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Assessing Relapse in Multiple Sclerosis (ARMS) Questionnaire: Pilot Study

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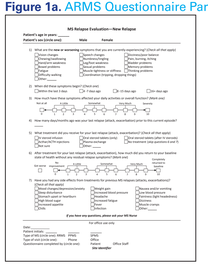
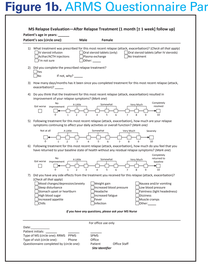
INTRODUCTION

- Relapses are a hallmark of multiple sclerosis (MS) and are often associated with significant disability.[1] The type and severity of relapse symptoms vary considerably (not only between patients, but also between relapses in the same patient).[2]
- Relapses are commonly treated with high-dose corticosteroids (administered intravenously or orally).[3] Adrenocorticotropic hormone (ACTH) gel (H.P. Acthar® Gel, repository corticotropin injection; Questcor Pharmaceuticals, Inc., Hayward, CA) is FDA-approved for the treatment of MS relapses[4] and is an alternative to corticosteroids.
- Many assessment tools for monitoring disability in patients with MS are available (eg, the Expanded Disability Status Scale [EDSS][5] and Multiple Sclerosis Functional Composite [MSFC][6]); however, none are specifically designed to evaluate patients when they present with a relapse and to assess relapse treatment effectiveness.
- In clinical practice, subjective or nonspecific assessments may result in overlooked relapse symptoms, unaddressed patient concerns (including adverse events [AEs]), suboptimal therapeutic response, or lack of patient satisfaction with treatment.
- Thus, a need exists for a brief but comprehensive objective assessment tool to help clinicians evaluate relapse symptoms and their impact on patients' daily functioning and to assess patients' perceived response to relapse treatment.
- The Assessing Relapse in Multiple Sclerosis (ARMS) questionnaire is a 2-part patient self-report assessment tool that was developed by a panel of expert MS nurses.[7]
  - Part 1 is used to evaluate patients when they present with a new relapse. It consists of 7 questions designed to evaluate relapse symptoms, impact on daily activities and overall functioning, and response to past treatments for previous relapses (**Figure 1a**).
  - Part 2 is used to evaluate patients after relapse treatment (approximately 1 month after the initial assessment). It consists of 7 questions to evaluate treatment response in terms of symptom relief, functioning, and tolerability (**Figure 1b**).

Figure 1a. ARMS Questionnaire Part 1 **Figure 1b.** ARMS Questionnaire Part 2





- The ARMS questionnaire was piloted in 5 clinical practice sites in the United States. The pilot study was designed to evaluate the ARMS questionnaire as an assessment tool for initial assessments of relapse and follow-up assessments of response to relapse treatment to help identify patients with a suboptimal response to treatment.

METHODS

- Patients
  - Patients who were at least 18 years of age and with a confirmed MS relapse were eligible to participate in the pilot study.
  - Patients experiencing a pseudorelapse were excluded.
- Study procedures
  - Part 1 of the ARMS questionnaire was administered at the clinical site after patient eligibility was established and written informed consent was obtained.
  - Part 2 of the ARMS questionnaire was administered at the clinical site or by phone 1 month (± 1 week) after initiation of relapse treatment.
  - The questionnaire was completed by the patient or by the investigator (after verbal questioning of the patient).
- Data analysis
  - Demographics and baseline characteristics were summarized using descriptive statistics.
  - Responses to each item in Parts 1 and 2 of the ARMS questionnaire were summarized using descriptive statistics. Responses to items in Part 2 were summarized for the overall population and stratified by relapse treatment; post hoc analyses evaluated differences between treatment groups.
  - Activities of daily living (ADL) and return to previous state of health (RSH)
    - Two questions (Part 1, Question 3 and Part 2, Question 5) both specifically refer to ADL; the change in ADL was estimated based on these 2 questions. For this analysis, the ADL score was calculated as 10 minus the value of the rating indicated by the patient; higher score values and greater positive changes from baseline indicate better functioning/improvement.
    - Two questions (Part 1, Question 6 and Part 2, Question 6) both specifically refer to RSH; the change in RSH was estimated based on these 2 questions (using the value of the rating indicated by the patient, with higher scores indicating a more complete RSH).
    - The internal consistency of the ADL and RSH questions in Part 1 and, separately, the ADL and RSH questions in Part 2, was examined using the Pearson correlation.
  - Total composite score (TCS)
    - The TCS was calculated based on Part 2, Questions 4, 5, and 6 (the sum of the responses of the 3 questions has a range of 0 to 30, with higher scores indicating greater improvement/better functioning).
    - Cronbach's coefficient α[8] was used to estimate the internal reliability and consistency of the 3 interrelated questions (Part 2, Questions 4, 5, and 6) and the TCS.
  - Partial composite score (PCS)
    - The PCS was computed based on the sum of the ADL and RSH questions (the sum of the item scores has a range of 0 to 20, with higher scores indicate better functioning/greater improvement).
    - The PCS was computed separately for Part 1 (new relapse) and Part 2 (after relapse treatment) and summarized descriptively. The change in the PCS was also computed and summarized.

RESULTS

Part 1—Assessment of New Relapse

- A total of 103 patients were enrolled and all completed the study (**Table 1**).

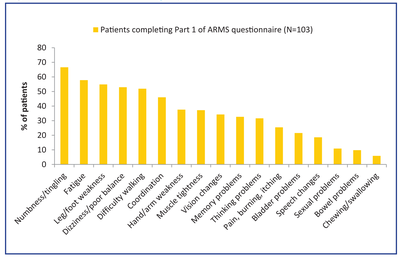
Table 1. Demographics and Characteristics of Current Relapse

Characteristic	Patients completing Part 1 of ARMS questionnaire (N=103)
Age, y, mean (SD)	42.5 (11.2)
Sex, n (%)	
Male	14 (14)
Female	89 (86)
Type of MS, n (%)	(n=97*)
RRMS	95 (98)
SPMS	2 (2)
Time since current relapse symptoms began, n (%)	
≤3 days	8 (8)
4-7 days	26 (25)
8-15 days	30 (29)
≥16 days	39 (38)
Effect of current relapse symptoms on ADL, n (%)	
A little	9 (9)
Somewhat	35 (34)
Very much	48 (47)
Severely	11 (11)
Mean (SD) ADL score during current relapse	6.62 (2.1)

ADL, activities of daily living; ARMS, Assessing Relapse in Multiple Sclerosis; MS, multiple sclerosis; RRMS, relapsing remitting MS; SD, standard deviation; SPMS, secondary progressive MS. *Type of MS was not specified for 6 patients.

- For Part 1 (new relapse assessment) of the questionnaire, the majority were administered in the office (93%) and were completed by the patient (86%).
- The most common new or worsening symptoms were numbness/tingling (67%), fatigue (58%), leg/foot weakness (55%), dizziness/poor balance (53%), and difficulty walking (52%) (**Figure 2**).
  - Approximately half of patients (54%) indicated their symptoms started between 4 and 15 days before the assessment (**Table 1**).
  - Over half (58%) of patients indicated their ADL or overall function were very much or severely affected by their symptoms (**Table 1**).

Figure 2. New or Worsening Symptoms of Current (New) Relapse



ARMS, Assessing Relapse in Multiple Sclerosis

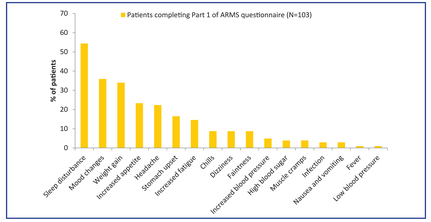
- Most patients (82%) were treated with corticosteroids for their last relapse; 72% of all patients indicated that they very much or completely returned to their baseline state of health (**Table 2**). The most commonly reported AEs from previous relapse treatments were sleep disturbance (54%), mood changes (36%), weight gain (34%), increased appetite (23%), and headache (22%) (**Figure 3**).

Table 2. Outcomes for Last Relapse

Outcome measure	Patients completing Part 1 of ARMS questionnaire (N=103)
Time since last relapse, months	
Mean (SD)	13.4 (12.0)
Range	0–36
Treatment for last relapse, n (%)	
Corticosteroids (IV or oral)	84 (82)
ACTH	5 (5)
Other, no treatment, or not sure	14 (14)
Effect of treatment on RSH, n (%)	(n=90*)
No improvement	1 (1)
A little	8 (9)
Somewhat	17 (19)
Very much	41 (46)
Returned to baseline	23 (26)
Mean (SD) RSH score	7.22 (2.5)

ACTH, adrenocorticotropic hormone; ADL, activities of daily living; ARMS, Assessing Relapse in Multiple Sclerosis; IV, intravenous; RSH, return to previous state of health; SD, standard deviation. *Responses were not provided by 13 patients who reported no treatment or not sure of treatment for their last relapse.

Figure 3. Adverse Events Associated With Last Relapse Treatment



ARMS, Assessing Relapse in Multiple Sclerosis

Part 2—Assessment After Relapse Treatment

- All patients also completed Part 2 (post-relapse assessment) of the questionnaire. Most questionnaires were administered by phone (74%) and were completed by the investigator/designee (79%).
  - The majority of patients were treated with corticosteroids for their current relapse (87%). ACTH was the only other treatment reported (13%) (**Table 3**).
- Nearly all patients (97%) completed their prescribed treatment; the mean (SD) time until completion of Part 2 of the questionnaire was 28.2 (9.7) days (**Table 3**).
- Nearly half of patients (49%) reported that their symptoms were very much or completely resolved after treatment; 49% reported that their ADL were affected not at all or a little; and 43% reported that they returned very much or completely to their baseline state of health (**Table 3**).

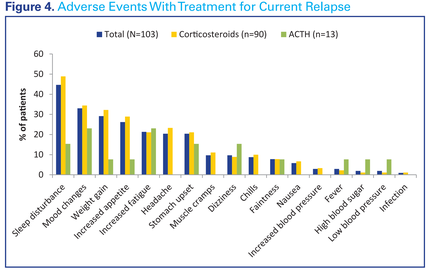
Table 3. ARMS Questionnaire Part 2—Treatment and Outcomes for Current Relapse

Variable	Patients completing Part 2 of ARMS questionnaire (N=103)			
Treatment for current relapse, n (% of total population)				
Any corticosteroids (IV or oral)		90 (87)		
IV corticosteroids only		89 (86)		
Oral corticosteroids only		1 (1)		
Oral corticosteroids after IV		23 (22)		
ACTH		13 (13)		
	Total (N=103)	**Corticosteroids (n=90)**	**ACTH (n=13)**	***P****
Completed prescribed treatment, n (%)	100 (97)	87 (97)	13 (100)	
Time since treatment completed, days				
Mean (SD)	28.2 (9.7)	29.0 (9.8)	22.2 (5.8)	
Range	8-90	8-90	14-30	
Treatment improved relapse symptoms, n (%)				0.756
Got worse	3 (3)	3 (3)	0	
No improvement	6 (6)	5 (6)	1 (8)	
A little	12 (12)	9 (10)	3 (23)	
Somewhat	32 (31)	28 (31)	4 (31)	
Very much	34 (33)	31 (34)	3 (23)	
Completely resolved	16 (16)	14 (16)	2 (15)	
Effect of symptoms on ADL after treatment, n (%)				0.228
Not at all	15 (15)	13 (14)	2 (15)	
A little	35 (34)	34 (38)	1 (8)	
Somewhat	37 (36)	30 (33)	7 (54)	
Very much	14 (14)	11 (12)	3 (23)	
Severely	2 (2)	2 (2)	0	
Effect of treatment on RSH, n (%)				0.444
Got worse	3 (3)	3 (3)	0	
No improvement	7 (7)	5 (6)	2 (15)	
A little	13 (13)	11 (12)	2 (15)	
Somewhat	35 (34)	29 (32)	6 (46)	
Very much	27 (26)	26 (29)	1 (8)	
Returned to baseline	18 (17)	16 (18)	2 (15)	

ACTH, adrenocorticotropic hormone; ADL, activities of daily living; ARMS, Assessing Relapse in Multiple Sclerosis; IV, intravenous; RSH, return to previous state of health; SD, standard deviation
*P values based on chi-square test comparing corticosteroids and ACTH treatment groups.

- The most common AEs reported (overall incidence) were sleep disturbance (45%), mood changes (33%), weight gain (29%), increased appetite (26%), increased fatigue (21%), headache (20%), and stomach upset (20%) (**Figure 4**).

Figure 4. Adverse Events With Treatment for Current Relapse



ACTH, adrenocorticotropic hormone

- Although the study was not designed or powered to evaluate differences between treatments, there were several notable differences between the corticosteroid and ACTH groups in the incidence of AEs, including sleep disturbance (49% vs 15%), increased appetite (29% vs 8%), weight gain (32% vs 8%), and headache (23% vs 0%). Post hoc analyses indicated a significant difference between groups in sleep disturbance (P=0.035, Fisher exact test).

Total Composite Score, Partial Composite Score, ADL, and RSH

- Mean scores for TCS, PCS, ADL, and RSH are summarized in **Table 4**. No significant differences in scores or change scores were observed between treatment groups.

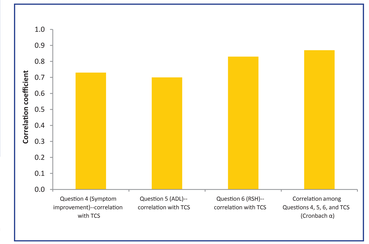
Table 4. Scores for Total and Partial Composite Scores, Activities of Daily Living, and Return to Previous State of Health

Score type	Patients completing Part 2 of ARMS questionnaire			
	Total (N=103)	**Corticosteroids (n=90)**	**ACTH (n=13)**	***P****
TCS after relapse, mean (SD) (N=100[†])	18.51 (7.6)	18.92 (7.4)	15.77 (8.8)	0.166
ADL score, mean (SD)				
Part 1—New relapse (N=103)	3.38 (2.1)	3.43 (2.1)	3.00 (1.9)	0.483
Part 2—After relapse treatment (N=103)	6.21 (2.7)	6.34 (2.7)	5.31 (2.8)	0.198
Change (N=103)	2.83 (2.8)	2.91 (2.9)	2.31 (2.4)	0.478
RSH score, mean (SD)				
Part 1—New relapse (N=90[†])	7.22 (2.5)	7.33 (2.3)	6.50 (3.3)	0.283
Part 2—After relapse treatment (N=100[†])	6.00 (3.0)	6.15 (3.0)	5.00 (3.2)	0.201
Change (N=87[†])	-1.11 (2.6)	-1.03 (2.7)	-1.67 (2.2)	0.438
PCS, mean (SD)				
Part 1—New relapse (N=90[†])	10.52 (3.6)	10.69 (3.4)	9.42 (4.6)	0.251
Part 2—After relapse treatment (N=100[†])	12.38 (5.2)	12.69 (5.0)	10.31 (6.0)	0.123
Change (N=87[†])	2.07 (4.4)	2.29 (4.5)	0.67 (3.4)	0.233

ACTH, adrenocorticotropic hormone; ADL, activities of daily living; ARMS, Assessing Relapse in Multiple Sclerosis; PCS, partial composite score; RSH, return to previous state of health; SD, standard deviation; TCS, total composite score. *P values based on t test comparing corticosteroids and ACTH treatment groups.[†]n values for RSH and PCS are lower due to patients who did not respond to these questions in Part 1 (n=13 patients who indicated no treatment or not sure of treatment for last relapse) or Part 2 (n=3 patients in corticosteroids group who responded "got worse," which was not assigned a numerical value).

- ADL and RSH scores in Part 1 of the questionnaire were not significantly correlated (Pearson r = 0.205; P=0.053), but scores in Part 2 were significantly correlated (Pearson r = 0.723, P<0.0001).
- Analysis of correlations among Questions 4 (symptom improvement), 5 (ADL), and 6 (RSH) from Part 2 of the questionnaire and the TCS showed a high correlation coefficient (Cronbach coefficient=0.87), suggesting good internal consistency among those 3 questions. The individual Cronbach αs for Question 4, ADL, and RSH with TCS were 0.84, 0.86, and 0.75, respectively. The corresponding correlation coefficients are shown in **Figure 5**. There were also significant correlations between Question 4 and ADL (r = 0.60, P<0.0001) and RSH (r = 0.76, P<0.0001).

Figure 5. Correlations Among Total Composite Score and Individual Items[a]



ADL, activities of daily living; RSH, return to previous state of health; TCS, total composite score. [a]Total composite score calculated as the sum of scores from Questions 4, 5, and 6 from Part 2 of the ARMS questionnaire.

CONCLUSIONS

- These data support the ARMS questionnaire as a useful tool for evaluating relapses and response to acute treatment for MS relapse.
- Differences in the incidence of some AEs associated with corticosteroids compared with ACTH suggest that there may be differences in the mechanisms underlying the physiological effects of these drugs and that further exploration of differences in clinical outcomes may be warranted.
- Systematic assessment of relapses and response to relapse treatment may help clinicians to optimize outcomes for patients.

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