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H.P. Acthar® Gel in Dermatomyositis and Polymyositis Treatment Registry: An Interim Analysis

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Abstract

Introduction: Therapies for dermatomyositis and polymyositis (DM/PM) include corticosteroids, immunosuppressants, and intravenous immunoglobulin (IVIg). A high proportion of patients with DM/PM are refractory to therapy. H.P. Acthar® Gel, repository corticotropin injection (RCI) is a potential anti-inflammatory treatment.

Methods: Patients enrolled in the Acthar in Dermatomyositis and Polymyositis Treatment registry were monitored for changes in the clinical parameters of DM/PM after initiation of RCI twice weekly in doses up to 80 IU per subcutaneous injection.

Results: RCI treatment effectively altered the clinical course of DM/PM in 14 of 24 patients. Positive responses to treatment were associated with disease activity at baseline and duration of treatment. Mild to moderate adverse events were reported.

Conclusions: This is the largest observational study of RCI in treatment of DM/PM to date and results indicate that RCI may be an effective, tolerable treatment for refractory patients. Controlled studies are necessary to identify any additional associations between disease state and response to RCI treatment.

Keywords: Dermatomyositis; Polymyositis; Adrenocorticotropic hormone; Repository corticotropin injection

Introduction

Incidence rates for idiopathic inflammatory myopathies (IIMs) are reported between 4.27 and 7.89 per 100,000 person-years in the United States [1-3]. It is estimated that between 50, 000 and 75,000 people in the US are affected by myositis [4]. Of the IIMs, dermatomyositis (DM) and polymyositis (PM) are amongst the most common autoimmune forms of myositis [5]. DM can affect patients of any age, usually initially manifesting with skin changes, including rash and erythema, accompanied by or followed by muscle weakness and myalgia [5]. Patients with PM also experience proximal muscle weakness without an associated rash. Pulmonary fibrosis, paraneoplastic implications, calcinosis, and joint and muscle pain can accompany either PM or DM, suggesting a common autoimmune pathology despite different pathologic findings on muscle biopsy [5,6].

The current treatment strategy for DM/PM includes corticosteroids as the first-line treatment. Prednisone is typically administered in high-dose (1 mg/kg/day up to six weeks) and tapered based on the responsiveness of the disease [5,7]. For acute patients, pulsed intravenous methylprednisolone is used initially, followed by a switch to oral corticosteroids [7]. If the patient does not respond to corticosteroid treatments, which can occur in up to 30% of all patients, or cannot tolerate the adverse effects (AEs) associated with steroid use, immunosuppressants, such as azathioprine, methotrexate, mycophenolate mofetil, or cyclosporine, may be added to the treatment regimen as corticosteroid-sparing agents [5,7,8]. Patients refractory to corticosteroids and/or immunosuppressant therapies, who suffer from significant side effects, or patients in which immunosuppressants are contra-indicated, often try intravenous immunoglobulin (IVIg) or even rituximab [5,7].

Despite the availability of multiple immunomodulatory treatments for DM/PM, a high proportion of patients with DM/PM who receive corticosteroids are not able to regain normal levels of activities, and 48% of patients report functional disability, which can include corticosteroid-induced myopathy and osteoporotic fractures [9]. Weight gain, exacerbation of diabetes, changes in mood, and gastrointestinal issues are also reported by patients with DM/PM on long-term corticosteroids [10]. Therefore, alternate treatment strategies are needed to provide patients with DM/PM amelioration of inflammation with reduced potential for adverse effects.

H.P. Acthar® Gel (repository corticotropin injection [RCI]) is a long-acting formulation of a porcine analogue of adrenocorticotropic hormone (ACTH1-39) [11]. ACTH is a member of the melanocortin

peptide family and, as such, may confer steroidogenic and non-steroidogenic effects in a variety of tissues by engaging the melanocortin receptors (MCRs), particularly those of the immune system [11,12]. ACTH affects anti-inflammatory circuits through targeting of MCRs in the adrenal cortex (MC2) via release of glucocorticoids and also by engaging either MC1, MC3, or MC5 on cells of the immune system (Figure 1) [11,13]. The effects of melanocortins on muscle are not fully characterized, but energy homeostasis, fatty acid oxidation, neuromuscular growth, and protection of muscle from damage may be mediated by this system as well [14-16]. RCI is an FDA-approved treatment for use during an exacerbation or as maintenance therapy in selected cases of systemic dermatomyositis (polymyositis) [17]. A previous, small retrospective case study demonstrated that patients with DM/PM who were refractory to or intolerant of corticosteroid therapy, immunosuppressive therapy, and/or IVIg therapy could effectively be treated with RCI without significant adverse effects [10,17]. All patients showed improvement in muscle tone, and three of the five patients regained the ability to ambulate independently [10].

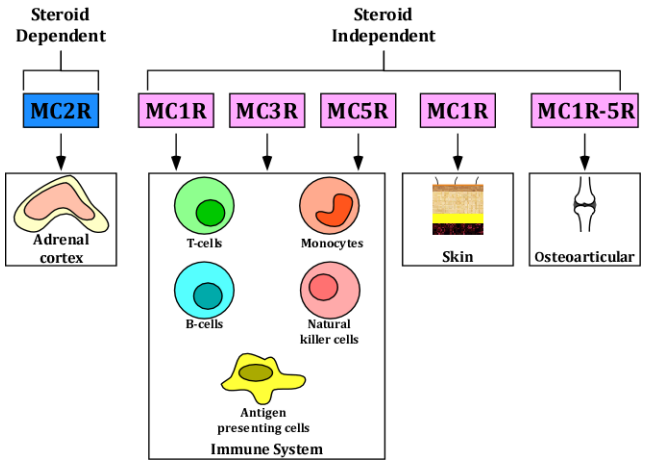

Figure 1: Potential targets of ACTH in the treatment of DM/PM.

Based on the preliminary success of use of RCI in treating patients with DM/PM, a registry was created to monitor the use of RCI in patients with DM/PM. Patients were enrolled in the Acthar in Dermatomyositis and Polymyositis Treatment (ADAPT) registry and demographic information, laboratory data, strength measurements, and qualitative outcome measures were collected at baseline and after 3, 6, 9, and 12 months of treatment. This interim analysis of the above registry aims to determine dosing, adverse effects, and efficacy of RCI in patients with refractory DM/PM.

Materials and Methods

Subjects

Adult male or female patients, aged 18 to 85 years, with clinical or pathological diagnosis of DM/PM were eligible to be included in the ADAPT registry (clinicaltrials.gov, NCT01637064). Diagnosis for all patients was confirmed by muscle biopsy based on the criteria of Bohan and Peter [18,19], and all participants were required to provide informed consent. Additionally, patients were included based on their status as refractory to first- and second-line therapies. Patients were excluded based on the following criteria: diagnosis with inclusion-body myositis (IBM), medical history of scleroderma, osteoporosis, fungal infections, or ocular herpes simplex, recent surgery, history of peptic ulcers, congestive heart failure, uncontrolled hypertension, allergy to porcine proteins, co-morbidities that would make trial completion unlikely, and women who were pregnant, breast-feeding, or unwilling or unable to use appropriate birth control.

Study design

This is an interim, observational case study of patients diagnosed with DM/PM refractory to corticosteroids, immunosuppressants, rituximab, and IVIg. The ADAPT registry was established for the purpose of determining the effect of RCI treatment on the clinical outcome of DM/PM. The secondary objective of this study was to determine if distinct subgroups of patients, as defined by myopathology or autoantibody status, have differential responses to RCI treatment. The study sites involved in this trial are private practices that specialize in neuromuscular diseases or academic centers and received approval from either the Western Institutional Review Board (IRB) or their local IRB, respectively, and have therefore been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Patient variables that were assessed for association with responsiveness to RCI treatment included: DM/PM diagnosis, sex, age, presence of autoantibodies at baseline, extra-muscular symptoms (rash) at baseline, and administration of concomitant medications. Outcomes were determined by an independent review of the prescribing physician's notes, clinical parameters, and laboratory data for each patient.

Study drug

Treatments with RCI (Mallinckrodt Pharmaceuticals, USA) were initiated using 80 IU twice weekly based on previous literature [10,20] and administered via subcutaneous injection. After initiating therapy, physicians adjusted doses at their discretion based on the disease severity, concomitant health issues, and response to therapy.

Data collection

At baseline, informed consent, demographic information, medical history, and muscle biopsy were collected for analysis. At baseline, and at months 3, 6, 9, and 12, a physical exam, manual muscle testing (MMT) of 18 muscle groups both proximal and distal and assessed bilaterally, as recommended by the International Myositis Assessment and Clinical Studies Group (IMACS) [21,22], assessment of the patient by both the inflammatory neuropathy cause and treatment (INCAT) disability scale [23] and the myositis activities profile (MAP) [24], and collection of both adverse events (AEs) and serious adverse events (SAEs) were conducted. Additionally, patient laboratory results were also reported, including myositis specific antibodies, glycated hemoglobin (HbA1c), and creatine phosphokinase (CPK).

Measures of patient response

Improvement in the INCAT score by at least one point, MMT scores of more than 20%, or improvement in MAP scores by two or more points were considered as patient response to RCI treatment.

Statistical analyses

Statistics were based on frequency distribution for all categorical values. Based on the outcome variables defined above, categorical responses to RCI were obtained for each patient (i.e., yes (responder) or no (no response or change). Analysis of these categorical values was achieved using the chi-square statistic with continuity correction or Fishers' exact. Statistics regarding continuous variables were based on the mean (standard deviation), median, and range. Non-parametric analysis of CPK was achieved using the Mann-Whitney U test. Independent samples were tested for association of RCI with age and length of treatment by t-test. All statistical tests were two-sided and any P-value of <0.05 was considered significant.

Results

Twenty-eight patients were screened for eligibility, and 24 patients were diagnosed with either DM (n=7, 29.2%) or PM (n=17, 70.8%) and included in this analysis (Table 1). Two patients that were excluded did not have myositis and the remaining two patients who were excluded were patients diagnosed with IBM upon review of the muscle biopsy. Most patients were female and over fifty years of age (Table 1). Baseline disease activity was detected in 62.5% of patients (Table 1). The eligible patients in this study had each received an average of 3.4 medications over an average of 3.2 years before beginning the RCI regimen.

Twenty-two of 24 patients (92%) were treated concomitantly with other medications for myositis during the study. Twelve patients received prednisone. The average daily dose among these 12 patients was 27.4 mg per day with a range of 5–60 mg per day and seven patients received IVIg with an average monthly dose of 1.6 gm/kg and a range of 1 gm/kg/month to 2 gm/kg/month. Sixteen study participants also received immunosuppressant therapies, which included methotrexate (n=9), mycophenolate mofetil (MMF) (n=5), azathioprine (n=1), and cyclosporine (n=1). Most patients (n=22) received 80 IU of RCI twice weekly via subcutaneous injection; one patient received 40 IU of RCI twice weekly and one patient received 80 IU of RCI once weekly. RCI treatments had a median duration of six months, with treatment periods lasting 2–18 months.

Characteristics	**n (%)**
Dermatomyositis	7 (29.2)
Polymyositis	17 (70.8)
Sex	
Female	18 (75)
Male	6 (25)
Age (years)	
Mean	55.4 (SD=15.42)
Median	58.5
Range	26–77
<50	7 (29.2)
≥50	17 (70.8)
Autoantibodies present?	
No	11 (45.8)
Myositis-specific	6 (25)
Other (SS-A, ANA)	7 (29.2)
CPK (IU/L)	
Mean	423.5 (SD=419.3)
Median	295
Range	53–1764
<200	11 (45.8)
≥200	13 (54.2)
Disease activity	
Yes	15 (62.5)

No	9 (37.5)
Characteristics n (%)	
Rash	
Yes	4 (16.7)
No	20 (83.3)
[a]Disease activity defined as elevated CPK or a decline in MMT within 90 days prior to initiation of RCI treatment. SD: Standard Deviation	

Table 1: Demographic and clinical characteristics at baseline (n=24).

Fourteen of the 24 refractory patients (58.3%) responded to RCI treatment. Study variables associated with response to treatment are listed in Table 2. Response to RCI treatment frequently occurred in patients with disease activity at their baseline measurement, which was defined by a decline in MMT, an elevated CPK, or an increase in rash in the 90 days before treatment (P<0.0001); however, there was no association between responsiveness and class of myositis or disease duration prior to RCI administration (Table 2). Patients with DM had a 57% response rate to RCI, while patients with PM had a 59% rate of response. Treatment duration also related to treatment response, as those who responded had a higher mean duration of treatment period (9.7 months) versus non-responders whose mean treatment duration was 3.5 months (P<0.0001) (Table 2). The lengthier RCI treatments also correlated with a larger percent change reduction in CPK levels from baseline measurements (P=0.0123). Use of only one concomitant medication, namely MMF, was associated with RCI treatment responsiveness. Of the five patients being concomitantly treated with MMF, 100% achieved response (P=0.053), while only 47.4% of the remaining patients prescribed an immunosuppressant responded to combination therapy with RCI.

Study variable	**Response to RCI?**		
	Yes	No	P-value
CPK at baseline, n (%)			
<200 IU/L	2 (18.2)	9 (81.8)	NS
≥200 IU/L	12 (92.3)	1 (7.7)	<0.001
CPK (IU/L) at baseline, median (range)	616 (84–1764)	105 (53–460)	0.0047
CPK (IU/L) at follow-up, n (%)			
<200 IU/L	5 (35.7)	9 (64.3)	NS
≥200 IU/L	9 (90.1)	1 (10.0)	0.0129
CPK (IU/L) at follow-up, median (range)	338 (34–870)	110 (34–420)	0.0461
Reduction of CPK from baseline ≥30%, n (%)			
Yes	8 (88.9)	1 (11.1)	0.0333
No	6 (40)	9 (60)	NS
% change in CPK from baseline, median (range)	-32.9 (-89.0, 2.4)	-9 (-35.9, 37.5)	0.0205
Disease activity at baseline, n (%)			
Yes	13 (86.7)	2 (13.3)	<0.001
No	1 (11.1)	8 (88.9)	NS
Treatment duration, n (%)			
≤6 months	4 (28.6)	10 (71.4)	NS
>6 months	10 (100)	0 (0.0)	<0.001
Months of treatment, mean (SD)	9.7 (4.0)	3.5 (1.4)	<0.0001

[a]Disease activity defined as elevated CPK or a decline in MMT within 90 days before initiation of RCI. NS: Variable not significantly associated with response to RCI treatment; SD: standard deviation.

Table 2: Association of study variables with response to RCI treatment (n=24).

Overall, RCI treatments were well tolerated. 41.7% of patients reported mild-to-moderate AEs, with worsening of diabetes (i.e., increase in HbA1c of >1%) and edema being reported most frequently (Table 3); however, no patient discontinued treatment exclusively due to AEs. Patients who chose to discontinue experienced AEs and did not achieve clinical response.

Adverse Event (AE)	n (%)
Any AE	10 (41.7)
Worsening of diabetes (increase in HbA1c of >1%)	3 (12.5)
Lower extremity edema	2 (8.3)
Edema	1 (4.2)
Gastric reflux	1 (4.2)
Headache	1 (4.2)
Increased blood pressure	1 (4.2)
Nausea	1 (4.2)
Vertigo	1 (4.2)
Weight gain	1 (4.2)

Table 3: Reported adverse events in patients with DM or PM treated with RCI (n=24).

Discussion

This study is the largest study to date of patients receiving RCI for refractory DM/PM. The primary objective of this study was to determine the efficacy of RCI treatment in the treatment of DM/PM. As such, we report that 58.3% of patients with DM/PM had clinically significant improvements after the addition of RCI to their treatment regimen. Both DM and PM patients responded to RCI treatment, regardless of their specific diagnosis. The patients registered in this study were classified as refractory to other DM/PM treatments and, as such, are a particularly appropriate population of patients to receive RCI therapy, as RCI is already an FDA-approved treatment for select cases of DM/PM.

Since the secondary objective of this study was to determine whether certain subgroups of patients with DM/PM have differential responses to RCI treatment, we analysed the association of response to treatment with several parameters; patients who had baseline disease activity at the start of treatment were more likely to respond to RCI treatments. This may be related to the fact that patients exhibiting declining clinical and laboratory measures of muscle health are still in a stage of their disease in which any reduction in inflammation resulting from RCI treatment can help stabilize the deterioration of muscle. Furthermore, patients who remained on RCI for longer periods of time had better response than did those who were treated for less than six months. However, this may be attributed to the fact that those patients who responded may have chosen to stay on treatment longer. It was clear that the vast majority of patients who responded to treatment had a significant response by 90 days, with further improvement past 90 days. This suggests that those patients who terminated treatment within the first few months because there was little improvement may have benefitted had they remained on RCI. Interestingly, no significant difference was detected in response amongst those with DM versus those with PM, indicating that RCI treatment can be effective in various sub-types of myositis.

RCI is an FDA-approved drug with a long history of clinical use in multiple diseases and has a well-established safety profile. Mild-to-moderate AEs were reported during this trial period; however, none of the AEs resulted in study discontinuation for those who were satisfied with their treatment response. Treatment with RCI may provide an alternative to corticosteroid treatments and other immunomodulatory drugs, which are frequently employed with significant risk for AEs. Few clinical trials have been carried out for RCI use in treatment of DM/PM and therefore, very little are known about the dosing regimen required for efficacy in patients with DM/PM. This study provides evidence that 80 IU of RCI administered twice weekly for up to eighteen months can be a well-tolerated, effective treatment. Importantly, we have observed that patients who initially respond to 80 IU of RCI twice weekly can have continued improvement on doses as low as 40 IU once weekly. It may be possible to use RCI at higher doses to induce remission of disease and taper the amount and frequency of dosing to maintain the reduction in disease activity long-term, similar to the clinical strategy for use of glucocorticoids.

The limitations of this study include a small sample size of 24 patients. While this is the largest observational trial to date, treatment and assessment of a larger population for a longer time period may provide further insight into predictors of responsiveness. Additionally, the lack of diversity in this trial may also be considered a limitation. The population in this study is primarily composed of female patients and as such, we cannot determine significance that gender may influence the efficacy of RCI in DM/PM. Finally, this study is an uncontrolled one and, as such, all patients were not receiving a uniform standard of care. Patients received different classes of medications and combinations of these medications at the time of intervention with RCI without a washout period or standardization of their concomitant treatments. No patient cohort was established to receive a standard of care for DM/PM lacking RCI regimens to compare to concurrently.

Conclusion

Overall, we have demonstrated that 58.3% of patients with DM/PM refractory to corticosteroid therapy were clinically responsive to RCI treatments. RCI treatment was well-tolerated and no patient discontinued treatment due to any AE. The observational case study here indicates that the clinical and enzymatic evidence of disease activity may be predictors of responsiveness to RCI treatment. While this interim report preliminarily identifies predictors of responsiveness to RCI treatment, the full study will confirm these findings and perhaps reveal additional predictors of RCI responsiveness. A

prospective, controlled study is necessary to further assess the effectiveness of RCI treatment in patients with steroid-refractory DM/PM. Based on data presented herein; these future clinical trials should be designed to include patient populations that have active disease, as there is a significant association of response to RCI with a patient's baseline myositis activity.

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Conflict of Interest

Dr. Levine is a consultant for Mallinckrodt Pharmaceuticals

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