5438

A Prospective Observational Registry of Repository Corticotropin Injection for the Treatment of Multiple Sclerosis Relapse: Baseline Characteristics and Interim Results

Bryan R. Due, PhD[1]; Patrice M. Becker, MD[1]*; Patricia K. Coyle, MD[2]

[1]Mallinckrodt ARD Inc., Bedminster, New Jersey, United States; [2]Stony Brook University, Stony Brook, New York, United States

Introduction

- Incomplete recovery from multiple sclerosis (MS) relapses may contribute to accrual of disability, highlighting the importance of effective relapse treatment[1-3]
- Although disease-modifying therapies (DMTs) are used to reduce the occurrence of MS relapses, relapses still occur[4,5]
- High-dose corticosteroid (CS) therapy is the mainstay of acute treatment of MS relapses[2,6]
  - Results from clinical trials suggest that up to 55% of patients may not adequately respond to intravenous or oral CS[7-10]
  - Older age and disease severity are positive predictors of nonresponse to CS therapy[11]
- Repository corticotropin injection (RCI, H.P. Acthar® Gel; Mallinckrodt ARD Inc., Bedminster, NJ, USA) contains a porcine-derived analogue of adrenocorticotropic hormone approved by the US Food and Drug Administration for treatment of MS relapses in adults[12]
  - Historically, the effects of RCI in MS were attributed to stimulation of endogenous cortisol production; more recent evidence suggests that CS-independent properties potentially contribute[13]
- RCI is an alternative to high-dose CS in patients with MS relapse[14]
  - In a study of patients who had previously failed CS therapy and experienced an acute exacerbation, physicians rated the clinical status of a majority of patients as good, very good, or excellent after RCI treatment[15]
- There is limited data describing the demographics and disease characteristics of patients treated with RCI for relapses of MS

Study Objectives

- To characterize patients receiving RCI for treatment of acute MS relapse, identify treatment patterns, and examine the efficacy and safety of RCI treatment in MS relapse
- This interim report summarizes preliminary data collected through August 30, 2017

Methods

Study Design

- Ongoing multicenter, prospective, 24-month, observational registry study
- Target enrollment: up to 160 patients at approximately 50 sites (ie, neurology practices in the United States that treat adult patients with MS)

Interim Enrollment and Data Collection

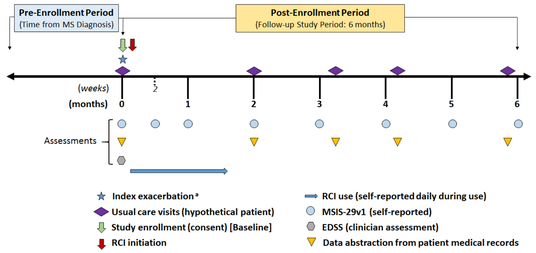
- Potentially eligible patients were recruited during routine care visits
  - Those who met the study eligibility criteria (**Table 1**) and provided informed consent were enrolled (**Figure 1**)

Table 1. Key Inclusion and Exclusion Criteria

Inclusion
Age ≥18 years
Relapsing form of MS according to the McDonald criteria (2010 revision)[16]
Acute MS exacerbation as determined by treating clinician
Planning to initiate RCI therapy for acute MS exacerbation
Exclusion
Diagnosis of primary progressive MS
Requirement for concomitant CS therapy
Receiving experimental drug therapy
Recent surgery or a history (within 6 months) or presence of a peptic ulcer, congestive heart failure, or sensitivity to proteins of porcine origin

Abbreviations: MS, multiple sclerosis; RCI, repository corticotropin injection; CS, corticosteroid.

Figure 1. Overview of Patient Enrollment and Data Collection



[a] *Index exacerbation* was defined as the MS exacerbation (relapse) that occurred at study enrollment and subsequent exacerbations were defined as *relapses*.
Abbreviations: EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; MSIS-29v1, 29-item Multiple Sclerosis Impact Scale, version 1; RCI, repository corticotropin injection.

- RCI was prescribed and dosed according to physicians' instructions
  - Patients administered intramuscular or subcutaneous RCI and documented actual use in electronic diaries (**Figure 1**)
- Patients completed the self-reported Multiple Sclerosis Impact Scale, version 1 (MSIS-29v1, 29-items) at the times specified in **Figure 1**
  - The instrument includes 2 subscales that measure the physical and psychological impacts of MS
- The Expanded Disability Status Scale (EDSS) was administered by the clinician at baseline (**Figure 1**)
- Adverse events (AEs) were documented at usual care visits and serious AEs (SAEs) were reported within 24 hours
- Data were abstracted from patient medical records at predefined time points (**Figure 1**)

Efficacy and Safety Assessments

- Baseline characteristics and efficacy were assessed in the intent-to-treat (ITT) population (N=62)
- AEs and SAEs were assessed in the safety population (ie, any patient who received at least 1 dose of RCI, N=62)
- Efficacy was defined as an improvement (ie, decrease) in MSIS-29v1 score from baseline at 2 weeks and 1, 2, 3, 4, 5, and 6 months
- Treatment responders were defined as patients who had a ≥8 point reduction in MSIS-29v1 score from baseline

Statistical Analysis

- The mean changes from baseline of MSIS-29v1 physical subscores were compared over time with a two-sided paired t-test
- The proportion of treatment responders were reported as percentages

Results

Patient Characteristics and Medication Use

- As of August 30, 2017, 80 patients had enrolled in the study
- Patient characteristics and DMT use at enrollment are shown in **Table 2**
- Thirty-seven patients (60%) reported a history of insufficient treatment response to, intolerance of, or intravenous access problems with high-dose CS therapy

Table 2. Patient Characteristics at Enrollment

Characteristic	ITT Population[a] (N=62)
Age, mean (SD), y	48.3 (10.9)
Gender, No. (%)	
Male	6 (10)
Female	56 (90)
Race, No. (%)	
Black/African American	6 (9.7)
White	53 (85.5)
Other	1 (1.6)
No information/missing	2 (3.2)
MSIS-29v1 physical subscore,[b] mean (SD)	55.8 (24.1)
EDSS score,[c] mean (SD)	4.2 (2.0)
Time since initial MS diagnosis, mean (SD), y	11.7 (9.4)
Time since onset of most recent relapse, mean (SD), mo	7.7 (5.8)
DMT use[d]	
Yes	52 (83.9)
No	11 (17.7)

[a] Baseline characteristics at enrollment in the ITT population (N=62).
[b] Scored on a scale from 0 to 100, with 100 representing the worst possible score.
[c] Rated on a scale from 0 (normal neurologic exam) to 10 (death due to MS).
[d] Some patients were receiving >1 medication within the previous 2 years at the time of enrollment.
Abbreviations: DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; ITT, intent-to-treat; MS, multiple sclerosis; MSIS-29v1, 29-item Multiple Sclerosis Impact Scale, version 1; SD, standard deviation.

- The median dose of RCI was 80 U daily for 5 days, with most patients dosing on consecutive days
- DMTs were used concomitantly with RCI in over 70% of patients; DMTs used are shown in **Table 3**

Table 3. Summary of Concomitant DMT Use

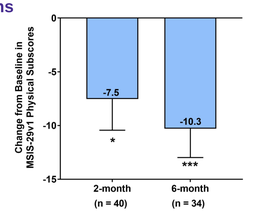
Characteristic	ITT Population[a] N=62 No. (%)
Any concomitant DMT use[b]	45 (72.6)
Specific DMT use	
Dimethyl fumarate	15 (24.2)
Natalizumab	13 (21.0)
Glatiramer acetate	7 (11.3)
Teriflunomide	7 (11.3)
Fingolimod	6 (9.7)
Ocrelizumab	4 (6.5)
Interferon β-1a	2 (3.2)
Alemtuzumab	1 (1.6)

[a] Assessed in the ITT population (N=62).
[b] Any DMT taken at any time during the study period.
Abbreviations: DMT, disease-modifying therapy; ITT, intent-to-treat.

Interim Efficacy Results

- RCI treatment significantly decreased mean MSIS-29v1 physical subscores at 2 and 6 months, both p<0.05 (**Figure 2**)

Figure 2. Change from Baseline in MSIS-29v1 Physical Subscores at 2 and 6 Months



Assessed in the ITT population (N=62). Data represents the mean + SEM.
* p<0.05; *** p<0.001; paired t-test.
Abbreviations: ITT, intent-to-treat; MSIS-29v1, 29-item Multiple Sclerosis Impact Scale, version 1; SEM, standard error of the mean.

- At 6 months, up to 56% of patients treated with RCI were responders based on MSIS-29v1 scores (**Table 4**)

Table 4. Treatment Responders Based on Changes in MSIS-29v1 Physical Subscores from Baseline

Visit	Responders Based on MSIS-29v1 Score[a,b] No. (%)
2-month	16 (40.0)
6-month	19 (55.9)

[a] Assessed in the ITT population (N=62).
[b] Responders were patients with a score change of ≥8 points on the MSIS-29v1 physical subscore.
Abbreviations: ITT, intent-to-treat; MSIS-29v1, 29-item Multiple Sclerosis Impact Scale, version 1.

Safety

- A total of 42 AEs were reported; the most common AEs were nausea (n=2), urinary tract infection (n=2), headache (n=2), and rash (n=2)
- Nine SAEs were experienced by 8 patients; the most common of 12 AE terms reported were MS exacerbation (5) and weakness (2)
  - Only one SAE, which included the terms dyspnea and atrial fibrillation, was reported as potentially related to RCI treatment and led to discontinuation from the study

Conclusions

- In this interim analysis of an observational study, RCI was effective in reducing MS relapse symptoms on the basis of MSIS-29v1 scores
- The AE and SAE profiles of RCI were similar to those observed in other RCI clinical trials; safety signals will continue to be assessed in future analyses of this trial
- Age and a higher MSIS-29 physical subscore at the time of relapse have been shown to be predictors of poor patient response to CS therapy,[11] which highlights the need for additional treatment options
- In addition to age at disease onset, longer disease duration and higher annualized relapse rates are predictors of poor response to relapse treatment with DMTs[17]
- Patients were considerably older in the current study (mean age 48) than in most previous reports on relapse recovery (mean ages in the mid 30s); therefore, the population in this study may be expected to experience greater rates of treatment resistance than previous studies[7,18,19]
- Ongoing disease activity and exacerbations early in the course of MS relapse may prevent full remission with CS treatment,[14] and limited data from previous studies showed that patients who previously failed CS therapy may benefit from RCI treatment[15]
- In this interim analysis, 60% of patients with MS relapse had previous nonresponse/failure/intolerance to high-dose CS therapy
  - An ongoing controlled study will examine the efficacy of RCI in this subpopulation (ClinicalTrials.gov Identifier: NCT03126760)

References

1. Goodin DS, Reder AT, Bermel RA, et al. Relapses in multiple sclerosis: relationship to disability. *Mult Scler Relat Disord*. 2016;6:10-20.
2. Kalincik T. Multiple sclerosis relapses: epidemiology, outcomes and management. A systematic review. *Neuroepidemiology*. 2015;44(4):199-214.
3. Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. *Neurology*. 2003;61(11):1528-1532.
4. Comi G, Radaelli M, Soelberg Sørensen P. Evolving concepts in the treatment of relapsing multiple sclerosis. *Lancet*. 2017;389(10076):1347-1356.
5. Doshi A, Chataway J. Multiple sclerosis, a treatable disease. *Clin Med (Lond)*. 2016;16(Suppl 6):s53-s59.
6. Berkovich R. Treatment of acute relapses in multiple sclerosis. *Neurotherapeutics*. 2013;10(1):97-105.
7. Le Page E, Veillard D, Laplaud DA, et al. Oral versus intravenous high-dose methylprednisolone for treatment of relapses in patients with multiple sclerosis (COPOUSEP): a randomised, controlled, double-blind, non-inferiority trial. *Lancet*. 2015;386(9997):974-981.
8. Sellebjerg F, Frederiksen JL, Nielsen PM, Olesen J. Double-blind, randomized, placebo-controlled study of oral, high-dose methylprednisolone in attacks of MS. *Neurology*. 1998;51(2):529-534.
9. Burton JM, O'Connor PW, Hohol M, Beyene J. Oral versus intravenous steroids for treatment of relapses in multiple sclerosis. *Cochrane Database Syst Rev*. 2009(3):CD006921.
10. Nickerson M, Marrie RA. The multiple sclerosis relapse experience: patient-reported outcomes from the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry. *BMC Neurol*. 2013;13:119.
11. Rakusa M, Cano SJ, Porter B, et al. A predictive model for corticosteroid response in individual patients with MS relapses. *PLoS One*. 2015;10(3):e0120829.
12. H.P. Acthar Gel [package insert]. Hazelwood, MO: Mallinckrodt Pharmaceuticals; 2017.
13. Arnason BG, Berkovich R, Catania A, Lisak RP, Zaidi M. Mechanisms of action of adrenocorticotropic hormone and other melanocortins relevant to the clinical management of patients with multiple sclerosis. *Mult Scler*. 2013;19(2):130-136.
14. Berkovich R, Agius MA. Mechanisms of action of ACTH in the management of relapsing forms of multiple sclerosis. *Ther Adv Neurol Disord*. 2014;7(2):83-96.
15. Berkovich R, Subhani D, Fernandez M. Adrenocorticotropic hormone treatment of multiple sclerosis exacerbation. *Int J MS Care*. 2012;14(Suppl 2):66.
16. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292-302.
17. Jokubaitis VG, Spelman T, Kalincik T, et al. Predictors of long-term disability accrual in relapse-onset multiple sclerosis. *Ann Neurol*. 2016;80(1):89-100.
18. Martinelli V, Rocca MA, Annovazzi P, et al. A short-term randomized MRI study of high-dose oral vs intravenous methylprednisolone in MS. *Neurology*. 2009;73(22):1842-1848.
19. Thompson AJ, Kennard C, Swash M, et al. Relative efficacy of intravenous methylprednisolone and ACTH in the treatment of acute relapse in MS. *Neurology*. 1989;39(7):969-971.

Acknowledgment and Funding

Professional writing and editorial support was provided by Justin Eddy, PhD, of MedLogix Communications, LLC, Itasca, Illinois, under the direction of the authors and was funded by Mallinckrodt Pharmaceuticals.
*Former employee of Mallinckrodt ARD Inc.