Demographic Characteristics and Progression of PPMS in the CLIMB Study Population

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Introduction

Background

- 10-15% of Multiple Sclerosis (MS) patients are diagnosed with primary progressive MS (PPMS), which has the worst prognosis of MS subtypes[1]
- Even though eight immunomodulatory treatments targeting RRMS have been approved by the FDA, no effective therapy for PPMS is currently available[2]
- Overall rates of disease progression are not clear, especially given recent data suggesting they may be changing with time or geographical location[3,4]
- Need for better estimates of the rate of disease progression in PPMS was highlighted when a recent clinical trial for glatiramer acetate in PPMS patients was terminated because short-term disease progression, measured by disability accumulation, was slower than anticipated [5] based on prior studies.
- Two recent studies have suggested MS consists of 2 independent phases, with Phase 1 being duration from onset to EDSS 3 or 4 and Phase 2 being duration from EDSS 3 or 4 to 6[6,7]. However, this 2-phase model has been sparsely validated [8] in well-defined PPMS patient populations.
- The CLIMB Study PPMS is a previously unstudied, modern cohort with widespread use of immunomodulatory therapy.

Objectives

1. *Characterize* demographic and clinical characteristics of the CLIMB study (Partners MS Center, Boston, MA) PPMS population
2. *Assess* the rate of PPMS disease progression, clinically evaluated by Expanded Disability Status Scale (EDSS) , in Phase 1, in Phase 2, from onset to EDSS 6
3. *Assess* the number of PPMS patients required for clinical trials with a primary clinical endpoint of time to 6-month sustained progression

Selected References

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Methods

Subjects: The Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital (CLIMB) at the Partners Multiple Sclerosis Center is a longitudinal prospective study of MS patients that has been following patients since 2000. All patients have detailed demographic, clinical, immunological, and MRI data validated and recorded in an Oracle-based electronic relational database. Analysis included patients with a most recent visit on or after 2010 and classified as either PPMS or relapsing onset MS (ROMS), which includes RRMS or secondary progressive MS (SPMS), based on the physician diagnosis. All patient data for this study were obtained via a database query on November 11, 2012.

Clinical Markers and Measures: EDSS is a standardized ordinal scale, ranging from 0-10, which describes MS-related disability. In this study, the time to two main landmark EDSS values were investigated: EDSS=3 and EDSS=6. Based on previous work, the time from disease onset to EDSS=3 was defined as Phase 1, and the time from EDSS=3 to EDSS=6 was defined as Phase 2. Time to sustained disease progression was also investigated. Sustained progression was defined as an increase of at least 1 point on the EDSS for patients with initial EDSS less than 5.5 or an increase of 0.5 points for patients with initial EDSS of 5.5 or greater that was subsequently maintained or increased for at least 180 days. The date of sustained progression was defined as the visit date at which sustained progression began.

Statistical Analysis: To evaluate the demographic characteristics of the PPMS patients compared to the ROMS patients, we used the Fisher Exact test and Student's t-test as appropriate. In each group, the time from disease onset to first EDSS 3 (Phase 1), from first EDSS 3 to first EDSS 6 (Phase 2), and from onset to first EDSS 6 was compared using survival analysis appropriate for interval censored event times. Also, time to 6-month sustained progression in PPMS patients was analyzed. Sample size calculations were made for hypothetical PPMS trials powered at 80% and alpha=0.05. with the outcome being a decrease of 30%, 50%, or 70% in the proportion of patients with sustained progression at 1, 2 or 3 years. The power calculation used Freedman's method and considered people who did not have sustained progression at the end of the trial as administratively censored.

Results

Table 1: Demographic characteristics of the patients

	PP	RO	p Value
N	73	1541	-
Male, %	52.1	25.7	<0.001*
White/Caucasian %	93.2	91.4†	1*
Hispanic/Latino %	1.4	3.6‡	0.69*
Age at onset, mean(SD)	44.4 (9.6)	32.7 (9.9)	<0.0001#
Time to first visit, mean(SD)	9.4 (7.4)	7.6 (8.7)	0.042#
EDSS at first visit, mean(SD)	4.1 (1.9)	1.9 (1.7)	<0.0001#
Ever treated, %	78.1	91.4	0.0006*

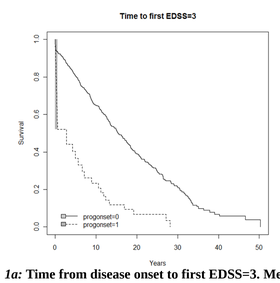
*Fisher exact text
#Student's t test
†28 patients had unknown or not reported race and did not contribute to analysis
‡22 patients had unknown or not reported ethnicity and did not contribute to analysis

Table 2: Clinical Characteristics of first symptoms

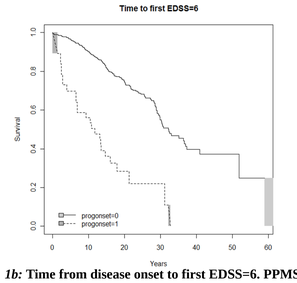
	PP	RO	p Value
First symptom, n(%)			
Visual	1 (1.4)	400 (26.0)	<0.001
Motor	55 (75.3)	325 (21.1)	<0.001
Sensory	16 (21.9)	805 (52.2)	<0.001
Coordination	6 (8.2)	150 (9.7)	0.84
Bowel/Bladder	5 (6.8)	46 (3.0)	0.08
Fatigue	1 (1.4)	66 (4.3)	0.36
Cognitive	0 (0)	33 (2.1)	0.40
Encephalopathy	0 (0)	1 (0.1)	1
Other	1 (1.4)	136 (8.8)	0.02
None of the above#	3	139	
First symptom location, n(%)			
Optic nerve	0 (0)	342 (22.2)	<0.001
Brainstem/cerebellum	8 (11.0)	368 (23.9)	0.01
Cerebrum	4 (5.5)	201 (13.0)	0.07
Spinal Cord	43 (58.9)	613 (39.8)	0.001
Not Defined	24 (32.9)	135 (8.8)	<0.001
None of the above#	1	139	

= patients excluded from analyses because of lack of information following database update

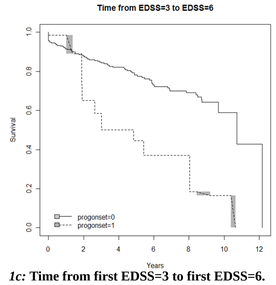
Figure 1: Estimated survival curves for time through Phase 1, through Phase 2, and onset to EDSS 6 [Dashed line: PPMS, Solid line: ROMS.]



1a: **Time from disease onset to first EDSS=3. Median time for progression through Phase 1 of disease was 2.8 years for the PP group, while the time in the RO group was 15.4 years (p<0.001).**

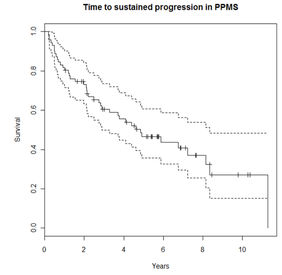


1b: **Time from disease onset to first EDSS=6. PPMS was associated with a shorter time to EDSS 6 (11.7 years) from onset compared with RO (32.2 years; p<0.001).**

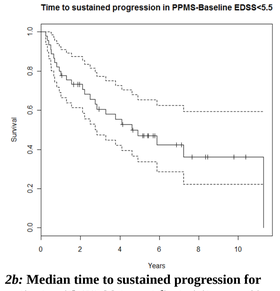


1c: **Time from first EDSS=3 to first EDSS=6. Median time through Phase 2 was 4.8 years for the PP group and 10.7 years for the RO group (p<0.005).**

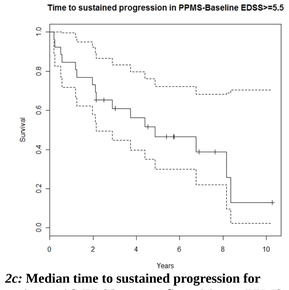
Figure 2: Kaplan-Meir curves showing time to sustained progression of disease



2a: **Median time to sustained progression for all PPMS patients was 4.85 years (95%CI 2.83-8.35), and this time was significantly faster than the time in RO patients (p<0.001)**



2b: **Median time to sustained progression for patients with EDSS<5.5 at first visit was 4.60 years.**



2c: **Median time to sustained progression for patients with EDSS>=5.5 at first visit was PPMS was 4.85 years**

Results

Table 3: Sample size estimates for theoretical PPMS clinical trials

Study duration (Years)	Estimated proportion with sustained progression in standard of care group	Hypothesized proportion with sustained progression in treatment group	Proportion change with sustained progression in treatment group	Sample size for 80% power
1	0.183	0.128	30%	1368
1	0.183	0.092	50%	446
1	0.183	0.055	70%	210
2	0.27	0.189	30%	850
2	0.27	0.135	50%	286
2	0.27	0.081	70%	136
3	0.394	0.276	30%	504
3	0.394	0.197	50%	174
3	0.394	0.118	70%	86

Legend: Sample size calculations are for both groups assuming equal allocation in the two treatment arms.

Discussion

- CLIMB PPMS patients were found to have similar demographic characteristics to previous cohorts and are a representative sample of PPMS patient seen at our clinic.
- Time to EDSS landmarks in our study are longer than previously reported, but the difference between ROMS and PPMS remained highly significant and more importantly clinically meaningful.
- The time from EDSS 3 to EDSS 6, termed Phase II in previous studies, was found to be significantly different in PPMS compared to ROMS, which contradicts previous findings of similar time through this phase of disease.
- Time to sustained progression showed that progression occurs at a slower rate in our sample than previously reported.
- Given this slower rate of progression, sample size estimates for future trials were provided and showed that larger studies may be necessary to observe clinically meaningful treatment effects.

Conclusions

- Faster progression through Phase 1, Phase 2, and from onset to EDSS 6 is associated with PPMS. In contrast to previous studies, we found faster Phase 2 progression to be clinically significant.
- Reevaluation of time to sustained progression provides a basis for sample size estimates and design of new clinical trials in PPMS.
- Future studies should assess natural history of PPMS in larger patient cohorts within the era of disease-modifying therapeutics. They must also assess the influence of demographic, clinical, and environmental factors and biomarkers, such as vitamin D and immune markers, on PPMS disease course.

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