

Treating refractory dermatomyositis or polymyositis with adrenocorticotrophic hormone gel: a retrospective case series

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Background: Effective and tolerable treatment options for patients with dermatomyositis and polymyositis are limited. This retrospective case review describes treatment with adrenocorticotrophic hormone (ACTH) gel in five patients who experienced a disease exacerbation and either failed or were unable to tolerate the side effects of previous therapy with steroids, intravenous immunoglobulins, and steroid-sparing drugs.

Methods: Patients received ACTH gel subcutaneous injections of 80 U (1 mL) twice weekly (four patients) or once weekly (one patient) over the course of 12 weeks for short-term treatment of symptom exacerbations. Manual muscle testing using the Medical Research Council scale was assessed at baseline and at 3 months.

Results: Improvement was seen in all patients, including improved muscle strength, decreased pain, and resolution of skin involvement. All patients tolerated the treatment well, and no significant side effects occurred.

Conclusion: The treatment of dermatomyositis and polymyositis is an approved use for ACTH gel, and these anecdotal reports would suggest consideration of ACTH gel as a therapeutic option. Further investigation is warranted.

Keywords: adrenocorticotrophic hormone gel, dermatomyositis, polymyositis, steroids, intravenous immunoglobulins

Introduction

Dermatomyositis and polymyositis are systemic inflammatory disorders characterized by symmetric proximal muscle weakness and commonly involve other organ systems, such as the skin (in dermatomyositis) and lung.¹ Treatment decisions are typically empirically based due to few controlled trials and a lack of targeted immunosuppression. Expert consensus supports high-dose oral prednisone as first-line therapy; however, as many as 30%–40% of patients may fail to respond, and up to 40% or more experience major adverse events with long-term steroid use.² Steroid-sparing or alternative immunosuppressive therapies, including methotrexate, azathioprine, cyclosporine, and mycophenolate mofetil, have a long onset of action and risks, including toxicity to the kidneys, liver, and bone marrow.¹ Intravenous immunoglobulin is considered a second-line therapy for dermatomyositis, but not for polymyositis.³ However, intravenous immunoglobulin does not have a US Food and Drug Administration (FDA) indication for myositis, and is very expensive with a risk of acute renal failure.^{1,4} Rituximab had shown some promise in anecdotal case series, but a large, international, multisite, randomized, controlled clinical trial (Rituximab in Myositis) showed no separation from placebo.^{5,6} Clearly, additional effective and tolerable treatment options are needed.

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Adrenocorticotrophic hormone (ACTH) gel (HP Acthar® Gel, repository corticotropin injection, Questcor Pharmaceuticals, Inc., Union City, CA) is a long-acting formulation of the full sequence ACTH_(1–39) that includes other pro-opiomelanocortin peptides. Dermatomyositis and polymyositis are approved uses of ACTH gel that were granted when the product was first approved in 1952.⁷ In 2010, the FDA reviewed and modernized the entire ACTH gel label alongside granting a new indication for infantile spasms, and the dermatomyositis and polymyositis indications were retained as approved uses. Despite FDA approval, clinical data are limited and many physicians treating these disorders are unaware of ACTH gel as a treatment option approved by the FDA. Therefore, ACTH gel represents a novel, approved therapeutic option for these disease states.

Emerging evidence related to the melanocortin system suggests that ACTH may have mechanisms of action in addition to steroidogenesis, resulting in anti-inflammatory and immunomodulatory effects. Five melanocortin receptors are known to be expressed on a variety of cells, including immune cells, glial cells, and podocytes. Through these receptors, melanocortins can induce a broad range of immune-modulating effects.⁸ Similarly, mechanisms of action now being considered for ACTH gel hypothesize effects beyond steroidogenesis. ACTH gel has been shown to be effective in patients refractory to steroids and other therapies in infantile spasms, nephrotic syndrome, and acute exacerbations of multiple sclerosis, with suggested immune-modulating mechanisms of action.^{9–11}

The retrospective case series presented here provides clinical observations relevant to treating patients with biopsy-confirmed, highly refractory dermatomyositis and polymyositis using the ACTH gel formulation described above. Five patients (three with dermatomyositis, two with polymyositis) with disease exacerbation who had failed or were unable to tolerate the side effects of previous therapy are described.

Materials and methods

All patients in this retrospective case series review were female, aged 25–68 years, with diagnoses confirmed on muscle biopsy (see Table 1). ACTH gel was approved and paid for by each patient's health insurance. All patients received 80 U (1 mL) of ACTH gel via subcutaneous injection. Four patients received ACTH gel twice weekly for 12 weeks and one patient received ACTH gel once weekly. The dosing regimen used with these patients was based on previous studies of ACTH gel in patients with exacerbations

of muscle sclerosis and nephrotic syndrome.^{10,11} Manual muscle testing, recommended in the assessment of treatment outcomes in patients with dermatomyositis and polymyositis, was performed using the Medical Research Council scale at baseline and at 3 months.^{12–14} A Medical Research Council manual muscle testing scale score of 2 reflects an inability to produce active movement against gravity, a score of 3 reflects active movement against gravity but not resistance, a score of 4 reflects active movement against gravity and resistance, and a score of 5 reflects normal power. Muscles tested included deltoids, biceps, triceps, wrist extensors, first dorsal interossei, grip strength, iliopsoas, quadriceps, hamstring, and tibialis anterior. Muscle groups that improved are described below. No muscles weakened from baseline testing during ACTH gel treatment, and muscles that remained the same are not discussed. Previous therapies and concomitant medications are summarized in Table 1. All patients had received stable dosing of concomitant therapy for a minimum of 60 days, and the treatment had failed to treat the disease exacerbation adequately before receiving ACTH gel. Patients were kept on existing treatments during ACTH gel treatment so that following short-term treatment with ACTH gel to quiet the disease exacerbation, the patients could continue their previous treatment regimen for longer-term maintenance therapy. Patients were examined for significant side effects in response to ACTH gel, including hyperglycemia, diabetic ketoacidosis, and hyperosmolar states. Glycosylated hemoglobin (HbA_{1c}) was assessed monthly. This retrospective review of the treatment received by patients during clinical care of dermatomyositis and polymyositis received institutional review board exemption from Western Institutional Review Board.

Case reports

Patient I

A 45-year-old woman diagnosed with dermatomyositis presented with a diffuse erythematous rash across her chest and finger extensors, clear periungual telangiectasias, and mechanic's hands, with progressive arm and leg muscle weakness. She had an elevated creatine phosphokinase of 4500, and muscle biopsy showed perifascicular atrophy and inflammation. Autoantibody testing showed no myositis-specific autoantibodies.

The patient's treatment history since 2004 included intravenous immunoglobulin, azathioprine, rituximab, cyclosporine, and methotrexate. The patient initially responded well to treatment with prednisone ≤40 mg/day (the patient would not agree to take >40 mg/day of prednisone

Table 1 Patient characteristics and response to 12 weeks of ACTH gel treatment

| Patient and diagnosis | Age (years) | Extramuscular organ involvement | Previous therapy | Concomitant medications | Treatment response |
|-----------------------|-------------|---------------------------------|---|---|---|
| 1 DM | 45 | Skin | Prednisone 40 mg/day, methotrexate 15 mg/week, azathioprine 150 mg/day, cyclosporine 200 mg/day, IVIG 2 g/kg/month, rituximab 375 mg/m ² , 2 doses 1 week apart, then every 3 months for 12 months | Prednisone 20 mg/day, IVIG 2 g/kg/month | Resolution of skin involvement; improved proximal leg strength; able to get out of chair and walk independently |
| 2 JDM | 25 | Skin, calcinosis | Prednisone 100 mg/day, IVIG 2 g/kg/month, cyclosporine 200 mg/day, azathioprine 200 mg/day, rituximab 375 mg/m ² , 2 doses 1 week apart, then every 3 months for 12 months, MMF 1500 mg BID, pulse methylprednisolone 1 g/week for 8 weeks | IVIG 2 g/kg/month, azathioprine 200 mg/day, cyclosporine 200 mg/day | Increased leg strength; improvement in skin involvement; return to independent ambulation and work |
| 3 DM | 43 | Dysphagia, joint pains | Prednisone 60 mg/day, pulse methylprednisolone 1 g/day for 5 days, IVIG 50 g/month to 2 g/kg/month | Prednisone 30 mg/day, IVIG 2 g/kg/month | Improved strength; decreased pain; able to hold her baby; independence with ADLs |
| 4 PM | 55 | Extraocular muscles | Prednisone 60 mg/day, IVIG 2 g/kg/month, MMF 1500 mg BID | MMF 1500 mg BID | Improved proximal muscle strength; no improvement in diplopia; able to participate in activities with grandchildren |
| 5 PM | 68 | None | Pulse methylprednisolone 1 g/week for 8 weeks, pulse cyclophosphamide 1 g/m ² /month for 6 months, IVIG 2 g/kg/month, MMF 1500 mg BID, rituximab 375 mg/m ² , 2 doses 1 week apart, then every 3 months for 12 months | MMF 1500 mg BID | Improved strength; return to independent ambulation |

Abbreviations: ADLs, activities of daily living; BID, twice daily; DM, dermatomyositis; IVIG, intravenous immunoglobulins; JDM, juvenile dermatomyositis; MMF, mycophenolate mofetil; PM, polymyositis.

due to side effects of weight gain, mood changes, and severe gastric symptoms), intravenous immunoglobulin 2 g/kg per month (she experienced moderate side effects to intravenous immunoglobulin, including headache, chills, and nausea), and azathioprine 150 mg/day. In 2007, she experienced a disease exacerbation, and rituximab 375 mg/m² for two doses and then a single dose every 3 months for 12 months was added to ongoing prednisone, azathioprine, and intravenous immunoglobulin. The patient showed good improvement in her rash and muscle strength. Her disease became more active in 2009, including muscle weakness, severe rash, and significant nail bed changes, and she had an inadequate response to treatment with prednisone, intravenous immunoglobulin, cyclosporine 200 mg/day, and methotrexate 15 mg/week.

The patient received treatment with ACTH gel concomitantly with prednisone 20 mg/day and intravenous immunoglobulin 2 g/kg per month. Her creatine phosphokinase levels prior to starting ACTH gel therapy were normal. By 8 weeks, her skin rash had improved markedly. Proximal leg strength increased from 3/5 to 4+/5 in her iliopsoas and quadriceps. She was able to get out of a chair and walk independently. The patient tolerated the treatment well without any significant side effects. HbA_{1c} remained normal. Since completing ACTH gel treatment, she has been managed adequately with intravenous immunoglobulin 2 g/kg per month, prednisone 20 mg/day, and methotrexate 15 mg/week.

Patient 2

A 25-year-old woman diagnosed with juvenile dermatomyositis presented at the age of 11 years with muscle weakness, classic skin changes, and calcinosis. She had an elevated creatine phosphokinase of 56,000 and a muscle biopsy showing perifascicular atrophy and inflammation. Autoantibody testing showed no myositis-specific autoantibodies. At the time of transition to adult care in 2004, she was very weak and required the use of a walker.

Her treatment history as a pediatric patient included prednisone up to 100 mg/day, resulting in significant cushingoid side effects, mycophenolate mofetil 3000 mg/day, which resulted in palpitations, azathioprine 200 mg/day, intravenous immunoglobulin 2 g/kg per month, cyclosporine 200 mg/day, and methotrexate 20 mg/week. Since transitioning to adult care, she had received rituximab, cyclosporine, intravenous immunoglobulin, azathioprine, and pulse methylprednisolone. The patient showed a good response to rituximab (375 mg/m² for two doses and then a single dose every 3 months for 12 months), and was maintained on intravenous

immunoglobulin, cyclosporine, and azathioprine until a disease exacerbation in 2007. The patient did not show improvement on rechallenge with rituximab over the next 6 months; her strength worsened, and she again required a walker for ambulation. She did not show improvement in response to pulse methylprednisolone 1 g/week for 8 weeks.

The patient received ACTH gel concomitant with ongoing intravenous immunoglobulin 2 g/kg per month, azathioprine 200 mg/day, and cyclosporine 200 mg/day. Her creatine phosphokinase and aldolase levels prior to initiation of ACTH gel were in the low-normal range, reflecting significant previous muscle atrophy. The patient noted improved strength and independent ambulation within 8 weeks of treatment. Her muscle enzymes decreased from 800 to 100. The patient's iliopsoas strength improved from 3/5 to 4/5 and her quadriceps strength increased from 3-/5 to 4+/5. She also reported improvement in her rash and nail bed changes. Within 6 months of completing ACTH gel, and while on intravenous immunoglobulin and azathioprine, weakness in her proximal leg muscles again declined to 3+/5. She was started on tacrolimus for 6 months with no benefit. The patient was restarted on ACTH gel, 80 U once a week with partial improvement in strength. Treatment with ACTH gel was increased to 80 U twice weekly, and the patient has shown a good response. Her leg muscle strength improved to 4+/5. She has continued on ACTH gel for 7 months, in combination with intravenous immunoglobulin and azathioprine. Her strength is 5/5 in all muscle groups except her iliopsoas, where it is 4/5. The patient has been able to return to work and is ambulating independently. The patient tolerated ACTH gel treatment well without any significant side effects. Her HbA_{1c} and fasting glucose levels have remained normal, and there has been no change in her bone density as measured by densitometry.

Patient 3

A 43-year-old woman diagnosed with dermatomyositis presented with diffuse erythematous rash, profound diffuse muscle weakness, and joint pains. The patient had an elevated creatine phosphokinase of 2500, and muscle biopsy showed perifascicular atrophy and inflammation. Autoantibody testing showed no myositis-specific autoantibodies.

Treatment history since 2009 included prednisone up to 60 mg/day, weekly pulse methylprednisolone 1 g/day, and intravenous immunoglobulin as high as 2 g/kg per month. Rituximab was denied by the patient's insurance company. The patient became pregnant in 2010, and during pregnancy and subsequent childbirth, she experienced a marked decrease

in muscle strength and difficulty walking. Lower extremity strength responded well to pulse methylprednisolone 1 g/day for 5 days, prednisone 60 mg/day, and monthly intravenous immunoglobulin 50 g increased to 2 g/kg. However, upper extremity muscle weakness continued, and she was not able to hold her baby. The patient disliked high-dose prednisone due to side effects of significant weight gain and elevated glucose. She also experienced severe side effects to high-dose intravenous immunoglobulin, including rash, headache, fevers, and malaise.

Treatment with ACTH gel was initiated concomitant with prednisone 30 mg/day and intravenous immunoglobulin 2 g/kg per month. Her creatine phosphokinase levels prior to starting therapy were mildly elevated at 647. The patient's diffuse strength increased after 12 weeks and was accompanied by a drop in her creatine phosphokinase to 154. She was able to hold her baby and she became independent with her activities of daily living. Most notably, deltoid strength increased from 2/5 to 4/5 and triceps strength from 3/5 to 4/5. Her myalgias also improved markedly. The patient tolerated the treatment well without any significant side effects or change in HbA_{1c}. Since completing ACTH gel, she has been managed adequately with prednisone 35 mg/day and intravenous immunoglobulin 50 g per month.

Patient 4

A 55-year-old woman diagnosed with polymyositis presented with marked limitation of her extraocular muscles bilaterally and mild proximal muscle weakness in her arms. She had a mildly elevated creatine phosphokinase of 650, and a muscle biopsy of the right deltoid showed inflammatory changes consistent with polymyositis. An orbital magnetic resonance imaging scan showed inflammation of the extraocular muscles. Testing for acetylcholine receptor antibodies and antithyroid antibodies, an electromyogram with repetitive nerve stimulation and single-fiber testing, and thyroid profile were all normal. Genetic testing for oculopharyngeal muscular dystrophy was normal. Autoantibody testing showed a positive rheumatoid factor, a positive antinuclear antibody 1:1260, and no myositis-specific autoantibodies.

Treatment history since 2007 included prednisone, mycophenolate mofetil, and intravenous immunoglobulin. The patient was initially treated with prednisone 60 mg/day. Her eye movements and double vision responded very well, and prednisone was tapered to 20 mg/day. The patient experienced a disease exacerbation in 2009 with increased arm and leg weakness that prevented her from engaging in activities with her grandchildren. Prednisone was increased

to 60 mg/day and resulted in improved muscle strength; however, the patient strongly disliked prednisone due to mood-related side effects. Mycophenolate mofetil 1500 mg twice daily was added to treatment and prednisone was tapered and withdrawn. The patient's strength and eye movements again worsened, and intravenous immunoglobulin 2 g/kg per month for 6 months showed no benefit.

The patient began treatment with ACTH gel concomitant with ongoing mycophenolate mofetil 1500 mg twice daily. She had normal creatine phosphokinase and aldolase levels prior to starting therapy with ACTH gel. Proximal muscle strength increased after 12 weeks; most notably, the patient's deltoids and triceps improved from 3/5 to 4+/5. No improvement occurred in her extraocular muscles, but the patient reported that she was again able to participate in activities with her grandchildren. The patient tolerated the treatment well, without any significant side effects or increase in HbA_{1c}. Since completing ACTH gel, she has been managed adequately with intravenous immunoglobulin 2 g/kg per month and mycophenolate mofetil 1500 mg twice daily.

Patient 5

A 68-year-old woman diagnosed with polymyositis presented with muscle weakness, difficulty getting out of a chair and climbing stairs, and weak grip strength that was reduced to 40 lb. Myositis-specific autoantibody tests were normal. Muscle biopsy of the quadriceps was negative for inclusion body myositis and was consistent with polymyositis.

The patient's treatment history since 2003 included pulse methylprednisolone, pulse cyclophosphamide, intravenous immunoglobulin, mycophenolate mofetil, and rituximab. The patient responded well to initial combination treatment with pulse methylprednisolone 1 g/week for 8 weeks and pulse cyclophosphamide 1 g/m² per month for 6 months. Treatment with pulse methylprednisolone was stopped due to recurrent infections, including hospitalization for severe pneumonia, and intravenous immunoglobulin 2 g/kg per month was started. The patient responded well to combination treatment with monthly pulse cyclophosphamide and intravenous immunoglobulin. The patient was weaned off intravenous immunoglobulin, and mycophenolate mofetil 1500 mg twice daily was added. In 2008, the patient experienced a disease exacerbation, and rituximab 375 mg/m² for two doses and then a single dose every 3 months for 12 months was added to ongoing mycophenolate mofetil. In 2011, the patient again experienced disease exacerbation that improved with pulse methylprednisolone and mycophenolate mofetil. Medicare then refused payment for continued pulse

methylprednisolone, and the patient had 3 months without steroid therapy. During this time, her energy and strength worsened and she returned to occasional use of a walker.

The patient began treatment with ACTH gel 80 U once weekly, concomitant with ongoing mycophenolate mofetil 1500 mg twice daily. Her creatine phosphokinase levels prior to starting therapy with ACTH gel were mildly elevated at 632. After 12 weeks of treatment with ACTH gel, her creatine phosphokinase decreased to 388. She tolerated the treatment well, without an increase in HbA_{1c} or any weight gain, sleep disturbance, or gastrointestinal symptoms, which had been significant side effects while on pulse methylprednisolone. The patient noted significant improvement in her strength and no longer required the use of a walker. Her muscle strength improved from 4/5 to 5/5 in her quadriceps and to 4+/5 in her iliopsoas. The patient will continue ACTH gel treatment as long as insurance coverage continues.

Discussion

This retrospective case review of the responses of five patients to ACTH gel in the short-term treatment of worsening dermatomyositis or polymyositis found clinically significant improvement in all patients. Effective and tolerable treatment options for patients with refractory dermatomyositis and polymyositis are limited. ACTH gel may provide a novel anti-inflammatory and immunomodulatory option, given its possible mechanisms of action beyond steroidogenesis.⁸

Although ACTH gel is approved for use in dermatomyositis and polymyositis, it is not well known as a potential treatment option because of a paucity of clinical data. In these five patients seen in our clinic over the past four years, the decision to use ACTH gel was motivated by increasing weakness in all patients (one patient also had worsening rash), increasing diplopia in one patient, and inadequate response to previous immunosuppressive therapies in all patients. Improvement on manual muscle testing and patient-reported function in daily activities was seen in all patients, and patients uniformly reported that these changes had a significant impact on their quality of life and their level of independent function. Manual muscle testing scores have been associated with functional abilities, such as walking and completion of activities of daily living in patients with polymyositis or dermatomyositis, as well as in patients with other neuromuscular diseases.¹⁵⁻¹⁷ In functional terms, mean manual muscle testing strength grade <3 has been associated with maximal or total assistance in children with Duchenne muscular dystrophy, whereas mean muscle strength grade ≥ 3 has been associated with relative independence

in activities of daily living.¹⁶ In this retrospective clinical case series of patients with dermatomyositis or polymyositis, a score ≤ 3 in proximal muscle groups was associated with a patient being unable to walk or complete activities of daily living independently. A score ≥ 4 in proximal muscle groups was associated with a patient being able to ambulate independently and complete activities of daily living. Three patients who had impaired ambulation prior to ACTH gel therapy returned to independent ambulation during treatment. Two patients who were unable to care independently for a child or grandchild prior to ACTH gel therapy regained this independence. One patient regained independence in her activities of daily living, and another patient was able to return to work following ACTH gel treatment. The patient with polymyositis and extraocular muscle involvement was atypical. However, other potential diseases, including myasthenia gravis, thyroid disorders, and oculopharyngeal muscular dystrophy, were excluded. The patient showed improved proximal limb muscle strength after ACTH gel treatment for 12 weeks but no improvement in her diplopia.

These patients all showed significant improvement in short-term responses to ACTH gel. Therapy was limited to a few months in most patients, so long-term responses and side effects were not evaluated. This small, retrospective case review included patients seen during the course of patient care, and as such, limitations include open-label treatment and unblinded outcome evaluation. Because ACTH gel treatment was short-term, patients received concomitant therapies during treatment with ACTH gel and continued those therapies as maintenance treatment following cessation of ACTH gel. The short-term treatment of symptom exacerbation with ACTH gel avoided the need to increase existing immunomodulatory therapy in all cases. Though effects of concomitant medications during ACTH gel therapy cannot be ruled out, patients were on stable dosing for at least 60 days prior to initiation of ACTH gel.

All patients tolerated ACTH gel 80 U twice weekly (once weekly for patient 5) for up to 3 months with no significant side effects and no need to taper therapy, indicating this treatment regimen may be more tolerable than high-dose corticosteroids for the short-term treatment of disease exacerbations. Patient 2 recently began a second ongoing period of ACTH gel treatment, with no side effects or change in HbA_{1c} over 7 months. The effectiveness of ACTH gel in patients refractory to corticosteroid therapy and in those unable to tolerate the side effects of high-dose corticosteroids suggests nonsteroidal mechanisms of action. The two patients on maintenance doses of prednisone while receiving ACTH

gel indicate that nonsteroidal aspects of ACTH activity may be important for a clinical response in such patients. The encouraging results from this small retrospective case series suggest that ACTH gel should be considered as a therapeutic option for the treatment of dermatomyositis and polymyositis, particularly in refractory cases. A more formal, long-term examination of patient responses and side effects to treatment with ACTH gel is warranted. Additionally, given the patient-reported significance of the improved functional abilities that occurred with ACTH gel treatment, inclusion of a quality of life measure would be beneficial.

Disclosure

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