H.P. Acthar Gel (repository corticotropin injection) treatment of patients with multiple sclerosis and diabetes

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Abstract

Background: Treatment of multiple sclerosis (MS) relapses can be complex in patients with concomitant diabetes. Corticosteroids and adrenocorticotropic hormones are known to cause alterations in glucose tolerance. Many patients have poor tolerability to therapy, necessitating alternative treatment options. Adrenocorticotropic hormone (H.P. Acthar Gel, repository corticotropin injection, Mallinckrodt ARD Inc., Hazelwood, MO, USA) is currently indicated for the treatment of MS relapses.

Objectives: The objective of this study was to review patients' experiences of Acthar Gel for the treatment of MS exacerbations in patients with MS and diabetes.

Methods: A retrospective review of 13 patients' experiences with treatment. Qualified healthcare providers completed a questionnaire following Acthar Gel treatment for MS relapse.

Results: Previous corticosteroid treatment with either intravenous methylprednisolone or prednisone was reported by 84.6% of patients; eight patients had complications following administration of prior steroid treatment, seven of whom experienced elevated blood glucose levels. Acthar Gel was administered daily for a mean of 5.3 days, with 61.5% of patients reporting relapse resolution. Two patients experienced elevated blood glucose.

Conclusion: The majority of patients experienced a timely resolution of their MS relapse with few hyperglycemic adverse events. Although more studies are necessary, these data suggest that Acthar Gel may be a well-tolerated and effective treatment option for patients with diabetes experiencing an MS relapse.

Keywords: Acthar Gel, blood glucose, diabetes mellitus, hyperglycemia, multiple sclerosis, steroids

Introduction

Approximately 80–85% of multiple sclerosis (MS) cases begin with a relapsing–remitting (RR) course [Compston and Coles, 2008]. A recent survey indicated that 44% of patients with MS (n = 2562) in the United States report having at least one acute exacerbation per year, ranging from less than 1 week to over 6 months in duration [Health Union LLC, 2013]. The primary treatment option for relapse is high-dose intravenous or oral corticosteroids [National Clinical Advisory Board of the National Multiple Sclerosis Society, 2008; Ross *et al.* 2013]; however, not all patients respond adequately to these agents [Milligan *et al.* 1987; Pascual *et al.* 2008]. A review of clinical trials that assessed the use of corticosteroids for MS relapse management concluded that based on both therapeutic response and tolerability profile it is difficult to predict which patients will respond favorably to such treatment [Krieger *et al.* 2014]. For example, a number of studies investigating the central nervous system have shown that sustained activity at intracellular glucocorticoid receptors can actually result in increased central nervous system inflammation, especially if steroid exposure occurs prior to the injury in question [de Pablos *et al.* 2006; Dinkel *et al.* 2003; MacPherson *et al.* 2005; Munhoz *et al.*

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2010; Uz *et al.* 1999]. This response could result in a lack of steroid efficacy in various patients experiencing an MS relapse. Corticosteroids have also been shown to result in various adverse events (AEs) that may negatively impact certain patients with MS, especially those with comorbid disorders, necessitating alternative treatments for acute MS exacerbations [Ross *et al.* 2013].

Diabetes, both type 1 and 2 (T1D and T2D), is a prevalent disease in the overall population. A recent retrospective study of administrative data assessed the comorbidity of various diseases in an MS population compared with a matched cohort of the general population over 28 years (1984–2012) [Marrie *et al.* 2015]. Results indicated that the prevalence of diabetes in the MS population did not differ from that of the matched general population at index start; however, patients with MS and diabetes were found to be at greater risk for mortality than patients with MS without diabetes. These data could suggest that treating patients with MS with concomitant diabetes may require increased monitoring and possible consideration of all treatment options based on individual patient needs.

Treatment for MS relapse can be complex among patients with diabetes for numerous reasons. Corticosteroids have been shown to cause alterations in glucose tolerance and metabolism, and hyperglycemia is a common and rapidly occurring AE following treatment with high-dose steroids during hospitalization [Berkovich, 2013; Fong and Cheung, 2013; Myhr and Mellgren, 2009; Ross *et al.* 2013]. In order to keep blood glucose levels steady during corticosteroid treatment of MS exacerbations in people with diabetes, increasing dosages of insulin may be necessary; however, a recent study found that 40% of patients with MS were insulin resistant [Oliveira *et al.* 2014]. Fluctuations in blood glucose are well known to increase diabetic complications; thus, maintaining steady glucose control throughout MS exacerbation treatment is of great importance.

Adrenocorticotropic hormone (H.P. Acthar Gel, repository corticotropin injection, Mallinckrodt ARD Inc., Hazelwood, MO, USA) is approved to treat MS relapses and is generally used as an alternative to high-dose corticosteroids [Mallinckrodt ARD Inc., 2015; Ross *et al.* 2013]. Preliminary data from a small crossover study (n = 18) presented in 2014 indicate that treatment of healthy controls with Acthar Gel results in fewer drug-related AEs than an intravenous methylprednisolone (IVMP) regimen [Bell *et al.* 2014]. In addition, preliminary results (n = 4) from a serum cortisol equivalent exposure ratio indicate that patients on Acthar Gel had <10% of the total steroid exposure of the comparator IVMP [Bell *et al.* 2014]. There have been reports of hyperglycemia in some individuals treated with Acthar Gel [Berkovich, 2013; Bomback *et al.* 2012; Hladunewich *et al.* 2014], although no large-scale clinical trials have assessed the prevalence of this AE. Similar to primary treatment with intravenous corticosteroids, the prescribing information for Acthar Gel indicates that it should be used with caution in patients with diabetes and that those treated with the drug should be monitored carefully for signs of hyperglycemia during and after discontinuation of therapy. Clinicians, therefore, should maintain vigilance over blood glucose levels [Mallinckrodt ARD Inc., 2015].

This case series reflects patient-reported and healthcare provider (HCP)-recorded data from patients with MS and T1D or T2D who either experienced complications or did not adequately respond to previous steroid use for the treatment of an MS relapse. The purpose of this study was to collect information and review patients' experiences with Acthar Gel treatment for MS exacerbations in patients with MS and concomitant diabetes.

Methodology

This is a retrospective description of patients with MS and either T1D or T2D who experienced complications during prior steroid use and had to use alternate treatment. Data were collected from HCP-completed questionnaires regarding their patients with MS and diabetes who were treated with Acthar Gel rather than steroids for MS relapse. The questionnaire was designed to assess the results of Acthar Gel treatment for MS relapse in this specific patient population and included items pertaining to patient demographics, MS history, type of MS, diabetes history, and experience with diabetes treatments (see Appendix). Additional questions addressed prior steroid use, duration of treatment, time to resolution of relapse, and AEs associated with Acthar Gel. HCPs completed the questionnaires based on information that was previously recorded for patients who received treatment with Acthar Gel under their supervision and included both patient-reported and HCP-recorded data. The questionnaire also

served as a vehicle to determine if, by chance, these patients kept blood glucose logs, with the understanding that patients with MS usually do not. This study was not designed or powered with the intention of conducting statistical analyses.

Patient confidentiality was maintained throughout the study. An IRB exemption was provided by Western Institutional Review Board, Puyallup, WA, USA, and patients were not required to provide consent.

Results

Approximately 30 HCPs received the questionnaire, and eight completed and returned them to the investigator. Thirteen patients with a mean age of 47.9 years (range 42–69 years) and mean MS disease duration of 11.9 years (range 4–19 years; Table 1) were included. Most patients had RR MS (92.3%), were female (84.6%), and were white (69.2%). Two patients had RR MS and T1D, 10 had RR MS and T2D, and one had progressive-relapsing MS and T2D.

The duration of diabetes varied greatly, ranging from 2 to 30 years (Table 1). Previous steroid treatment with either Solu-Medrol or prednisone was reported by 84.6% of patients (n = 11; 'unknown', n = 2); following administration of prior steroid treatment, seven reported elevated blood glucose levels and one reported gastrointestinal (GI) upset and fatigue.

Acthar Gel (80 units) was administered subcutaneously daily for a mean of 5.3 days (range 3–10 days) with 61.5% (n = 8) of patients reporting exacerbation resolution (all others 'unknown') at various times (range 7–90 days; Table 2). A total of seven patients reported having no AEs following treatment with Acthar Gel. Four patients reported side effects and two of those experienced elevated blood glucose levels. Patient 8 (T1D) required an increase in insulin dose to correct blood glucose levels. A total of five patients' blood glucose levels were unknown, and no further assessments were conducted to evaluate the impact, if any, of the elevated glucose levels. Of the other reported AEs, only edema affected more than one individual (n = 2).

Approximately half of patients assessed their relapse recovery as 'positive' (53.8%, n = 7), two rated their recovery 'equivocal', one felt it was 'negative', and the remaining three patients' responses were unknown.

Limitations

The limitations of this study include that it was retrospective, which led to a low number of HCPs who responded to the survey. Additionally, this was an unvalidated pool of patients and much of the information that the survey was designed to acquire was not provided by the respondents. The questionnaire was brief and outstanding information could not be obtained prospectively; however, the obtained responses to this questionnaire suggest that blood glucose measurements should be routinely monitored during a relapse with concomitant T1D or T2D.

Discussion

In this retrospective review of experiences, data were collected from HCPs who previously treated patients with relapsing MS with concomitant diabetes using Acthar Gel. The HCPs were asked to complete questionnaires based on previous patient-reported and HCP-recorded information that was collected during and after treatment. Although this resulted in some missing data, it allowed for a real-world, albeit limited, assessment of variables, such as how often patients' blood sugar levels are monitored during treatment in a clinical setting. Many patients in this study indicated that they did not keep a blood glucose log, and whether or not they monitored their glucose but did not record this information is not known. Without proper monitoring, especially during treatment for an MS exacerbation, blood glucose levels could shift significantly and lead to complications without proper medication adjustments. Both HCPs and patients with MS and diabetes should be made aware of the possible risks of treatment and the need for regular blood glucose monitoring during relapse therapy as well as when MS is stable.

The average age of patients at the time of MS onset is 30 years [Weinshenker *et al.* 1989], and 85% of individuals with the disease present with an RR MS course [Confavreux *et al.* 2003]. Patients included in this study were slightly older than 30 years at the time of MS onset (mean 36 years) but predominately had RR MS, which is reflective of the general MS population. Most patients in this study were reported to have previously received corticosteroids for treatment of an MS relapse (corticosteroid treatment status was 'unknown' for two patients) that resulted in AEs, including elevations in blood glucose levels. Following treatment with Acthar Gel, only two

Table 1. Demographic data, diabetes history, and prior steroid use.

Subject	1	4	5	7	8	9	10	11	12	13	14	15	16
Age	58	52	50	44	53	53	44	52	50	69	59	50	42
Sex	F	F	F	F	M	F	F	F	F	F	F	F	M
Race	W	W	W	B	W	W	W	W	W	W, H	W, H	NR	W
MS history													
Duration of MS (years)	19	15	18	8	19	13	9	7	16	8	12	4	7
Type	RR	RR	RR	RR	RR	RR	RR	RR	PR	RR	RR	RR	RR
Disease-modifying therapy	Tecfidera, Avonex, Gilenya, Betaseron	Tecfidera, Tysabri, Betaseron, Copaxone, Avonex	Tysabri	Betaseron, Avonex, Copaxone	No	Gilenya	Tysabri	Copaxone	Copaxone, Avonex, Novantrone	Avonex, Copaxone, Tysabri	Tysabri, Gilenya, Copaxone, Interferon	Copaxone, Tecfidera	Betaseron, Copaxone, Rebif, Avonex, Gilenya
Diabetes history													
Duration of diabetes (years)	2	12	5	6	Unknown	Unknown	Unknown	~30	5	Unknown	8	Unknown	28
Type	Type 2	Type 2	Type 2	Type 2	Type 1	Type 2	Type 2	Type 2	Type 2	Type 2	Type 2	Type 2	Type 1
Treatment	No	Metformin	Metformin	Glucophage	Insulin pump, Novolog	Metformin, glyburide	Meformin, Novolog	Humalog, Lantus	Levemir, insulin	Byetta, Lantus, Humalog	Metformin	Glipizide, Onglyza	Insulin pump
Does subject keep glucose monitoring log?	No	Yes	No	Yes	No	No	No	Unknown	Unknown	NR	Unknown	Unknown	No
Prior steroid use													
Solu-Medrol	Yes	Yes	Yes	Yes	Unknown	Yes	Yes	Unknown	Yes	Yes	NR	Yes	Yes
Prednisone	NR	Yes	No	Yes	Unknown	Unknown	Unknown	Unknown	Yes	Yes	Yes	No	No
Complications from steroid use (any time in patient history)	NR	Elevations in blood glucose levels, modifications to diabetes meds required	Elevations in blood glucose levels, no modifications to meds, hypertension, osteopenia	Elevations in blood glucose levels, modifications to diabetes meds required, hypertension, mood disorder with mania	Elevations in blood glucose levels, modifications to diabetes meds required	NR	GI upset, fatigue	Unknown	Elevations in blood glucose levels, unknown if modifications to diabetes meds, adrenal insufficiency	NR	NR	Elevations in blood glucose levels, unknown if modifications to diabetes meds	Elevations in blood glucose levels, no modifications to diabetes meds

F, female; GI, gastrointestinal; H, Hispanic; M, male; NR, no response; PR, progressive relapsing; RR, relapsing remitting, W, white.

Table 2. Acthar Gel treatment for multiple sclerosis relapse.

Patient	1	4	5	7	8	9	10	11	12	13	14	15	16
Number of treatment days	10	5	5	5	5	3	3	3	5	10	5	5	5
Time to resolution of exacerbation	10 days	7–10 days	Unknown	14 days	7 days	Unknown	Unknown	Unknown	47 days	Unknown	Resolved at 3-month follow up	30 days	30 days
Side effects	None noted	'Felt like I'd been hit by truck', mood swings, body aches	Swollen legs, 12 lb weight gain	None	Elevated blood glucose	None	None	NR	None	None	N/A	Headache, Swelling, numbness, heaviness in chest	None
Subject's assessment of relapse recovery	Positive	Negative	Equivocal	Equivocal	Positive	Positive	Positive	Unknown	Unknown	Positive	Positive	Unknown	Positive
Elevations in blood glucose level	Unknown	No	Yes	No	Yes	No	No	NR	Unknown	Unknown	Unknown	Unknown	No
Did diabetes meds need to be adjusted?	No	No	No	No	Yes, increased	No	No	Unknown	Unknown	Unknown	Unknown	Unknown	No
Did subject record glucose levels during Acthar Gel treatment?	No	Yes	Yes	Yes	No	No	Unknown	NR	Unknown	Unknown	Unknown	Unknown	No

N/A, not applicable; NR, no response.

patients were reported as having elevated blood glucose levels by the HCPs, while seven of these patients previously experienced hyperglycemia with corticosteroid treatment.

The majority of patients taking Acthar Gel experienced resolution of their acute MS exacerbation within a similar timeframe to that typically seen with corticosteroids. Because this patient population either experienced AEs or did not respond adequately to previous treatments with steroids, these data suggest that Acthar Gel may be a therapeutic option for MS relapse in patients with diabetes and who do not tolerate or adequately respond to standard corticosteroid treatments.

The AEs that occurred in this study that have previously been noted with Acthar Gel include swelling or weight gain and elevated blood glucose. Both patients who experienced elevated blood glucose following Acthar Gel treatment also had increases in blood glucose in response to their prior corticosteroid treatment. Additionally, the patient who required an increase in insulin dosage with Acthar Gel treatment (patient 8) was one of a number of patients who needed modifications to diabetes medications following prior corticosteroid therapy. Because five patients' blood glucose levels were not available during treatment, further studies are required to assess the effects of Acthar Gel on blood glucose levels in this population.

All patients in this study did not tolerate or respond to previous corticosteroid treatment and only one patient rated his or her experience with Acthar Gel as negative; therefore, future prospective studies on the use of Acthar Gel to relieve MS exacerbations in patients with diabetes would be valuable. Practical design of such studies should include close monitoring of blood glucose levels during treatment, changes made to diabetes medications, AEs, and patient-reported outcomes regarding experiences during treatment.

The majority of patients (n = 8) in this study experienced timely resolution of their MS exacerbations with few AEs. These results are of interest because this patient population encountered complications, AEs, or lack of efficacy during previous steroid treatment. Data from this study population underscore the need for prospective studies to determine the necessity of close blood glucose monitoring during relapse treatment, as this could help to determine the best approach to managing MS exacerbations in steroid-intolerant patients. Additional prospective data on the response to Acthar Gel treatment among patients who experience an MS relapse and have either T1D or T2D are necessary to provide more clinical insight.

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Conflict of interest statement

The author is a speaker for Mallinckrodt.

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Appendix

Questionnaire: Acthar Gel Use in Multiple Sclerosis Patients with Diabetes

Year of Birth _____

Gender

- ❑ Male
- ❑ Female

Race

- ❑ White
- ❑ Black
- ❑ Hispanic
- ❑ Non-Hispanic
- ❑ Other

Multiple Sclerosis History

- Year of Diagnosis _____
- Type of Multiple Sclerosis
  - ❑ Relapsing-Remitting
  - ❑ Primary Progressive
  - ❑ Secondary Progressive
  - ❑ Progressive-Relapsing
- Disease Modifying Treatment
  - ❑ Yes List: _____
  - ❑ No

Diabetes History

- Year of Diagnosis _____
- Type of Diabetes
  - ❑ Type I
  - ❑ Type II
- Treatment for diabetes
  - ❑ Yes List: _____
  - ❑ No
- Does subject keep a glucose monitoring log?
  - ❑ Yes
  - ❑ No

Prior Steroid Use

- Solu-Medrol
  - ❑ Yes
  - ❑ No
- Prednisone
  - ❑ Yes
  - ❑ No
- Complications from steroid use (please check all that apply):
  - ❑ Elevations in blood glucose levels

    If yes, were modifications to diabetes medications required?
    - ❑ Yes
    - ❑ No
  - ❑ Hypertension
  - ❑ Osteopenia
  - ❑ Osteoporosis
  - ❑ Mood disorder

    If yes, was there evidence of mania?
    - ❑ Yes
    - ❑ No

Acthar Gel Treatment for Multiple Sclerosis Relapse

- Route of Administration
  - ❑ Subcutaneous
  - ❑ Intramuscular
- Number of treatment days _____days
- Time to resolution of exacerbation _____days
- Please list any side effects present in the space below

  _____
- Subject's assessment of relapse recovery
  - ❑ Positive
  - ❑ Negative
  - ❑ Equivocal
- During Acthar Gel treatment, were there elevations in blood glucose level?
  - ❑ Yes
  - ❑ No
- Did diabetes medications need to be adjusted?
  - ❑ Yes
    - ❑ Increased
    - ❑ Decreased
  - ❑ No
- Did subject record blood glucose levels during Acthar Gel treatment?
  - ❑ Yes
  - ❑ No