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Incomplete relapse recovery and sustained disability progression in MS

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INTRODUCTION

- Relapses are understood to be the hallmark of multiple sclerosis (MS), but the relevance of relapses in the development of long-term neurological deficits, also known as sustained disability progression, is unclear.
- Some data have suggested that relapses are minimally associated with disease progression,[1] whereas other data have shown that approximately 40% of patients display sustained disability progression following an exacerbation.[2]
- Sustained progression in MS likely occurs both with and without relapses; further research to establish a more comprehensive understanding of this relationship is recommended.

OBJECTIVE

- Determine the relative frequency with which disability progression occurred with or without clinical relapses in placebo-treated patients with relapsing-remitting MS (RRMS) using data collected during two phase 3 clinical studies.

METHODS

Studies

- The Multiple Sclerosis Collaborative Research Group (MSCRG) trial was a phase 3, multicenter, double-blind, placebo-controlled, randomized pivotal study investigating the use of intramuscular interferon beta-1a (IM IFNβ-1a) in patients with relapsing MS.[3]
  - This study demonstrated that IM IFNβ-1a administered weekly for up to 104 weeks (n=85) reduced the risk of disability progression by 37% compared with placebo (n=87).
  - Mean time to sustained disability progression was significantly longer in patients treated with IM IFNβ-1a than in those receiving placebo (P=0.02). The number of exacerbations per patient was significantly higher in placebo recipients than in IM IFNβ-1a recipients (P=0.03), giving an annual relapse rate of 0.90 for placebo patients and 0.61 for IM IFNβ-1a patients (P=0.002).
- The Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) trial was a phase 3, multicenter, double-blind, placebo-controlled, randomized pivotal study investigating the treatment of patients with RRMS with natalizumab.[4]
  - The study demonstrated that natalizumab therapy reduced the risk of sustained disability progression by 42% over 2 years compared with placebo (P<0.001).
  - Natalizumab therapy was associated with a 68% reduction in clinical relapse rate at 1 year relative to placebo (P<0.001).

Analyses

- Data from MSCRG and AFFIRM were retrospectively analyzed to determine the frequency with which placebo-treated patients with RRMS developed disability progression without relapse.
- Disability progression was characterized as disease progression either with or without prior relapse. Sustained disability progression was defined as a change in Expanded Disability Status Scale (EDSS) score of ≥1 point sustained for ≥6 months for patients in MSCRG and a change in EDSS score of ≥1 point sustained for ≥3 months for patients in AFFIRM. Prior relapse was defined as the appearance of a new symptom or the reappearance of old symptoms lasting >24 hours at any point during the 180 days before the start of sustained disease progression.
- Patients with sustained disability progression were evaluated for simultaneous worsening on multiple functional system scores (FSS) in both studies.
- For both studies, patients receiving placebo were categorized into 1 of 4 groups:
  - Sustained disease progression due to incomplete recovery from relapses.
  - Sustained disease progression not associated with relapses.
  - No sustained disease progression but with relapses.
  - No sustained progression and no relapses.
- Baseline characteristics were compared between groups using the t test or Wilcoxon rank-sum test for continuous variables and the Chi-squared test for categorical variables. Overall intergroup differences were assessed using the Kruskal-Wallis test.

RESULTS

- Data for 87 placebo patients from MSCRG (mean disease duration, 6.1 years) and 315 placebo patients from AFFIRM (mean disease duration, 7.7 years) were analyzed.

Baseline characteristics

- Baseline demographics were generally similar among groups in each study (Table 1).

Table 1: Baseline characteristics by group for placebo patients in the MSCRG[a] and AFFIRM[b] studies

	MSCRG (N=87)				AFFIRM (N=315)			
	Sustained disease progression		No sustained disease progression		Sustained disease progression		No sustained disease progression	
Characteristic	Incomplete recovery from relapses (n=20 [23.0%][c])	Not associated with relapses (n=9 [10.3%][c])	With relapses (n=44 [50.6%][c])	No relapses (n=14 [16.1%][c])	Incomplete recovery from relapses (n=48 [15.2%][c])	Not associated with relapses (n=36 [11.4%][c])	With relapses (n=106 [33.7%][c])	No relapses (n=125 [39.7%][c])
Age, years, mean (SD)	35.5 (7.3)	38.0 (4.9)	34.8 (7.5)	37.9 (4.7)	36.2 (8.3)	39.6 (6.7)	35.1 (7.6)	37.4 (7.8)
Gender, female, n (%)	18 (90.0)	6 (66.7)	32 (72.7)	9 (64.3)	34 (70.8)	26 (72.2)	73 (68.9)	78 (62.4)
EDSS, mean (SD)	2.7 (0.9)	2.1 (0.6)	2.4 (0.9)	2.4 (1.0)	2.4 (1.2)	2.1 (1.4)	2.5 (1.2)	2.2 (1.1)
ARR, mean (SD)	1.2 (0.5)	0.9 (0.3)	1.2 (0.6)	1.4 (0.6)	1.6 (0.8)	1.5 (0.6)	1.6 (0.8)	1.4 (0.8)
Disease duration, years, median (range)	6.1 (1.1–26.5)	5.3 (1.8–12.3)	4.7 (1.2–31.0)	2.3 (1.0–18.0)	6.0 (1.0–27.0)	7.0 (1.0–27.0)	6.5 (0–31.0)	5.0 (0–33.0)
T2 lesion volume, mm^3, median (range)	13,410 (90–66,900)[c]	21,130 (415–49,035)	13,830 (345–59,415)[c]	13,065 (820–48,590)[c]	13,654 (320–53,206)	11,824 (1347–83,296)[c]	8207 (343–83,126)	7132 (288–83,289)[c]
Gd+ lesion volume, mm^2, median (range)	55 (0–2752)	52 (0–199)	56 (0–1153)	0 (0–1839)	0 (0–3149)	0 (0–2989)[c]	77 (0–5338)	0 (0–9667)[c]

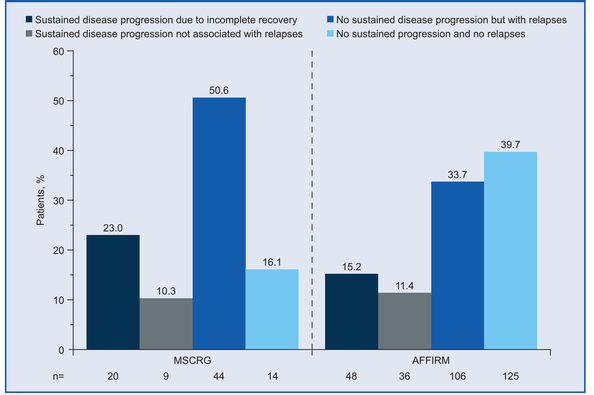
For continuous variables, significance was evaluated using the Wilcoxon rank-sum test [Kruskal-Wallis for overall test]; for categorical variables, the Fisher exact test was used. SD=standard deviation; ARR=annualized relapse rate; Gd+=gadolinium enhancing.
[a]There were no significant differences between the groups for any of the baseline characteristics in this study; [b]statistically significant differences were seen across groups in age [P=0.0189] and Gd+ lesion volume [P=0.0178]; [c]percentage of patients from the placebo group in MSCRG; [d]percentage of patients from the placebo group in AFFIRM; [e]n=19; [f]n=43; [g]n=12; [h]n=35; [i]n=124.

- No significant differences in baseline characteristics were seen in the MSCRG study.
- Some significant differences in baseline characteristics were seen in the AFFIRM study (data not shown).
  - Patients with sustained disease progression not associated with relapses were significantly older than:
    - Patients with sustained disease progression due to relapse (P=0.0460).
    - Patients with no sustained progression but with relapse (P=0.0034).
  - Patients with no disease progression and no relapses were significantly older than those with relapses (37.4 years vs 35.1 years; P=0.0292) and had a significantly smaller mean Gd+ lesion volume than those with relapses (282 mm^3 vs 409 mm^3; P=0.0015).
  - Patients with no disease progression and no relapses also had a significantly lower mean T2 lesion volume than patients with sustained disease progression not associated with relapses (13,298 mm^3 vs 20,012 mm^3; P=0.0436).

Sustained disease progression

- In both studies, more patients had sustained progression due to incomplete recovery from relapses than sustained progression without relapses (Figure 1). Differences between these groups were statistically significant in the MSCRG study (P=0.04) but not in AFFIRM (P=0.19).
- In the MSCRG study, the majority of patients with no sustained disease progression had relapses (44 of 58, 75.8%). In AFFIRM, a smaller proportion of patients with no sustained disease progression had relapses (106 of 231, 45.9%) (Figure 1).
- In both MSCRG and AFFIRM, only 31% of all relapses were associated with disability progression.
- Combined data showed a similar trend; more patients had sustained progression due to incomplete recovery from relapses than sustained progression without relapses (P=0.05; data not shown).

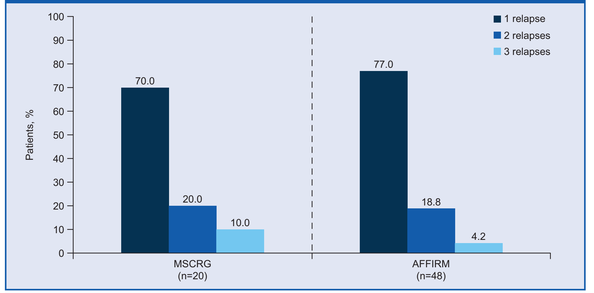
Figure 1: Summary of sustained disease progression in placebo patients in MSCRG and AFFIRM



Sustained disease progression and number of relapses with incomplete recovery

- Of the 20 patients in the MSCRG study who had sustained progression due to incomplete recovery from relapse, 14 patients (70.0%) had only 1 relapse during the study period, 4 patients (20.0%) had 2 relapses, and 2 patients (10.0%) had 3 relapses (Figure 2).

Figure 2: Relapse count in patients with incomplete recovery leading to sustained EDSS progression in MSCRG and AFFIRM

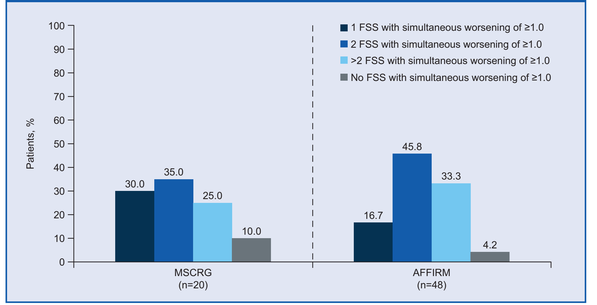


- Similar results were seen for patients in AFFIRM. Thirty-seven of 48 patients (77.1%) who had sustained progression due to incomplete recovery from relapse had only 1 relapse during the study period; 9 patients (18.8%) had 2 relapses, and 2 patients (4.2%) had 3 relapses.

Functional system score and sustained EDSS progression

- In both studies, the majority of patients (MSCRG: 18 of 20 [90.0%]; AFFIRM: 46 of 48 [95.8%]) who had sustained EDSS progression due to incomplete recovery from relapses had simultaneous sustained worsening of ≥1.0 in at least 1 functional system. Only 2 patients in each study (10.0% in MSCRG and 4.2% in AFFIRM) had no simultaneously sustained worsening of ≥1.0 on any functional system (Figure 3).
- A similar percentage of patients in both studies had simultaneously sustained worsening of ≥2.0 in ≥1 functional system (MSCRG: 40.0% [n=8]; AFFIRM: 45.8% [n=22]; data not shown).

Figure 3: Simultaneous worsening in FSS in patients with sustained EDSS progression due to incomplete recovery from relapse in MSCRG and AFFIRM



CONCLUSIONS

- In this analysis, sustained disability progression occurred more frequently in association with protocol-defined relapse than with no associated relapse.
  - The majority of patients who had sustained disability progression due to incomplete recovery from relapse had only 1 relapse during the study period.
  - Less than one-third of relapses in either study led to sustained disability progression.
- Examination of data for patients with sustained EDSS progression revealed simultaneous sustained changes in FSS, further supporting the reliability of using sustained EDSS progression as a measure of disability progression.
- It is possible that in this group of patients, inflammatory events rather than a more slowly occurring "relapse-free" degenerative process were the underlying cause of disease progression.
  - This variable phenotypic expression of MS may be associated with differing responses to existing therapies.
- Further investigation into the association between relapse and disease progression is needed to better understand the results of this study.

References

1. Scalfari A, Neuhaus A, Degenhardt A, et al. *Brain*. 2010;133:1914-1929.
2. Lublin F, Baier M, Cutter G. *Neurology*. 2003;61:1528-1532.
3. Jacobs L, Cookfair D, Rudick R, et al. *Ann Neurol*. 1996;39:285-294.
4. Polman C, O'Connor P, Havrdová E, et al. *N Engl J Med*. 2006;354:899-910.

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