 1-α hydroxylase activity in sarcoidosis macrophages that converts 25-hydroxy vitamin D, the inactive form of vitamin D, to 1,25 – dihydroxy-vitamin D, the active form of the vitamin (5-7). This usually results in a low serum 25-hydroxy vitamin D level, a high-normal to elevated serum 1,25-dihydroxy vitamin D level (8, 9), and a low serum PTH levels as PTH is suppressed by the elevated 1,25-dihydroxy vitamin D level (10). The elevated serum 1,25-dihydroxy vitamin D levels may cause increased gut absorption and renal excretion of calcium leading to hypercalcemia, hypercalciuria, nephrolithiasis and kidney injury (11, 12). Because vitamin D dysregulation is directly related to granulomatous inflammation from sarcoidosis, it typically responds to anti-granulomatous therapy such as corticosteroids and other anti-sarcoidosis agents (12).

In this pilot open-label prospective trial, we administered RCI to nine patients with sarcoidosis-induced vitamin D dysregulation and hypercalciuria. We examined the effect of RCI therapy on vitamin D levels, PTH, urinary calcium excretion, symptoms related to vitamin D dysregulation and quality of life measures.

Methods

This study was approved by the Albany Medical College Institutional Review Board (study number 3901). This trial was registered with clinicalTrials.gov (NCT02155803). Subjects were eligible for enrollment in this trial if they met the following inclusion criteria: a) A diagnosis of sarcoidosis on the basis of standard criteria (13, 14); b) biopsy evidence of granulomatous inflammation with no alternative cause other than sarcoidosis; c) English speaking proficiency; d) age >18 years; and e) 24-hour urinary calcium concentration of >4 mg/kg/day with no other alternative etiology of hypercalciuria identified. The exclusion criteria included a) a history of Cushing's disease; b) concurrent calcium or vitamin D supplementation; c) concurrent use of calcium containing antacids; d) presence of osteoporosis or osteopenia; e) adrenal insufficiency or dysfunction; f) a change in anti- sarcoidosis medications within three months of study entry; g) history of hyperparathyroidism; h) a non- sarcoidosis cause for hypercalcuria or hypercalcemia; i) use of diuretics for hypertension or other medical disorders; j) a history of scleroderma; k) systemic fungal infections; l) ocular herpes simplex; m) recent surgery; n) history of or the presence of peptic ulcer disease; o) a history of congestive heart failure; p) uncontrolled hypertension; q) a sensitivity to proteins of porcine origin; r) having used an investigational drug within one month prior to screening or within five half-lives of the investigational agent, whichever is longer; and lastly, s) subject requiring live, attenuated vaccines.

All enrolled subjects received H.P. Acthar® Gel (repository corticotropin injection) (RCI) in an open-label unblinded fashion. All subjects were administered 80 units of RCI subcutaneously twice weekly for 12 weeks. During the course of the study, the subjects' baseline anti-sarcoidosis treatment regimen was to remain unchanged. The primary study endpoint was reduction in 24-hour urine calcium excretion between week 0 and week 12. The following additional parameters were measured at weeks 0, 4, 8, 12 and 16: physical examination, extra-cutaneous physician organ severity tool (ePOST) (15), patient global health assessment via visual analog scale, sarcoidosis health questionnaire (SHQ) (16), short form 36 (SF-36) (17) (we used the RAND 36-item Health Survey v1.0 Questionnaire items: http://www.rand36calculator.com/), serum chemistries (principally calcium, phosphorus, blood urea nitrogen, creatinine, and bicarbonate), serum 25-OH vitamin D, serum 1,25- diOH vitamin D and serum parathyroid hormone levels (PTH). In addition, at each visit, each subject was asked if each of the following 8 urinary symptoms were present or absent: polyuria,

dysuria, pyuria, hematuria, urgency, flank pain, kidney stone attack. Each symptom question received a score of "1" if the symptoms was present and "0" if the symptom was absent, so that the total score of the urinary symptom evaluation ranged from 0 to 8.

Results

Nine patients were enrolled in this trial, and their demographics and clinical characteristics are displayed in Table 1. Five of the nine (56%) were not receiving any anti-sarcoidosis therapy during the trial.

Table 1. Basic clinical characteristics of the cohort (N = 9)

Characteristic	
Age (yrs), mean±SD	49±11
Sex, female N, %	5, 56%
Race, Caucasian N, %	9, 100%
Number of organs involved, mean±SD	2.0±1.0
Extrapulmonary manifestations N, %	5, 56%
On any anti-sarcoidosis therapy N, %	4, 44%
Steroid treatment N, %	3, 33%
Prednisone dose (mg), mean±SD	5.8±1.4
Infliximab treatment N, %	1, 11%

Table 2 shows the 24-hour urine calcium, serum vitamin D and PTH levels of the cohort at weeks 0, 12, and 16. There was no significant change in the primary study endpoint, the 24-hour urine calcium level. Although there were no consistent findings over the 16 weeks, there were statistically significant differences between various weeks that suggested a potential signal in improving vitamin D dysregulation (serum 1,25-di-hydroxy vitamin D levels lowered between week 0 and week 12, serum PTH increased between week 0 and week 16). The urinary symptom score decreased significantly between week 0 and 16 (Table 3), and there was a general trend toward improvement over the study period (figure 1).

Table 4 shows the SHQ scores of the cohort over the 12 weeks of drug administration and 16 weeks of observation. There was an improvement in the total SHQ score and all the SHQ domains over these time periods. However, a statistically significant increase was only demonstrated in the total SHQ score at week 16 compared to week 0 and in the emotional domain of the SHQ score at week 12 compared to week 0 and week 16 compared to week

Table 2. Vitamin D parameters of cohort between week 0 vs. week 12, and week 0 vs. week 16

	Mean±SD ***p-value*: compared to week 0***		
	Week 0	Week 12	Week 16
24 hr urinary calcium (mg/dl)	366±85.1	343±172.0 *0.66*	-
25-OH Vit. D (ng/ml)	22.0±9.9	21.5±7.1 *0.83*	21.5±8.3 *0.85*
1,25 di-OH Vit. D (ng/ml)	66.4±16.6	49.1±19.5 ***0.008***	59.4±23.7 *0.41*
PTH (pg/ml)	25.8±21.3	30.2±18.5 *0.16*	40.0±29.0 ***0.003***

*two-tailed test

Table 3. Clinical parameters of cohort weeks 0, 12, and 16

	Mean±SD ***p-value*: compared to week 0***		
	Week 0	Week 12	Week 16
Urinary symptom score	2.3±1.6	2.2±2.9 *0.89*	1.4±1.3 ***0.01***
ePOST score	1.9±0.9	1.6±0.7 *0.35*	2.0±1.3 *0.76*

*two-tailed test

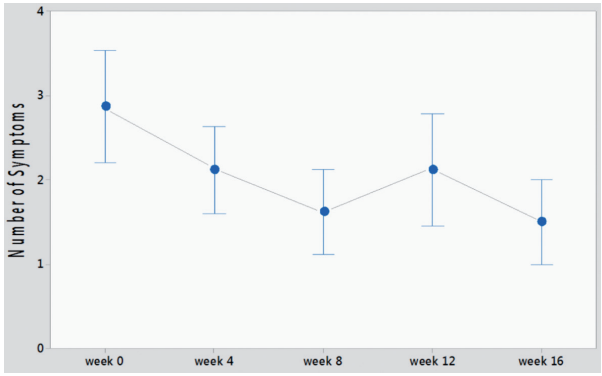

Fig. 1. Plot of mean and standard deviation of urinary symptom score during the weeks of the study. Each of 8 urinary symptoms received a score of "1" if it was present and a score of "0" if it was not. The total score could range from 0 to 8

0. Table 5 shows the SF-36 scores for the eight SF-36 domains over the 12 weeks of drug administration and 16 weeks of observation. Although, in general, there was an improvement in the SF-36 scores over time in most domains, only the improvement in physical functioning statistically significantly improved at both week 12 and 16 compared to week 0 and health change improved statistically significantly at week 16 compared to week 0.

Table 6 shows the change in weight and blood pressure in the cohort between week 0 and 12 and between week 0 and week 16. Over both time periods, there was statistically significant increase in weight (more than 3 kg). There was no clear change observed in terms of the diastolic, systolic and mean blood pressure over both time periods. In terms of specific adverse events that could probably be attributed to corticosteroid toxicity, glucose intolerance occurred in 2 subjects, and each of the following adverse events occurred one subject (each event occurred in a different subject): water retention, facial swelling, acne, bruising, thrush.

Discussion

In this open-label pilot study of 80 units of RCI subcutaneously twice weekly for 12 weeks for the treatment of sarcoidosis-induced vitamin D dysregulation and hypercalciuria, we were unable to demonstrate that the drug significantly reduced the 24-hour urine calcium excretion. There was a statistically significant increase in weight over the 12 weeks.

Although this was a negative study in terms of 24-hour urine calcium excretion which was the primary endpoint, there were signals that RCI may have lessened sarcoidosis-induced vitamin D dysregulation of the cohort. Specifically, there was a statistically significant reduction in serum 1,25-di-hydroxy vitamin D between week 0 and week 12 in the cohort, as well as a statistically significant increase in serum PTH between week 0 and week 16. Both of these changes are in the direction of resolution of sarcoidosis-induced vitamin D dysregulation that results in an elevation of serum 1,25-di-hydroxy vitamin D that suppresses PTH secretion (8-10).

We chose to examine the change in symptoms and quality of life over 12 and 16 weeks because we suspect that the resolution of symptoms related to vitamin D dysregulation may be delayed after correction. There was a general trend in improvement in the symptoms associated with nephrolithiasis over

Table 4. Sarcoidosis Health Questionnaire Scores during the study

	Mean±SD (median) ***p-value*: compared to week 0***				
	Week 0	Week 4	Week 8	Week 12	Week 16
Total score	4.29±1.08 (4.06)	4.63±1.03 (4.44)	4.57±0.98 (4.23)	4.76±1.28 (4.73) *0.15*	4.79±0.99 (4.51) ***0.04***
Emotional score	4.29±0.95 (4.6)	4.481±0.8 (4.6)	4.61±0.63 (4.3)	4.78±0.96 (4.65) ***0.005***	4.83±0.77 (4.5) ***0.03***
Physical score	4.43±1.25 (4.17)	4.94±1.42 (4.67)	4.89±1.18 (4.50)	4.79±1.57 (4.00) *0.35*	5.09±1.09 (5.17) *0.07*
Daily score	4.42±1.28 (3.92)	4.48±1.15 (4.62)	4.21±1.33 (4.39)	4.53±1.47 (4.46) *0.41*	4.47±1.28 (4.00) *0.18*

*two-tailed test

Table 5. Short-Form 36 scores during the study

	Mean±SD (median)				
			p value: compared to week 0		
	Week 0	Week 4	Week 8	Week 12	Week 16
Physical functioning	68.89±25.47 (75)	74.44±21.42 (80)	60±33.35 (65)	72.78±26.94 (80) ***0.023***	76.11±23.29 (80) ***0.008***
Role limitation due to physical health	36.11±43.5 (25)	55.56±48.05 (75)	47.22±50.69 (25)	38.39±46.96 (25) *0.84*	58.33±43.3 (50) *0.20*
Role limitation due to emotional problem	51.67±37.78 (33)	74.11±43.38 (100)	77.78±37.31 (100)	55.56±40.89 (67) *0.77*	66.67±44.13 (100) *0.31*
Energy/fatigue	42.78±23.47 (45)	47.22±25.26 (50)	48.89±26.31 (40)	45±26.57 (50) *0.82*	49.44±25.43 (50) *0.38*
Emotional wellbeing	79.56±12.72 (80)	69±15.82 (66)	76±15.42 (78)	69±22.40 (74) *0.39*	75.5±15.92 (78) *0.83*
Social functioning	70.89±27.88 (75)	61±29.46 (56.5)	76.62±30.11 (87.5)	67.38±33.99 (75.5) *0.99*	73.5±31.57 (87.5) *0.69*
Pain	63.56±32.54 (68)	59±22.77 (61.5)	71.12±27.04 (73)	65.88±33.09 (78) *0.68*	60.25±34.65 (73) *0.94*
General health	48.33±25.62 (50)	41.88±26.85 (40)	41.88±24.92 (40)	44.38±25.7 (50) 0.94	45±27.65 (47.5) *0.90*
Health change	44.44±24.30 (50)	50±35.35 (50)	56.25±34.72 (50)	56.25±39.53 (50) *0.38*	59.38±29.69 (50) ***0.04***

Table 6. Mean of change in blood pressure and weight in each patient in the cohort at weeks 12 and 16 compared with week 0

	Mean±SD	
	Week 12	Week 16
Weight (kg)	+3.6±3.0	+4.4±3.7
MAP (mmHg)	+4.1±7.8	-0.1±6.4
SBP (mmHg)	+0.2±7.9	-3.2±9.2
DBP (mmHg)	+6.0±10.1	+1.4±7.7

the 16-week period of observation. In addition, quality of life measures tended toward improvement with RCI therapy in this cohort, although few of the parameters reached statistical significance. Although this pilot study was not adequately powered to detect statistically significant differences, particular caution is advised in attributing changes in symptoms and quality of life in an open label study of an active drug without a placebo control group. An additional issue is that RCI may cause a euphoric effect related to its effect on corticotrophin pathways that may improve quality of life in the short-term.

RCI therapy demonstrated significant corticosteroid-related side effects in this cohort. Such side effects have been demonstrated previously in a trial of RCI for pulmonary sarcoidosis (4). In that trial, both an 80 units twice weekly dose and 40 units twice weekly dose of RCI were used. There was no difference in terms of efficacy of the two doses and less corticosteroid side effects were observed with the lower dose. Therefore, it is possible that we would have observed less corticosteroid toxicity in our cohort if this lower dose had been used.

Our study had several limitations. First, it was a small pilot study aimed at detecting a signal of amelioration of sarcoidosis-induced vitamin D dysregulation and hypercalciuria. It was not powered to detect significant differences. Therefore, even though the primary endpoint was not reached, we detected changes in vitamin D dysregulation that make it plausible that RCI may be useful for this condition. Second, we used a fixed dose of RCI that was demonstrated to be no more efficacious and more toxic than half of our dose in a pulmonary sarcoidosis trial (4). Third, as previously mentioned, the positive changes in quality of life measures and symptoms are problematic to interpret in an open label trial without a placebo group.

In summary, in this small pilot open label trial of RCI for sarcoidosis-induced vitamin D dysregulation and hypercalciuria, we did not demonstrate sig-

nificant improvement in hypercalciuria, the primary endpoint. However, we did detect some statistically significant changes in serum vitamin D and PTH levels consistent with some amelioration of sarcoidosis-induced vitamin D dysregulation. Several corticosteroid-related side effects were demonstrated in this cohort. We believe that these data, coupled other clinical sarcoidosis trials of RCI, suggest that lower doses of the drug may be beneficial for sarcoidosis-induced vitamin D dysregulation. This postulation could potentially be examined in larger clinical trials.

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