Progressive Multiple Sclerosis: A Comprehensive Update

Reports from a CMSC Consensus Meeting

1  Natural History of Primary Progressive Multiple Sclerosis
9  Issues Related to the Diagnosis of Primary Progressive Multiple Sclerosis
16 Immunology and Pathology of Primary Progressive Multiple Sclerosis
19 The Genetics of Primary Progressive Multiple Sclerosis
23 Imaging of Primary Progressive Multiple Sclerosis
30 NARCOMS Data and Patients with Primary Progressive Multiple Sclerosis
32 Prognosis of Primary Progressive Multiple Sclerosis
33 Rehabilitation of PPMS Patients
36 Psychosocial Issues and Cognitive Functioning in Primary Progressive Multiple Sclerosis (PPMS)
38 Clinical Trials in Primary Progressive Multiple Sclerosis
41 Presentation of Group I Discussion
43 Presentation of Group II Discussion
45 SPMS and PPMS: Same or Different?
49 Controversies in PPMS with Timothy Vollmer, MD—Discussion
Take a closer look at BETASERON (interferon beta-1b)

- Over 20 years of efficacy and safety data
- BETAPLUS™—the MS support program patients have come to depend on
  - 24/7 MS-trained BETA Nurse support
  - $0 monthly copay*
  - Peer Mentor Program

**Indications:** BETASERON (interferon beta-1b) is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

**Important Safety Information:** The most commonly reported adverse reactions are lymphopenia, injection-site reaction, asthenia, flu-like symptom complex, headache, and pain. Gradual dose titration and use of analgesics during treatment initiation may help reduce flu-like symptoms. BETASERON should be used with caution in patients with depression. Injection-site necrosis has been reported in 4% of patients in controlled trials. Patients should be advised of the importance of rotating injection sites. Female patients should be warned about the potential risk to pregnancy. Cases of anaphylaxis have been reported rarely. See “Warnings,” “Precautions,” and “Adverse Reactions” sections of full Prescribing Information.

Please see brief summary of full Prescribing Information on following page.


*Some restrictions apply. Copay assistance is limited to $9500 per patient per calendar year. Patients who are enrolled in any type of government insurance or reimbursement programs are not eligible. As a condition precedent of the copayment support provided under this program, eg, copay refunds, participating patients and pharmacies are obligated to inform insurance companies and third party payors of any benefits they receive and the value of this program, as required by contract or otherwise. Void where prohibited by law, taxed, or restricted. Patients enrolled in Bayer’s Patient Assistance Program are not eligible.

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Betaseron®
(INTERFERON beta-1b) FOR SC INJECTION

Suggested Dosage

BAYER HEALTHCARE PHARMACEUTICALS INC.
Part Number 6700501BS Revision Date 5/08

Bayer HealthCare Pharmaceuticals Inc.
Montville, NJ 07045

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In patients with depression, a reduced interferon beta, Albumin (Human), USP, or any other component of the formulation.

CONTRAINDICATIONS

Betaseron (Interferon beta-1b) should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression and suicide have been reported in clinical trials of interferon beta-1b, including Betaseron. Patients treated with Betaseron should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. If a patient develops depression, cessation of Betaseron should be considered.

In the four randomized controlled studies there were three suicides and eight suicide attempts among 1530 patients in the Betaseron treated groups compared to two suicides and four suicide attempts among the 965 patients in the placebo groups.

Injection Site Necrosis

Injection site necrosis (doses > 0.028 mg/kg/day) has been reported in 4% of patients in controlled clinical trials (see ADVERSE REACTIONS). Typically, injection site necrosis occurs within four hours of intramuscular injection. Necrosis may occur at a single or multiple injection sites. Treatment of injection site necrosis is dependent on the extent of necrosis. For patients who continue therapy with Betaseron, injection site necrosis that occurs within one hour of the time of the last injection is not treated. In most cases healing was associated with scar formation. Injection site necrosis that occurs after one hour of the time of the last injection was treated. In most cases healing was associated with scar formation. In some instances, patients have experienced re-occurrence of necrosis while Betaseron therapy continued.

Anaphylaxis

Anaphylaxis has been reported as a rare complication of Betaseron use. Other allergic reactions, including urticaria and angioedema, have been reported.

Geriatric Use

The safety and effectiveness of Betaseron in patients aged 65 years and older have not been established.

Pregnancy

Teratogenic Effects

Category C

Betaseron was not teratogenic at doses up to 0.42 mg/kg/day when given to pregnant female mice on gestation days 7–16 (7.5 mg/kg/day to rats during gestation from 0.02 mg/kg/day to 0.42 mg/kg/day). There was no evidence of functional or structural abnormalities in the offspring of mice or rats given Betaseron. Lower doses were not studied in monkeys. Spontaneous abortions while on treatment were reported in 7% of rats dosed with 0.42 mg/kg/day for 6 months. No adverse effects were noted on the reproductive system in monkeys.

Nursing Mothers

It is not known if Betaseron is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Betaseron, a decision should be made whether to discontinue nursing or to discontinue the medication, taking the importance of the nursing infant into account.

Pediatric Use

Pediatric patients have not been evaluated.

PRECAUTIONS

Screening and product manufacturing processes, it carries an extremely remote risk for transmissible spongiform encephalopathy (TSEs) in humans. There are no adequate and well-controlled studies in pregnant women. If the patient becomes pregnant while taking Betaseron, the patient should be apprised of the potential hazard to the fetus and it should be recommended that the patient discontinue Betaseron.

The incidence of injection site reactions tended to decrease over time. In the four placebo-controlled clinical trials, the incidence of injection site necrosis was 4% of patients treated with Betaseron and 0% with placebo injection site necrosis. Injection site necrosis, i.e. the following terms: injection site necrosis, injection site pain, injection site erythema, injection site redness, and injection site induration.

Flu-Like Symptom Complex

Injection site reactions were approximately 57% in the four controlled clinical trials. The incidence decreased over time, with only 10% of patients reporting flu-like symptoms at the end of the first month of treatment compared to approximately 40% at the end of the study.

In the four placebo-controlled clinical trials, injection site reactions occurred in 78% of patients receiving Betaseron injection site reactions in 4%. Injection site inflammation (54%), injection site pain (56%), injection site erythema (4%), injection site redness (4%), injection site mass (2%), injection site edema (2%) and non-specific injection site reactions were reported in patients treated with Betaseron (see WARNINGS AND PRECAUTIONS). The incidence of injection site reactions tended to decrease over time. In the four placebo-controlled clinical trials, the incidence decreased over time. In the four placebo-controlled clinical trials, injection site necrosis occurred in 0% of patients treated with Betaseron and 0% of patients treated with placebo.

The observed incidence of neutralizing activity in an assay may be influenced by several factors including interference of immune sera to inhibit the production of the interferon-inducible protein, MxA. Neutralization antibody formation was observed in 9.4% (94/996) of patients treated with Betaseron. Studies in normally cycling, female rhesus monkeys at doses up to 25.2% of the Betaseron treated patients. Such observations were not seen in placebo treated patients. The most commonly reported adverse reactions were injection site reactions, injection site pain, injection site erythema, injection site redness, and injection site induration. Injection site reactions were most frequently reported in areas of skin discoloration or edema, or the need for concomitant medication to treat an adverse reaction symptom were flu-like symptom complex (see Table 2). Most flu-like symptom complex occurred within one month of initiating Betaseron treatment.

Table 2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=965)</th>
<th>Betaseron (N=1407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Rash</td>
<td>15%</td>
<td>21%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2%</td>
<td>13%</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>3%</td>
<td>6%</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<td></td>
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<tr>
<td>Bronchitis</td>
<td>8%</td>
<td>17%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Diarrhea</td>
<td>15%</td>
<td>21%</td>
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<tr>
<td>Nausea</td>
<td>15%</td>
<td>21%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6%</td>
<td>11%</td>
</tr>
<tr>
<td>Other</td>
<td>15%</td>
<td>21%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Rash</td>
<td>2%</td>
<td>4%</td>
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<tr>
<td>Skin disorders</td>
<td>3%</td>
<td>5%</td>
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<tr>
<td>Vascular tissue disorders</td>
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<td></td>
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<tr>
<td>DVT</td>
<td>1%</td>
<td>1%</td>
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<tr>
<td>Thrombophlebitis and connective tissue disorders</td>
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<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Hypertension</td>
<td>33%</td>
<td>43%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14%</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>Renal and urinary disorders</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>6%</td>
<td>11%</td>
</tr>
<tr>
<td>Gastrointestinal and breast disorders</td>
<td></td>
<td></td>
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</table>
Great progress has been made in the management of relapsing forms of MS since the advent of disease-modifying therapies in 1993. Our understanding of the cause, pathogenesis, natural history and treatment of the disease has increased greatly since then, aided by advances in imaging, immunology and molecular genetics amongst other disciplines. Despite these advances, our understanding of the mechanisms and treatment of progressive forms of MS is very limited and the real needs of our MS patients lend a sense of urgency in the search to find solutions to this problem.

Currently we divide MS into differing clinical phenotypes: relapsing remitting, secondary progressive, primary progressive and progressive relapsing disease. However, current research including particular findings from longitudinal MRI evaluation of patients, suggests that progression may be more or less continuous from the onset of the disease. The mechanisms that drive progression in these clinical forms of MS may be more alike than different.

In February of 2008, a symposium on progressive multiple sclerosis was organized by the Consortium of Multiple Sclerosis Centers to discuss this subject, and in particular, to examine whether progression in different forms of multiple sclerosis is best explained by the same or similar mechanisms. An understanding of the pathogenesis of progressive MS is of critical importance given the failure of conventional anti-inflammatory therapy to show efficacy in large well-designed randomized clinical trials. Clearly, novel therapeutic agents are needed.

Topics reviewed include natural history, diagnosis, immunology, genetics, prognosis, imaging, cognition, rehabilitation and treatment of progressive MS. The results of these discussions have been compiled in this publication. Every answer created new questions and a great deal more work remains to be done.

Our hope is that this symposium will help stimulate research into the understanding and management of this enigmatic and vexing form of MS.

Kathleen Hawker, MD
Paul O’Connor, MD
Symposium Co-chairs

Acknowledgments: The authors acknowledge the Consortium of Multiple Sclerosis Centers, which provided a grant in support of this consensus conference; and Lori Saslow, an editorial consultant funded by the CMSC, for her assistance in manuscript preparation.
Natural History of Primary Progressive Multiple Sclerosis

Sean J. Pittock, MD

Introduction

A n understanding of the natural history of multiple sclerosis (MS) and the underlying pathophysiology of this debilitating disease provides important research implications related to trial design, healthcare economics, and service provision. Mapping the course of this disease also provides benchmarks against which we can compare therapeutic trial efficacy.

Understanding primary progressive multiple sclerosis (PPMS) is especially challenging because attempts to investigate the pathologic mechanisms of this subtype are often confounded by the long delay from symptom onset to diagnosis, which can span up to seven years. This delay inhibits efforts to uncover pathologic processes that drive the initial stages of disease and precludes the early diagnosis and treatment that may one day prevent the irreversible disability that characterizes PPMS.

The focus of this talk is to discuss our present knowledge of the natural history of PPMS, much of which is based on findings from a small number of population-based cohorts.

Frequency of PPMS

How frequent is primary progressive MS? In a population based study of MS in Olmsted County, Minnesota, the raw prevalence of MS was determined to be 177 per 100,000 population on December 1, 2000 and only 5% of these patients were diagnosed as having PPMS, and these patients were not further subclassified.

Confavreux and colleagues conducted a study in Lyon, France that included 1844 patients with MS. Of these, 15% had PPMS; 9% had progressive nonrelapsing MS and 6% had the progressive relapsing form.

Kremenchutzky and colleagues studied 1099 patients with MS in London-Ontario, Canada. Of the 34% of patients with primary progressive disease, 19% had PPMS and 15% had progressive relapsing (PR) MS.

In a study in British Columbia, Tremlett and colleagues studied 2837 patients with MS, with 12.4% further classified as primary progressive. This same group has recently reported findings from a larger population based cohort of 5779 patients with MS of whom 552 (10%) had PPMS. In progressive MS the male-to-female ratio is similar in patients with progressive disease which is in sharp contrast to that observed in those with relapsing-remitting (RR) MS, which is typically associated with a preponderance of females across all age groups (Table 1, Figure 1).

Figure 1. Sex and age at onset in the primary progressive (A) and relapsing populations (B). (Tremlett et al., Neurology 11165:1919-1923, 2005, reproduced with permission).
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**Table 1. Comparative demographic and disease-related characteristics of cases with an exacerbating-remitting initial course and cases with a progressive initial course of multiple sclerosis, among 1844 patients with multiple sclerosis**

<table>
<thead>
<tr>
<th></th>
<th>Multiple sclerosis with an exacerbating-remitting initial course(^t) (n = 1562)</th>
<th>Multiple sclerosis with a progressive initial course(^s) (n = 282)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>536 (34)</td>
<td>121 (43)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Females</td>
<td>1026 (66)</td>
<td>161 (57)</td>
<td></td>
</tr>
<tr>
<td>Age at onset of multiple sclerosis: no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>29.6 ± 9.5</td>
<td>39.3 ± 11.3</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>Median</td>
<td>29.0</td>
<td>40.1</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>5-62</td>
<td>11-67</td>
<td></td>
</tr>
<tr>
<td>Initial symptoms of multiple sclerosis: no. (%)</td>
<td></td>
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<tr>
<td>Isolated optic neuritis</td>
<td>330 (21)</td>
<td>5 (2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Isolated brainstem dysfunction</td>
<td>158 (10)</td>
<td>1 (0)</td>
<td></td>
</tr>
<tr>
<td>Isolated dysfunction of long tracts</td>
<td>727 (47)</td>
<td>236 (84)</td>
<td></td>
</tr>
<tr>
<td>Combination of symptoms</td>
<td>347 (22)</td>
<td>40 (14)</td>
<td></td>
</tr>
<tr>
<td>Kaplan-Meier estimates of the time (median [95% CI]): (years) From onset of multiple sclerosis to assignment of</td>
<td></td>
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<td></td>
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<tr>
<td>DSS 4</td>
<td>11.4 [10.5-12.3]</td>
<td>0.0</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>DSS 6</td>
<td>23.1 [20.1-26.1]</td>
<td>7.1 [6.3-7.9]</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>DSS 7</td>
<td>33.1 [29.2-37.0]</td>
<td>13.4 [11.0-15.9]</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>From assignment of DSS 4 to assignment of</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DSS 6</td>
<td>5.7 [4.9-6.4]</td>
<td>5.4 [4.3-6.6]</td>
<td>0.74**</td>
</tr>
<tr>
<td>DSS 7</td>
<td>12.1 [10.0-14.2]</td>
<td>12.0 [10.1-13.9]</td>
<td>0.70**</td>
</tr>
<tr>
<td>From assignment of DSS 6 to assignment of</td>
<td></td>
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<tr>
<td>DSS 7</td>
<td>3.3 [2.8-3.9]</td>
<td>4.0 [2.9-5.1]</td>
<td>0.48**</td>
</tr>
<tr>
<td>Kaplan-Meier estimates of the age (median [95% CI]) at the time of assigning DSS (years)</td>
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<tr>
<td>DSS 4</td>
<td>44.8 [43.8-45.9]</td>
<td>42.1 [40.2-44.0]</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>DSS 6</td>
<td>55.3 [54.2-56.7]</td>
<td>53.0 [51.1-54.9]</td>
<td>0.002**</td>
</tr>
<tr>
<td>DSS 7</td>
<td>62.8 [60.3-65.4]</td>
<td>63.1 [60.0-66.2]</td>
<td>0.24**</td>
</tr>
<tr>
<td>Duration of multiple sclerosis: (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>11.5 ± 9.9</td>
<td>10.1 ± 8.0</td>
<td>0.02***</td>
</tr>
<tr>
<td>Median</td>
<td>10.0</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0-52</td>
<td>0-62</td>
<td></td>
</tr>
</tbody>
</table>

\(t\)Denotes the pooling of cases with ‘relapsing-remitting multiple sclerosis’ and of cases with ‘secondary progressive multiple sclerosis’ (Lublin and Reingold, 1966). \#Denotes the pooling of cases with ‘progressive relapsing multiple sclerosis’ and of cases with ‘primary progressive multiple sclerosis’ (Lublin and Reingold, 1996). SD denotes standard deviation; CI, confidence intervals; DSS, Kurtzke Disability Status Scale. P-values are calculated with use of the *chi-squared test, ** the log rank test, ***the Student’s t-test. (Confavreux C, et al. Natural history of multiple sclerosis: a unifying concept. *Brain*. 2006;129:606-616, reproduced with the permission of Oxford University Press).}\(^4\)

Progressive MS is associated with an older age of onset when compared with RRMS.

**Symptom Onset and Predicting Outcome**

Can we use onset symptoms to predict outcome in patients with primary progressive MS? Investigators of the British Columbia study compared the onset symptoms reported in patients with PPMS and RRMS. Their results showed that a significantly greater number of patients with PPMS presented with motor symptoms and cerebellar, ataxia or brain stem symptoms. Sensory symptoms and optic neuropathy were more common in patients with RRMS.\(^6\)

Investigators also concluded that outcome cannot be determined solely by symptom type at onset, despite a trend for cerebellar, ataxia and brain stem symptoms to be associated with the worst prognosis.\(^6\)
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PPMS: A Separate Entity or Part of a Continuum? Relapses and Progression

As discussed in the Lyon study, PPMS is the subtype of MS most frequently associated with irreversible disability. What is not yet known is whether it is a distinct entity or an integral point on the disease spectrum. In 2000, Confavreux and colleagues reported that once a point of irreversible disability is reached, the rate of progression is similar regardless of the initial course of the disease. Furthermore, the time from EDSS 4 to EDSS 6 is not influenced by the presence or absence of relapses. Thus, according to the investigators, the occurrence of superimposed relapses in patients with PPMS or SPMS has no impact on the rate of progressive disability (Figure 2).

Relapses and progression are the core clinical features of MS. Relapses are considered by many investigators to be the clinical product of an acute inflammatory focal lesion, whereas progression is the product of a chronic diffuse degenerative process. Recent population-based studies in Canada and France suggest a dissociation at the biologic level between this acute inflammatory process (relapse) and the progressive degenerative process (disability progression). Though disease modifying agents reduce clinical relapse rate, the magnitude of clinical benefit in terms of disability progression may be quite small. The most important out-

In another cohort, the number of years from onset to the need for a cane (score of EDSS 6 on the Expanded Disability Status Scale [EDSS]), was compared in patients with PPMS, secondary progressive (SP) MS, RRMS, and total cohort (N=201). Of note, 50% of the patients with PPMS were at EDSS 3 at onset, a finding that underscores the difficulty in identifying patients early in the course of the disease for study and treatment. Patients with PPMS had the worst outcome, with a time to EDSS 6 of approximately 7 years. Similar findings were reported by Confavreux and colleagues (Table 1).

Koch and colleagues reported two predictors of a slower disease progression in PPMS: Sensory onset symptoms and younger age at disease onset, but unfortunately patients with an early disease onset despite having a slower rate of progression still required a cane at a younger age also.

Overall, statistically significant associations have generally been reported in the context of univariate, and less frequently multivariate analysis. Few predictors of outcome have been reported for PPMS. Though often statistically significant when considering large population based cohorts, their clinical prognostic applicability to an individual MS patient is much less reliable.

Figure 2. Effect of relapses on time from EDSS 4 to EDSS 6.

Among patients with primary or secondary progressive MS, the time course of progressive irreversible disability (from EDSS 4 to EDSS 6) was not significantly influenced by the presence or absence of superimposed relapses. Kaplan–Meier Estimates of the Time from the EDSS 4 to EDSS 6 according to the presence or absence of superimposed relapses among A) 496 patients with SPMS and B) 282 Patients with the PPMS (Confavreux et al., Relapses and progression of disability in multiple sclerosis. N Engl J Med. 2000;343:1430-1438. Reproduced with permission. Copyright © 2000 Massachusetts Medical Society. All rights reserved.).

Figure 3. Age at reaching disability milestones.

For the 1844 patients from the Lyon, France population based cohort, median ages at time of assignment of EDSS 4, EDSS 6 and EDSS 7 were 44.3 years (95% CI 43.3-45.2), 54.7 years (95% CI 53.5-55.8) and 63.1 years (95% CI 61.0-65.1) respectively. These results were essentially similar whether the initial course of multiple sclerosis was exacerbating-relmitting or progressive. Kaplan–Meier estimates of the age of the patients at EDSS 4 (A), EDSS 6 (B) and EDSS 7 (C) according to the initial course of multiple sclerosis (Confavreux and Vukusic. Age at disability milestones in multiple sclerosis. Brain. 2006;129:595-605, reproduced with permission from Oxford University Press.).
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Age of Onset and Disability within MS Subtypes: A New Way of Looking at MS Natural History

Recently, Confavreux and colleagues analyzed their natural history data with a focus on the age at which disability milestones were reached, rather than the time from onset to disability milestone. This reduces reliance on imprecise dates (for onset) when analyzed in this manner (Table 1, Figure 3). Though patients with a relapsing onset took much longer to reach EDSS 7 (33.1 years) compared with patients with a progressive onset (13.4 years), both groups had a tendency to reach disability milestones at similar ages, 62.8 years for relapsing onset patients and 63.1 years in progressive onset patients. A comparison of progressive subtypes shows a similar age of onset in those with PPMS, PRMS, and SPMS. MS appears to have a very homogenous prognosis and the initial course of the disease, whether relapsing or progressive, does not appear to have substantial influence on the age at which disability milestones are reached suggesting relapses have a limited influence on development of long-term disability (Table 1, Figure 3).

For patients with SP, PP, and single attack progressive (SAP) MS, the age at symptom onset differs (29.8, 33.6 and 33.3, respectively) but the age at which progressive disability begins appears similar (39.4, 38.6).
Table 2. Survival times (medians in years) to DSS 6, 8, and 10 from onset of progressive phase for SAP, SP and PP

<table>
<thead>
<tr>
<th></th>
<th>SP with OPP at DSS2 or less</th>
<th>SAP with OPP at DSS2 or less</th>
<th>PP from disease onset</th>
<th>P-value for SAP, SP and PP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSS 6</td>
<td>6.63 (0.60)</td>
<td>5.71 (0.92)</td>
<td>6.4 (0.44)</td>
<td>0.08</td>
</tr>
<tr>
<td>DSS 8</td>
<td>18.20 (0.73)</td>
<td>13.62 (0.50)</td>
<td>16.81 (0.77)</td>
<td>0.47</td>
</tr>
<tr>
<td>DSS 10</td>
<td>NA</td>
<td>32.96 (0.95)</td>
<td>31.24 (1.98)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

OPP = onset of progressive phase; NA = insufficient data points for analysis. *P-value for testing the equality of the survival curves.


and 40.9, respectively) and is independent of the number of previous relapses.5 Although times from MS onset to disability landmarks are longer for patients with RRMS, SPMS and SAP MS than for PPMS, the times from irreversible disability (progressive phase) to disability landmarks are similar in all three groups (Table 2, Figure 4).5,9

The natural history data suggests that the progressive phase of MS (which accounts for most of the time course of the disease and most of the disability) could be an age-dependent degenerative process independent of previous clinical relapses.5,13

Variable Outcome in Progressive MS

The British Columbia study investigators evaluated the progression of PPMS in 352 patients with a median follow-up time of 17.2 years.5 Tremlett reported a median time to EDSS 6 (need for a cane) of 13.3 years from disease onset, with 25% of patients requiring a cane by 7.3 years. Of note, 25% of patients did not require a cane after 25 years. In addition, 15% of patients needed a wheelchair after 20 years; however, 30% did not need a wheelchair until 30 years after disease onset. This wide range of progression rates is potentially problematic in the design of drug trials in terms of determining outcome measures as patients may need to be followed for decades before benefits of treatment are observed.6

The only factor that predicted outcome in this study was time from onset to cane; faster progression to the cane was associated with a faster progression to the wheelchair.6

Summary

Efforts to uncover the natural history of PPMS should begin with serious consideration of the idea that this subtype may not actually be a distinct entity from relapsing MS. Viewed in this context, MS may be regarded as a single disease with distinct clinical phenotypes rather than as a group of related, but discrete heterogeneous processes, each with its own defined course. This “unifying concept”4 may provide researchers with a new approach to their investigations, with the collective goal of understanding a complex, but singular disease.

In order to provide an illustration of current knowledge of the natural history of MS, Figure 5 encompasses data from all natural history studies mentioned in this review. 0

References

AMPYRA™ (dalfampridine) is indicated as a treatment to improve walking in patients with multiple sclerosis (MS). This was demonstrated by an increase in walking speed.

When MS impairs their walking... now there’s a path forward

Important Safety Information

AMPYRA can cause seizures; the risk of seizures increases with increasing AMPYRA doses. AMPYRA is contraindicated in patients with a prior history of seizure. Discontinue AMPYRA use if seizure occurs.

AMPYRA is contraindicated in patients with moderate or severe renal impairment (CrCl ≤ 50 mL/min); the risk of seizures in patients with mild renal impairment (CrCl 51-80 mL/min) is unknown, but AMPYRA plasma levels in these patients may approach those seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures; estimated CrCl should be known before initiating treatment with AMPYRA.

AMPYRA should not be taken with other forms of 4-aminopyridine (4-AP, fampridine), since the active ingredient is the same.

Urinary tract infections were reported more frequently as adverse reactions in patients receiving AMPYRA 10 mg twice daily compared to placebo.

No additional benefit was demonstrated at doses greater than 10 mg twice daily.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch http://www.fda.gov/Safety/MedWatch/default.htm, or call 1-800-FDA-1088.
AMPYRA™ (dalfampridine) Extended Release Tablets

First in a new class of approved MS agents indicated to improve walking.

Well-tolerated oral therapy at the recommended dose, which should not be exceeded.¹

Significantly improved walking speed.¹

Improved walking in patients:
- Across all 4 major types of MS
- With or without use of immunomodulators
- With EDSS scores ranging from 2.5 to 6.5²

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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION
This does not include all the information needed to use AMPYRA safely and effectively. See full prescribing information for AMPYRA.

DOSAGE AND ADMINISTRATION
The maximum recommended dose of AMPYRA is one 10 mg tablet twice daily, taken with or without food, and should not be exceeded. Doses should be taken approximately 12 hours apart. Patients should not take double or extra doses if a dose is missed. No additional benefit was demonstrated at doses greater than 10 mg twice daily and adverse reactions and discontinuations because of adverse reactions were more frequent at higher doses. Tablets should only be taken whole; do not crush, chew, or dissolve.

AMPYRA is contraindicated in patients with moderate or severe renal impairment. The risk of seizures in patients with mild renal impairment (CrCl 51–80 mL/min) is unknown, but AMPYRA plasma exposure in these patients may approach that seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures. Estimated CrCl should be known before initiating treatment with AMPYRA.

WARNINGS AND PRECAUTIONS
Seizures AMPYRA is contraindicated in patients with a history of seizures. Incidence of seizures has been observed at 20 mg twice daily in controlled clinical studies of 9–14 weeks duration with dalfampridine in patients with MS. There was one seizure seen in the placebo group (5%) and at a dose of 10 mg twice daily (2.5%), no seizure seen at 15 mg twice daily and 2 seizures (3.5%) seen at 30 mg twice daily. In open-label extension trials in MS patients, the incidence of seizures during treatment with dalfampridine 15 mg twice daily (1.7/100 person-years) was over 4 times higher than the incidence during treatment with 10 mg twice daily (0.4/100 person-years). AMPYRA has not been evaluated in patients with a history of seizures or with evidence of epileptic activity on EEG, as these patients were excluded from clinical trials. The risk of seizures in patients with epileptic activity on EEG is unknown. AMPYRA should not be substantially different than that observed in AMPYRA clinical studies. AMPYRA should be discontinued and not restarted in patients who experience a seizure while on treatment.

Renal Impairment AMPYRA is eliminated through the kidneys primarily as unchanged drug. Because patients with renal impairment would require a dose lower than 10 mg twice daily and no strength smaller than 10 mg is available, AMPYRA is contraindicated in patients with moderate or severe renal impairment. Creatinine Clearance (CrCl) of 40 mL/min. The risk of seizures in patients with mild renal impairment (CrCl 51–80 mL/min) is unknown, but AMPYRA plasma exposure in these levels may approach that seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures. If unknown, CrCl should be estimated prior to initiating treatment with AMPYRA. CrCl can be estimated using the following equation (multiply by 0.85 for women): CrCl (mL/min) = [(72 age) x (70 kg body weight)] / (serum creatinine mg/dl) x 72

Concurrent Treatment with Other Forms of 4-Aminopyridine AMPYRA should not be taken with other forms of 4-aminopyridine (4-AP) since the mechanisms for the same side effects. Patients should discontinue use of any product containing 4-aminopyridine prior to initiating treatment with AMPYRA in order to reduce the potential for dose-related adverse reactions.

Urinary Tract Infections Urinary tract infections were reported more frequently as adverse reactions in controlled studies in patients receiving AMPYRA 10 mg twice daily (12%) as compared to placebo (8%).

ADVERSE REACTIONS
Controlled Clinical Trials Experience In three placebo-controlled clinical trials of up to 14 weeks duration, 4% (1,540) of patients treated with AMPYRA 10 mg twice daily experienced one or more treatment emergent adverse events leading to discontinuation, compared to 2% (828) of placebo-treated patients. The treatment emergent adverse events leading to discontinuation of at least 2 patients treated with AMPYRA and that led to discontinuation more frequently compared to placebo were headache (AMPYRA 0.5%, placebo 0.5%), balance disorder (AMPYRA 0.5%, placebo 0.0%), dizziness (AMPYRA 0.5%, placebo 0.0%), and constipation (AMPYRA 0.3%, placebo 0.0%).

Table 1 lists adverse reactions that occurred in ≥2% of patients treated with AMPYRA 10 mg twice daily and more frequently than in placebo-treated patients in controlled clinical trials.

Table 1: Adverse reactions with an incidence ≥2% of AMPYRA treated MS patients, and more frequent with AMPYRA compared to placebo in controlled trials

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=439)</th>
<th>AMPYRA (N=238)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>4% (12)</td>
<td>8% (19)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4% (9)</td>
<td>5% (12)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4% (9)</td>
<td>7% (16)</td>
</tr>
<tr>
<td>Headache</td>
<td>4% (9)</td>
<td>5% (11)</td>
</tr>
<tr>
<td>Rash</td>
<td>3% (7)</td>
<td>3% (7)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4% (9)</td>
<td>6% (14)</td>
</tr>
<tr>
<td>Black pain</td>
<td>2% (5)</td>
<td>5% (12)</td>
</tr>
</tbody>
</table>

Other Adverse Reactions AMPYRA has been evaluated in a total of 1,952 subjects, including 917 MS patients. A total of 741 patients have been treated with AMPYRA for over one year and 352 for over two years. The experience in open-label clinical trials is consistent with the safety profile observed in the placebo-controlled clinical trials. As in controlled clinical trials, a dose-dependent increase in the incidence of seizures has been observed in open-label clinical trials with AMPYRA in patients with MS as follows: AMPYRA 10 mg twice daily 0.1% per 100 person-years (95% confidence interval 0.1–0.3), dalfampridine 15 mg twice daily 1.7 per 100 person-years (95% confidence interval 0.2–6.3).

Other in vivo studies with cultured human hepatocytes with 0.25 μM, 0.5 μM, 2.5 μM and 25 μM dalfampridine had little or no effect on CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. AMPYRA is not likely to affect the pharmacokinetics of drugs that are substrates of the p-glycoprotein transporter, and AMPYRA is not likely to affect the pharmacokinetics of drugs that are substrates of the p-glycoprotein transporter.

Drug Interactions Effects of Coadministered Drugs on Seizures
Inferferon Dalfampridine kinetics were not affected by co-administration of subcutaneous injections of 8 million units interferon beta 1b. Bactroban® (mupirocin) The drug-drug interaction was observed with co-administration of dalfampridine 15 mg and baclofen 10 mg. Effects of Dalfampridine on Coadministered Drugs in vitro data with human liver microsomes showed that dalfampridine was not a direct or time-dependent inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2D6, or CYP3A4. AMPYRA does not appear to affect the pharmacokinetics of drugs that are substrates of metabolizing enzymes, or that are inhibitors or inducers of the p-glycoprotein transporter. The pharmacokinetics of AMPYRA are unlikely to be affected by drugs that inhibit the p-glycoprotein transporter.

USE IN SPECIFIC POPULATIONS
Pregnancy Pregnancy Category C. There are no adequate and well-controlled studies of AMPYRA in pregnant women. Administration of dalfampridine to animals during pregnancy and lactation resulted in decreased offspring viability and growth at doses similar to the maximum recommended human dose (MRHD) of 20 mg/day. AMPYRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In developmental toxicity studies in rats and rabbits, dalfampridine was administered orally at doses up to 10 and 5 mg/kg/day, respectively, during the period of organogenesis. These doses are approximately 5 times the MRHD on a body surface area (mg/m²) basis. No evidence of developmental toxicity was found in either species at the highest doses tested, which were maternally toxic. Oral administration of dalfampridine at doses of 1, 3, and 9 mg/kg/day, high dose reduced during the second week of dosing to rats throughout the pregnancy and lactation periods resulted in decreased offspring survival and growth. The no-effect dose for pre- and postnatal developmental toxicity in rats (1 mg/kg) is approximately 0.5 times the MRHD on a mg/m² basis. Recombinant human gonadotropins were used experimentally in advanced women with MS, and no evidence of toxic effects in the offspring was seen. No human studies are available. It is not known whether dalfampridine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from dalfampridine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Pediatric Use and effectiveness of AMPYRA in patients younger than 18 years of age have not been established. Geriatric Use Clinical studies of AMPYRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. A population PK analysis showed that dalfampridine clearance modestly decreased with increasing age, but not sufficiently to necessitate a modification of dose with age. Other reported clinical experience has identified no differences in responses between the elderly and younger patients. AMPYRA is known to be substantially different than the kidney and the risk of adverse reactions, including seizures, is greater with increasing exposure of dalfampridine. Because elderly patients are generally more sensitive to the anticholinergic effects of the p-glycoprotein transporter, and dalfampridine is not likely to affect the pharmacokinetics of drugs that are substrates of the p-glycoprotein transporter.

OVERDOSAGE
Three cases of overdose were reported in controlled clinical trials with AMPYRA, involving two MS patients. The first patient took six times the currently recommended dose (60 mg) and was taken to the emergency room with altered mental state. The second patient took 40 mg doses on two separate occasions. In the first instance, she experienced a complex partial seizure and, in the second instance, a period of confusion. Both patients recovered by the following day without sequelae.

Several cases of overdose are found in the scientific literature in which various formulations of dalfampridine were used, resulting in numerous adverse events including seizure, confusion, tremulousness, dizziness and amnesia. In some instances, patients developed status epilepticus, requiring intensive supportive care and were responsive to standard therapy for seizures. In one published case report, a MS patient who ingested 300 mg of 4-aminopyridine (dalfampridine) developed a condition that resembled LEMS encephalitis. The patient developed weakness, reduced awareness, memory loss, hypochonic speech, and temporal lobe hyperventilation on MRI. The patient’s speech and language and ambulation improved over time, and an MRI 4 months after the overdose no longer showed signal abnormalities. One year after the patient continued to have difficulty with short term memory and learning new tasks. PATIENT COUNSELING INFORMATION See FDA-approved Patient Labeling See FDA-approved Patient Labeling Risk of Seizures Inform patients that AMPYRA causes seizures in a dose-dependent fashion, and that they must discontinue use of AMPYRA if they experience a seizure.

AMPYRA dosing Instruct patients to take AMPYRA exactly as prescribed. Instruct patients not to take a double dose after they miss a dose. Instruct patients not to take more than two tablets in a 24-hour period and to make sure that there is an appropriate 12-hour interval between doses.

Storage Advise patients to store AMPYRA at 25°C (77°F), with excursions permitted to 15–30°C (59–86°F). Advise patients to safely throw away AMPYRA that is out of date or no longer needed.

See www.ampyra.com for full prescribing information and medication guide.
Introduction

Primary progressive multiple sclerosis (PPMS) is one of the four clinical subtypes of MS and the one most frequently misdiagnosed, in part because PPMS lacks the pattern of relapses and remissions that characterize the other forms. Accurately diagnosing this subtype is crucial in determining long-term prognosis, ruling out other disorders and initiating potential treatment as early as possible in the course of this debilitating form of the disease.

Approximately 80–85 % of patients with MS present with relapsing-remitting multiple sclerosis (RRMS), characterized by acute exacerbations, or relapses, followed by periods of remission. Secondary-progressive multiple sclerosis (SPMS) may develop over time as the underlying pathology progresses, leading to a gradual worsening of disease independent of subsequent exacerbations.

The two remaining subtypes are progressive from onset. These include progressive-relapsing multiple sclerosis (PRMS) and PPMS. In PRMS, a patient follows a PPMS initial course and then experiences acute exacerbations, with or without complete recovery, with continued progression between relapses. PPMS, however, follows an insidious course and may escape diagnosis for years because it is not associated with the typical pattern of relapses and remissions. Instead, the underlying disease process steadily progresses, leading to increasing disability.

It has been suggested that the clinical subtypes of MS are not distinct disease entities, but separate phenotypes of a single disease process. It is my viewpoint that PPMS represents a point on the MS spectrum and that these are all part of the same disease process. However, while physicians can identify the signs of worsening disease, we have not yet identified the distinct pathophysiological processes underlying the progression, although recent research has provided some insights.

Overview of Clinical Pathology

Despite the heterogeneity of the individual phenotypes, most patients exhibit a pattern of disease activity that appears to occur in two phases. In the initial phase, inflammation predominates and is associated with axonal injury, a crucial early pathology that contributes to the permanent disability that occurs in later stages of the disease. Of note, injured axons are detected in specimens during the first year of diagnosis.

As inflammation subsides, the disease transitions to a later phase dominated by neurodegeneration. As nerve damage continues, the patient becomes increasingly disabled and the disease becomes more resistant to treatment.

What is not yet known is whether MS, is at its core, a disease of inflammation or one of degeneration, and how each process impacts the other. Is MS primarily a disease of inflammation that leads to degeneration or does the degenerative process initiate the inflammatory phase or are they independent?

A study by Kutzelnigg compared the pathology of SPMS and PPMS, including the distribution of inflammation in the brain. The results suggest that the differences between the two phenotypes are quantitative rather than qualitative; the patterns of inflammation may differ, but the inflammatory process is present in both.

Other findings suggest, however, that the pathophysiology of MS is mediated, at least in part, by a process other than inflammation. Data from early studies of alemtuzumab in patients with SPMS demonstrated steady disease progression despite effective suppression of inflammation by the drug. Another study reported that MS is characterized by severe axonal degeneration and loss of oligodendrocytes and myelin.

Diagnosing Primary Progressive Multiple Sclerosis

Diagnosis of PPMS is challenging. It is often difficult to get a complete and accurate history of early events from the patient that might signify a diagnosis of PPMS. Magnetic resonance imaging (MRI) is a useful tool in cases of suspected primary progressive multiple sclerosis.

In 2001, the original McDonald Criteria for the diagnosis of MS was published and included specific criteria for establishing a diagnosis of PPMS as adapted from the work of Thompson and colleagues. The original McDonald Criteria included the presence of oligoclonal bands in the cerebrospinal fluid (CSF) and a combination of MRI evidence.
and paraclinical laboratory examinations to demonstrate dissemination in space and dissemination in time.11

The 2005 revisions to the McDonald Criteria updated the guidelines for making a diagnosis of MS in patients with disease progression from symptom onset. The 2005 revisions simplify the MRI requirements for dissemination in space, and de-emphasize the importance of CSF findings based on new research showing that primary progressive MS can be accurately diagnosed without positive CSF results. While the original criteria made positive CSF findings mandatory, the 2005 revision included CSF along with positive brain MRI and positive spinal cord MRI, and stated that any two of these criteria are required along with one year of disease progression.11

Importantly, spinal cord MRI can also help rule out other potential causes of myelopathy in patients with suspected MS and a normal brain MRI.12 Spinal cord MRI can also be used to support a diagnosis in older patients with age-related changes in T2-weighted brain MRI scans that can confound the diagnosis of MS. This type of age-related lesion is not seen in spinal MRIs of normal elderly individuals. Therefore, hyperintense areas on spinal MRIs in elderly patients with symptoms of MS are believed to be more specific for demyelination than similar findings on brain MRIs.12,13

Further, spinal cord MRI has been shown to be an important contributor to the diagnosis of MS when used in conjunction with a brain MRI. In a study by Bot et al, the diagnosis of MS increased from 66% using brain MRI alone to 85% when spinal cord MRI was included in the diagnostic process.14

Differential Diagnosis

The potential differential diagnosis for PPMS is extensive (Table 1). It can include any condition that produces a myelopathy; less commonly a cerebellar syndrome; or rarely, a cognitive disorder.

Age is a factor in the differential diagnosis of PPMS, as cervical spondylosis is more commonly seen in older adults. Family history may indicate hereditary cerebellar ataxias, leukodystrophies, or other conditions with a genetic component. Geographic location and travel history are also considerations, since other diseases, such as human T-cell lymphotropic virus-related myelopathy (HTLV-1, tropical spastic paraparesis) are seen in Latin America and Asia.15,16,17,18

Of note, the patient should be carefully assessed for the presence of arteriovenous (AV) fistulas of the cord as these are frequently missed during the differential diagnosis of PPMS. The spinal cord should also be evaluated for spinal cord disease, particularly cervical spondylosis or tumors, that can cause spinal cord compression resulting in myelopathy that can mimic or coexist with PPMS.13

### Table 1. Differential Diagnosis of Primary Progressive Multiple Sclerosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>SVI, migraine, emboli, APLAS, CADASIL, cavernous angioma of brainstem</td>
</tr>
<tr>
<td>Inflammatory/immune</td>
<td>SLE, SS, Behcets, Wegeneres, PAN, isolated CNS vasculitis, Susac, Sneddon, sarcoid, celiac disease, stiff-person, anti-TNF</td>
</tr>
<tr>
<td>Infectious</td>
<td>Lyme, syphilis, HIV, HTLV1, PML, Whipples, Herpes viruses, Mycoplasma, Chlamydia</td>
</tr>
<tr>
<td>Genetic/degenerative</td>
<td>mitochondrial, HSP, hereditary cerebellar ataxias, Presenilin-1, leukodystrophies, ALD, Fabry, Alexander, Niemann-Pick, GCDH deficiency, Pelizaeus Merzbacher, Krabbe, OPCA, MND, Hereditary Episodic Ataxia</td>
</tr>
<tr>
<td>Metabolic</td>
<td>thyroid, B12, nitrous oxide, copper, porphyria</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>CNS lymphoma, intravascular lymphoma, metastasis, histiocytosis, paraneoplastic</td>
</tr>
<tr>
<td>Spine</td>
<td>vascular malformations, tumor, degenerative spine disease</td>
</tr>
</tbody>
</table>

Provided courtesy of Dr. Jeffrey Cohen

General Considerations in the Diagnosis of Primary Progressive MS

Analysis of patients enrolled in the PROMiSe trial19 reveal factors common to patients with PPMS. Patients with PPMS are generally older, with a median age 10 years greater at diagnosis than patients with relapsing forms of MS. Age at diagnosis is an important consideration because the differential diagnosis broadens with increasing age, further confounding the diagnostic process. In addition, older age is associated with increased incidence of concomitant illnesses and incidental pathologies that can complicate the brain MRI.

Because diagnosis of PPMS does not reflect time of disease onset, patients frequently experience the first symptoms of the disease years before diagnosis. Analysis of data from the PROMiSe trial show a span of at least five years from time of first symptom to diagnosis.19 Early diagnosis is further constrained by phenotype. The insidious onset of PPMS may impede the patient’s awareness of symptom onset, especially if progression is gradual.

Conclusion

The 2005 revised McDonald Criteria should aid clinicians in obtaining an accurate diagnosis of PPMS and detecting the disease at an earlier stage, allowing for prompt initiation of therapy. In addition, identifying patients earlier in the clinical course of PPMS provides researchers with an opportunity to investigate the underlying pathophysiological mechanisms before the onset of severe symptoms, with the goal of uncovering targets for therapeutic intervention and potentially altering the course of this disabling disease.


AVONEX® (Interferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

Important Safety Information

AVONEX should be used with caution in patients with depression or other mood disorders and in patients with seizure disorders. Rare cases of anaphylaxis have been reported. Severe hepatic injury, including cases of hepatic failure, has been reported rarely in patients taking AVONEX. Patients should be monitored for signs of hepatic injury and caution exercised when AVONEX is used concomitantly with other drugs associated with hepatic injury. Patients with cardiac disease should be closely monitored.

EDSS=Expanded Disability Status Scale.
CDMS=clinically definite multiple sclerosis.
Median of 13 T2 lesions at baseline.
10-year open-label, follow-up (n=155) to a 3-year study of patients with a first acute demyelinating event and MRI features consistent with MS.
Adjusted for age, qualifying event, baseline MRI T2 lesion volume, and baseline number of Gd+ lesions on MRI.
Immediate treatment (IT) group began AVONEX within 30 days of first event. Delayed treatment (DT) group began 2.5 years later. IT and DT groups included patients regardless of therapy.
AVONEX reduced the risk of CDMS conversion

- 51% reduction in risk of second event vs placebo at 3 years adjusted, \( p<0.001 \); 44% unadjusted, \( p=0.002 \)
- At 10 years, immediate treatment with AVONEX reduced the risk of CDMS conversion by 40% vs delayed therapy (\( p<0.001 \))

**AVONEX slowed physical disability by 37% vs placebo at 2 years (\( p=0.02 \)).**

Routine periodic blood chemistry and hematology tests are recommended during treatment with AVONEX. AVONEX is not recommended for use in pregnant women.

The most common side effects associated with AVONEX treatment are flu-like symptoms including myalgia, fever, fatigue, headache, chills, nausea, vomiting, pain and asthenia.

Please see brief summary of full Prescribing Information for additional important safety information on the following pages.

FDA-approved labeling includes up to 3 years of clinical data.

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AVONEX® (Interferon beta-1a)

30 mcg Lophylial Vial
30 mcg Prefilled Syringe
IM Injection

Brief summary of full prescribing information

INDICATIONS AND USAGE

AVONEX® (Interferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis, to decrease the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and who have MRI features consistent with demyelination. Safety and efficacy in patients with chronic progressive multiple sclerosis have not been established.

CONTRAINDICATIONS

AVONEX® is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, or any other component of the formulation. The lophylial vial formulation of AVONEX® is contraindicated in patients with a history of hypersensitivity to albumin (human).

WARNINGS

Depression and Suicide

AVONEX® should be used with caution in patients with depression or other mood disorders, conditions that are common with multiple sclerosis. Depression and suicide have been reported to occur with increased frequency in patients receiving interferon compounds, including AVONEX®. Patients treated with AVONEX® should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. If a patient develops depression or other severe psychiatric symptoms, cessation of AVONEX® therapy should be considered. In Study 2, AVONEX®-treated patients were more likely to experience depression than placebo-treated patients. An equal incidence of depression was monitored for signs of hepatic injury (see Precautions: Laboratory Tests).

REACTIONS). Some cases of thrombocytopenia have had nadirs below 10,000/µL. Some cases reoccur with rechallenge (see ADVERSE REACTIONS). Patients should be monitored for these adverse effects (see Precautions: Laboratory Tests).

Hepatic Injury

Severe hepatic injury, including cases of hepatic failure, has been reported rarely in patients taking AVONEX®. Asymptomatic elevation of hepatic transaminases has also been reported, and in some patients has recurred upon rechallenge with AVONEX®. In some cases, these elevations have occurred in the presence of other drugs that have been associated with hepatic injury. The potential risk of AVONEX® in combination with known hepatotoxic drugs or other products (e.g., alcohol) should be considered prior to AVONEX® administration or when another product is added to the patient’s regimen. Patients should be monitored for signs of hepatic injury (see Precautions: Laboratory Tests).

Albumin (Human)
The lophylial vial of AVONEX® contains albumin, a derivative of human blood. Based on effects seen with human albumin and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have been identified for albumin. The prefilled syringe of AVONEX® does not contain albumin.

PRECAUTIONS

Seizures

Caution should be exercised when administering AVONEX® to patients with pre-existing seizure disorders. In the two placebo-controlled studies in multiple sclerosis, 4 patients receiving AVONEX® experienced seizures, while no seizures occurred in the placebo group. Three of these 4 patients had no prior history of seizure (see ADVERSE REACTIONS). It is not known whether these events were related to the effects of multiple sclerosis alone, to AVONEX®, or to a combination of both. The effect of AVONEX® on administration of patients with seizure disorder is unknown.

Cardiomyopathy and Congestive Heart Failure

Patients with cardiac disease, such as angina, congestive heart failure, or arrhythmia, should be closely monitored for worsening of their condition during initiation and continuation of AVONEX®. While AVONEX® has not been studied in patients with known cardiomyopathy or concomitant heart failure, cardiomyopathy and congestive heart failure have been reported in patients without known predilection to these events, and without other known etiologies being established. In rare cases, these events have been temporally related to the administration of AVONEX®. In some of these instances recurrence upon rechallenge was observed.

Autoimmune Disorders

Autoimmune disorders of multiple target organs have been reported post-marketing including idiopathic thrombocytopenia, hyper- and hypothyroidism, and rare cases of autoimmune hepatitis have also been reported. Patients should be monitored for signs of these disorders (see Precautions: Laboratory Tests) and appropriate treatment implemented when observed.

Information to Patients

All patients should be instructed to read the AVONEX® Medication Guide supplied to them. Patients should be cautioned not to change the dosage or the schedule of administration without medical consultation. Patients should be informed of the most serious (see WARNINGS) and the most common adverse events associated with AVONEX® administration, including symptoms associated with flu syndrome (see ADVERSE REACTIONS). Symptoms of flu syndrome are most prominent at the initiation of therapy and decrease in frequency with continued treatment. Concurrent use of antipyretics and/or antipyretics may help ameliorate flu-like symptoms on treatment days. Patients should be cautioned to report depression or suicidal ideation (see WARNINGS).

Patients should be advised about the abortifacient potential of AVONEX® (see Precautions: Pregnancy - Teratogenic Effects). If a woman becomes pregnant while receiving AVONEX®, she should be advised to consider enrolling in the AVONEX® Pregnancy Registry by calling 1-800-456-2255. A woman determines that AVONEX® can be used outside of the physician’s office, persons who will be administering AVONEX® should receive instruction in reconstitution and injection, including the review of the injection procedures. If a patient is to self-administer, the physical ability of that patient to self-inject intramuscularly should be assessed. The first injection should be performed under supervision of a qualified health care professional. A puncture-resistant container for disposal of needles and syringes should be used. Patients should be instructed in the importance and purpose of proper syringe and needle disposal and be cautioned against reuse of these items.

Laboratory Tests

In addition to these laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential white blood cell counts, platelet counts, and blood chemistries, including liver function tests, are recommended during the post-marketing period (see ADVERSE REACTIONS: Hepatic Injury). Seizures, cardiovascular adverse events, and autoimmune disorders tests should be performed according to standard medical practice.

Drug Interactions

No formal drug interaction studies have been conducted with AVONEX®. In the placebo-controlled studies in multiple sclerosis, therapy was continued in patients already using AVONEX®. In some of these instances recurrence upon rechallenge was observed in patients concurrently receiving AVONEX®. In addition, some patients receiving AVONEX® were also treated with anti-epileptic therapy and/or oral contraceptive therapy. No unexpected adverse events were associated with these concomitant therapies. However, the potential for hepatic injury should be considered when AVONEX® is used in combination with other products associated with hepatic injury or when new products are added to the regimen of patients already on AVONEX® (see WARNINGS: Hepatic Injury).

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis: No carcinogenicity data for AVONEX® are available in animals or humans.

Mutagenesis: AVONEX® was not mutagenic when tested in the Ames bacterial test and in an in vitro cytogenetic assay in human lymphocytes in the presence and absence of metabolic activation. These assays are designed to detect agents that integrate DNA and cause damage to cellular DNA. AVONEX® is a glycosylated protein that does not bind to DNA.

Impairment of Fertility: No studies were conducted to evaluate the effects of AVONEX® on fertility in female or male rats or mice. AVONEX® is not likely to affect human reproductive capacity.

Menstrual irregularities were observed in monkeys administered AVONEX® at a dose 100 times the recommended weekly human dose (based upon a body surface area comparison). If the monkey is pregnant or lactating, decreased serum progesterone levels were also noted transiently in some animals. These effects were reversible after discontinuation of drug.

Pregnancy - Teratogenic Effects

Pregnancy Category C: The reproductive toxicity of AVONEX® has not been studied in animals or humans. In pregnant monkeys given AVONEX® at 100 times the recommended weekly human dose (based upon a body surface area comparison), no teratogenic or other adverse effects on fetal development were observed. Abortifacient activity was evident in pregnant animals administered AVONEX® at 100 times the recommended weekly human dose (based upon a body surface area comparison). Although no teratogenic effects were seen in these studies, it is not known if teratogenic effects would be observed in humans. There are no adequate and well-controlled studies with interferons in pregnant women. If a woman becomes pregnant or plans to become pregnant while taking AVONEX®, she should be informed of the potential hazards to the fetus and the need to discontinue AVONEX® therapy should be considered.

If a woman becomes pregnant while taking AVONEX®, consider enrolling her in the AVONEX® Pregnancy Registry by calling 1-800-456-2255.

Nursing Mothers

AVONEX® should be used with caution in patients who are breast feeding. Information on AVONEX® exposure in breast fed infants is not available. It is not known how long they will persist following treatment.

Pediatric Use

Safety and effectiveness of AVONEX® in pediatric patients below the age of 18 years have not been evaluated.

Geriatric Use

Clinical studies of AVONEX® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

ADVERSE REACTIONS

Depression, suicidal ideation, and new or worsening other psychiatric disorders have been observed to be increased in patients using interferon compounds including AVONEX® (see WARNINGS: Depression and/or Suicidality). Suicidal ideation and behavior have been reported in patients using AVONEX® (see WARNINGS: Anaphylaxis). Depression decreased peripheral blood counts have been reported in patients using AVONEX® (see WARNINGS: Decreased Peripheral Blood Counts and PRECAUTIONS: Cardioangiopathy and Congestive Heart Failure, and Autoimmune Disorders). During the placebo-controlled studies in multiple sclerosis, at least 6% of patients randomized to AVONEX® had significant differences between the placebo and AVONEX® groups in the incidence of liver enzyme elevation, leukopenia, or thrombocytopenia. However, these are known to be dose-related effects, and have been demonstrated in patients who have experienced a first clinical episode and have MRI features consistent with demyelination. Safety and efficacy in patients with chronic progressive multiple sclerosis have not been established.
also have been reported in association with the use of AVONEX® (see Precautions).

The adverse reactions most commonly reported in patients associated with the use of AVONEX® were flu-like and other symptoms occurring within hours to days following an injection. Symptoms can include myalgia, fever, fatigue, headaches, chills, nausea, and vomiting. Some patients have experienced paresthesias, hyperthermia and myasthenia. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of AVONEX®, or the need for concomitant medication to treat an adverse reaction symptom) were flu-like symptoms and depression. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of AVONEX® cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

The data described below reflect exposure to AVONEX® in 351 patients, including 319 patients exposed for 6 months, and 288 patients exposed for greater than one year in placebo-controlled trials. The mean age of patients receiving AVONEX® was 35 years, 74% were women and 89% were Caucasian. Patients received either 30 mcg AVONEX® or placebo. Table 3 enumerates adverse events and selected laboratory abnormalities that occurred at an incidence of at least 2% higher frequency in AVONEX®-treated subjects than was observed in the placebo group. Reported adverse events have been classified using standard COSTART terms.

### Table 3. Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Studies

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N = 333)</th>
<th>AVONEX® (N = 351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>55%</td>
<td>58%</td>
</tr>
<tr>
<td>Flu-like symptoms (otherwise unspecified)</td>
<td>29%</td>
<td>49%</td>
</tr>
<tr>
<td>Pain</td>
<td>21%</td>
<td>23%</td>
</tr>
<tr>
<td>Anemia</td>
<td>18%</td>
<td>24%</td>
</tr>
<tr>
<td>Fever</td>
<td>9%</td>
<td>20%</td>
</tr>
<tr>
<td>Chills</td>
<td>5%</td>
<td>19%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Infection</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Injection site inflammation</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Toothache</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>14%</td>
<td>18%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Respiratory System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>19%</td>
<td>23%</td>
</tr>
<tr>
<td>Musculoskeletal System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>22%</td>
<td>29%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Urogenital</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>Urine constituents abnormal</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Skin and Appendages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Special Senses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorder</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Hemic and Lymphatic System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site ecchymosis</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Anemia</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Cardiovascular System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>0%</td>
<td>2%</td>
</tr>
</tbody>
</table>

No AVONEX®-treated patients attempted suicide in the two placebo-controlled studies. In Study 2, AVONEX®-treated patients were more likely to experience depression than placebo-treated patients (20% in AVONEX® group vs. 13% in placebo group). The incidences of depression in the placebo-treated and AVONEX®-treated patients in Study 1 were similar. In Study 1, suicidal tendency was seen more frequently in AVONEX®-treated patients (4% in AVONEX® group vs. 1% in placebo group) (see WARNINGS). Seizures Seizures have been reported in 4 of 351 AVONEX®-treated patients in the placebo-controlled studies, compared to none in the placebo-treated patients (see Precautions: Seizures).

### Post-Marketing Experience

The following adverse events have been identified and reported during post-approval use of AVONEX®. New or worsening of psychiatric disorders, and anaphylaxis (see WARNINGS). Autoimmune disorders including autoimmune hepatitis, idiopathic thrombocytopenia, hyper- and hypothyroidism, and seizures in patients without prior history (see Precautions).Infrequent reports of congestive heart failure, cardiomyopathy, and cardiomyopathy with congestive heart failure with rare cases being temporally related to the administration of AVONEX® (see Precautions: Cardiomyopathy and Congestive Heart Failure). Overdosage

Safety of doses higher than 60 mcg once a week have not been adequately evaluated. The maximum amount of AVONEX® that can be safely administered has not been determined.

### References:

1. Biogen Idec, internal data on file.

Manufactured by: BIOGEN IDEC, INC. 14 Cambridge Center Cambridge, MA 02142 USA ©2008 Biogen Idec, Inc. All rights reserved. 1-800-456-2255 Rx only 161023-4 Brief Summary

Also have been reported in association with the use of AVONEX® (see Precautions). The adverse reactions most commonly reported in patients associated with the use of AVONEX® were flu-like and other symptoms occurring within hours to days following an injection. Symptoms can include myalgia, fever, fatigue, headaches, chills, nausea, and vomiting. Some patients have experienced paresthesias, hyperthermia and myasthenia. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of AVONEX®, or the need for concomitant medication to treat an adverse reaction symptom) were flu-like symptoms and depression. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of AVONEX® cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

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Immunology and Pathology of Primary Progressive Multiple Sclerosis

Amit Bar-Or, MD, FRCP(C)

Introduction

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disease that has been considered to follow four primary clinical courses. The relapsing-remitting form (RRMS) of the disease is identified by exacerbations followed by total or partial remission of symptoms. The secondary progressive (SPMS) phase of the disease is marked by progression after an initial phase of RRMS. Primary progressive MS (PPMS) is the progressive form of the disease that occurs without disease remission. The fourth clinical course, as described by Lublin and Reingold, is PRMS or progressive relapsing MS, which is a form of the disease that progresses from the onset of MS; the patient experiences exacerbations and remissions, but progression continues between relapses.

According to the clinical definitions, PPMS differs from the relapsing forms. However, differences in the immunologic and pathologic patterns between PPMS and the relapsing forms of the disease have yet to be fully elucidated. To more fully explore the differing forms of the disease, this paper attempts to answer these key questions: Are PPMS and SPMS biologically distinguishable? In particular, are the biological mechanisms that underlie clinical progression in PPMS and SPMS the same? What is the relationship, if any, between “biology of relapse” and “biology of progression?”

There are a large number of studies that identify differences between RRMS and PPMS. However, the direct comparison between PPMS and SPMS will provide additional important information that will be useful from an immunologic and neurobiological perspective.

Generally, fewer studies have been done in the area of PPMS and as a result, it is less well understood. By identifying the immunologic and biologic markers of disease, it may be possible to develop more targeted immunotherapies that improve the effectiveness of treatments for MS in its various forms.

Biologic Mechanisms

Later in the course of MS, there appears to be a disconnect between imaging parameters and clinical progression. For example, over time, there is less accumulation of new burden of focal inflammatory disease (based on T2 lesion volume) as well as fewer time points where there is evidence of focal breach of the blood-brain barrier (based on presence of contrast enhancing lesions). Despite these observations suggesting decreased new disease activity over time, patients with progressive forms of MS continue to worsen clinically.

This apparent paradox, can be reconciled by the view that progressive disease is characterized by two distinct pathologies (Figure 1). The first process which predominates earlier in the disease course involves episodic immune-mediated injury that may represent primarily a peripherally-initiated inflammatory process (‘relapse biology’). It is, in fact, unknown whether these inflammatory episodes are invariably initiated in the periphery or possibly triggered by something in the central nervous system (CNS). Regardless of the site of initiation, the process involves an important component of mobilizing activated cells from the periphery and into the CNS. Later in the disease course, such focal inflammatory injury may contribute less to ongoing injury, at a time where CNS compartmentalized processes predominate. The latter may represent a combination of inflammation and degeneration. CNS compartmentalized inflammation, could be relatively independent of the immune response in the periphery, and such compartmentalization may in part explain the lack of effectiveness of therapeutic interventions in the periphery. If the course of MS involves a combination of these two potential biologies (a
with PPMS could represent the minority in whom a primary immunology' occurs under the surface). In the context of (B), patients visible dysregulated immune response (i.e. the 'relapse biology') represent a situation where individuals do not have a sufficiently degenerative injury (perhaps in part even as an attempt to be adaptive). The consequence, however, may be a period of degenerative process is not accompanied by the triggering of superimposed waves of peripherally mediated inflammation.

In a relatively recent series of brain pathology studies, many patients with MS have been shown to have large areas of demyelination involving the cortex. Kutzelnigg and colleagues assessed normal appearing white matter (NAWM) as well as cortex in brain tissue from 52 patients with acute MS, RRMS, PPMS, or SPMS and 30 controls.3 New and active focal inflammatory demyelinated white matter plaques represented the primary injury in patients with acute MS or RRMS. Different pathologies predominated in patients with PPMS and SPMS, characterized by demyelination of the cortex and more diffuse (rather than focal) injury in NAWM. Further, there was a relative paucity of classical immune components, including CD8 and CD4 T cells, within the NAWM of patients with progressive forms of MS, with a predominance of microglial activation associated with injury both to myelin and to the axons.3

These findings suggest that PPMS and SPMS appear to share a common pathology that is distinct from that of RRMS.3 The caveat is that the autopsy specimens were taken from patients with advanced disease. This raises the question: do PPMS and SPMS share only a common final pathway or are these subtypes biologically more similar than different throughout the disease course?

**Immunology of MS Subtypes**

Currently, there are no methods available to clearly distinguish between the immune responses of PPMS and SPMS. Also of interest is whether a connection exists between the immune profiles of PPMS and SPMS that may contribute to the progression of both subtypes.

To this end, two types of animal models of MS would be of interest to compare. In the first, peripheral inflammation is initiated that results in CNS injury and chronic disability, although it would need to be determined if the model is truly 'progressive' or perhaps more accurately 'non-remitting'. The second model would involve introducing a primary neurobio-

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**Figure 2. ‘Immune’ and ‘Degenerative’ Biologies in MS**

![Diagram showing the relationship between immune and degenerative responses in MS](https://example.com/diagram)

2. Kutzelnigg and colleagues assessed normal appearing white matter (NAWM) as well as cortex in brain tissue from 52 patients with acute MS, RRMS, PPMS, or SPMS and 30 controls.
3. New and active focal inflammatory demyelinated white matter plaques represented the primary injury in patients with acute MS or RRMS. Different pathologies predominated in patients with PPMS and SPMS, characterized by demyelination of the cortex and more diffuse (rather than focal) injury in NAWM. Further, there was a relative paucity of classical immune components, including CD8 and CD4 T cells, within the NAWM of patients with progressive forms of MS, with a predominance of microglial activation associated with injury both to myelin and to the axons.

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**Supplement to the International Journal of MS Care**

17
logical insult that triggers a degenerative process. The clinical expression, or phenotype, of the disease in either model could be influenced by the genetic background of the animal. Future studies with such animal models may help clarify the underlying biological pathways that lead to specific clinical subtypes and help us consider how an immune response can result in a progressive smoldering type of CNS injury that may be independent of peripherally-mediated inflammation.

Studies in patients with MS have evaluated over the years CSF from a range of MS patients, with respect to cellularity, cytokines, presence or absence of oligoclonal bands, as well as several specific markers of injury, including neurofilament and myelin components. However, these have not been able to consistently distinguish between PPMS and SPMS.

Other studies are attempting to determine if specific immune responses differ in PPMS compared to SPMS. For example, does production of target specific antibodies or T-cell responses directed against myelin or other CNS components vary according to disease subtype? To date, no consistent differences related to subtype have been found in the immune response to specific CNS antigens. In a study of patients with PPMS, Prat and colleagues reported that patients with a high T2-weighted lesion volume (> 10 cm\(^2\)) had increased in vitro migration and interferon-gamma production as compared to patients with lower T2-weighted lesion volume (< 30 cm\(^2\)) and controls.\(^5\) These findings suggest that a lesser degree of inflammatory abnormality is found in PPMS, but one that is not necessarily qualitative.

Durán and colleagues studied the expression of adhesion molecules in patients with MS. The results showed abnormalities of the adhesion molecule profiles in SPMS and RRMS compared with PPMS and healthy controls, which were similar. The investigators concluded that the transport of autoreactive leukocytes through the blood-brain barrier is a major step in the pathogenesis of both SPMS and RRMS, but not of PPMS.\(^6\)

Some studies have reported similar abnormalities in PPMS and RRMS/SPMS. Still other investigations have reported abnormalities in SPMS, but not in PPMS. Further research is clearly needed to determine the qualitative differences between disease profiles. Early results from antibody profiles may provide helpful methods of fingerprinting patients with different subtypes of MS.\(^6\)

**Ectopic Lymphoid Tissue in the Meninges of Patients with SPMS**

The work by Aloisi and colleagues suggests that, within the meninges, there can be found collections of immune cells and in some cases, these collections are described as recapitulating certain features of a germinal center reaction.\(^7\)

Within these immune cell collections, one sees the presence of B cell lineage cells, including what appear to be chronically activated B cells and plasma cells. It is attractive to think that biological responses of these cells may be relevant to the cortically based demyelination described above.

According to the authors, these meningeal based ectopic collections of immune cells were found in about 50 percent of patients with secondary progressive MS, but not in the primary progressive MS brains.

Thus, from the standpoint of understanding MS compartments and in fact sub-compartments, the biology related to the typical perivascular lesions and the biology that may be subjacent to the cortex are importantly different and need to be understood better.

**B-Cells as Antigen-Presenting Cells (APC)**

One way by which B cells (for example in ectopic immune cell collections) may participate in CNS-compartmentalized inflammation could be through the capacity of B cells to stimulate T cells. In the normal circulation of a non-MS individual, a considerable number of memory B cells have been shown to express CD80, an important co-stimulatory molecule used by APCs to enhance signaling cascades and T cell activation. This subpopulation of B cells has been shown to have a lower threshold of activation; secrete 3-10 \(\times\) more IgM, IgG, and IgA; and elicit significantly stronger and more rapid antigen-dependent T cell responses. In addition, the expression pattern of molecules (CD11b, CD72) is particularly suited to B cell:T cell interactions.\(^8,9,10,11\)

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**References**


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**Supplement to the International Journal of MS Care**
The Genetics of Primary Progressive Multiple Sclerosis

Sergio Baranzini, PhD

Introduction

To date, any discussion of the genetics of primary progressive multiple sclerosis (PPMS) is limited by the prevalence of this subtype and the power needed to establish genetic studies. Accordingly, this discussion will focus on the genetics of multiple sclerosis (MS) as a whole, rather than a specific subtype. While this presentation focuses on the genetics of MS, it is important to consider placing PPMS on the map of genetics in future work.

Evidence of a genetic component to MS can be found by observing the increased risk to siblings of affected individuals. The lifetime relative risk of an unaffected sibling of an individual with MS is 20 to 40 times greater than that of the general population. In addition, the sibling pairs tend to cluster by age rather than by year of onset, a finding that is indicative of a genetic basis for this disease.

The recurrence rates for MS are strongly associated with genetic similarity. For example, a monozygotic twin of an affected individual has a lifetime risk of developing MS that is approximately 30 times greater than the risk to the general population. The risk of a sibling with two affected parents is 25 times greater than that of the general population, and a sibling with only one affected parent has a lifetime risk that is approximately half that of the monozygotic twin. As the genetic similarity across the family decreases, the relative risk continues to decline until it reaches the general population risk of approximately 1 in 1000.

We also know that susceptibility to MS is polygenic. In fact, depending on the research model used, a suggested conservative estimate is that between 10 and 50 genes may contribute to the genetic susceptibility to MS. While the full complement of genes involved is still unknown, the HLA region of chromosome 6 has been implicated with almost certainty (Figure 1).

The strongest single genetic susceptibility factor in MS is the HLA-DRB1*1501 gene. However, this effect can be modified by the inheritance of genetic variants in at least a dozen other genes. It is yet unclear exactly how many genes and in what combination confer susceptibility to MS.

Modern approaches for genetic analysis involve sophisticated technologies and analytical platforms. The technique called SNP (single nucleotide polymorphism) Gene Chip Assay (Figure 2) requires as little as 250 ng of genomic DNA and can interrogate a million DNA variants in a single individual overnight. The sample DNA is digested with a restriction endonuclease and adapters ligated to the ends of the resulting fragments, facilitating PCR amplification of the desired sequences. The reproduced fragments are tagged with fluorescence-based labels and hybridized onto a silicon chip containing microscopic sequences of oligonucleotide DNA, each targeting a particular polymorphism. After washing, identification of the fluorescence-based fragments that have hybridized to the oligonucleotide DNA indicates the frequency of specific genotypes in the sample.

Ongoing Research Projects

The University of California at San Francisco has participated in two large consortia that generated two Genomewide

Figure 1. Susceptibility to MS is Polygenic

The strongest single genetic susceptibility factor in MS is the HLA-DRB1*1501 gene. However, this effect can be modified by the inheritance of genetic variants in at least a dozen other genes. It is yet unclear exactly how many genes and in what combination confer susceptibility to MS. [Oksenberg JR, et al. The genetics of multiple sclerosis: SNPs to pathways to pathogenesis. Nat Rev Genet. 2008;9(7):516-26, reproduced with permission.]
association studies (GWAS) in MS. The first consortium is the International Multiple Sclerosis Genetics Consortium (IMSGC). This group has been very successful in completing a recent genomewide association study to search for alleles linked to multiple sclerosis. The group studied 931 family trios, each including an affected child and both parents.5

Results of the IMSGC analysis are presented as the minus logarithm of the P value of each of the SNPs sorted by chromosome. The major susceptibility region has been identified as the HLA-DR risk locus on chromosome 6, and is associated with a very impressive P value (P<10^{-8}).6 A larger GWAS, part of the Wellcome Trust Case Control Consortium version 2 (WTCCC2), is currently underway (expected conclusion by spring 2010) and includes more than 10,000 cases (www.WTCCC2.org.uk/ccc2).

The second completed GWAS in MS is the GeneMSA Project and included 1,000 MS patients and 1,000 controls. The cohort included a high percentage of patients with the relapsing-remitting subtype. As this is a longitudinal cohort, investigators collect yearly MRI scans, deep phenotyping data. Furthermore, gene expression analysis is currently underway. More recently, a new GWAS using patients from Australia and New Zealand (ANZgene) was published.2

The genomewide threshold for multiple comparison testing in most GWAS is approximately 10^{-7}-10^{-8}. Because we hypothesize that genes that do not exceed this adjusted threshold for multiple comparisons may exist, new approaches are needed to analyze data from these large studies.

Pathway Analysis

Pathway analysis is a strategy whereby the significance of DNA markers in genes that belong to the same pathway is combined. Network-based pathway analysis is a recently developed method that allows us to search for modestly associated genes that interact physically or functionally. This process is based on the assumption that genes with modest, but significant P values are not functionally or physically related more often than non-associated genes. Accordingly, there may be genes that do not exceed the nominal threshold for multiple comparisons, but may be part of the same pathway. In such cases, the pathway itself is relevant, while each gene within the pathway is not.

When searching for genes, focus should be limited to moderately associated genes that are known to interact physically or functionally because such genes are most likely to be part of the same pathway. Theoretically, we could then study every possible gene-to-gene interaction in a statistical model; however, the number of possible combinations of genes, even when studied in pairs, is greater than 3 million. A simpler approach is to study the interaction of specific proteins in the protein-protein interaction network.

To illustrate, we can assume that 40 genes are moderately associated in 16 individuals, except for the HLA region (Figure 3). In several individuals, the P value for the HLA is highly significant. However, in most individuals, the P values will be only nominally significant and will not exceed the threshold for multiple comparison.

When analyzing pathways in this example, we had to first consider that certain genes within a specific pathway may only be positive in a fraction of individuals. Further, additional genes in that same pathway may also be positive in the same fraction of individuals, while patients in other subgroups of MS may be positive for a different pathway. The key point behind pathway analysis is to focus primarily on pathways instead of individual genes.

Protein-Protein Interaction Network

Because highly connected proteins organize into specific complexes or modules known to share biological functions, we can assume that interacting proteins within the same module perform similar tasks. This allows us to search for proteins, instead of genes, that may be associated with MS and restrict our search to those that have been previously identified rather than all theoretically possible interactions.

The protein-protein interaction network in humans has been primarily determined through yeast-two hybrid experiments and validated by immunoprecipitation assays. This has provided researchers with a general understanding of interactions between specific proteins and a means to identify modules associated with specific diseases.

Protein-protein interaction analysis was used to evaluate data from both the GeneMSA and IMSGC studies (Figure 4).6 7,8 The process began with these two studies eliminating all SNPs not located near or within a gene. Those located within a single gene were then filtered and condensed and a P value assigned to the entire gene. Genes with the lowest P values were selected from both study groups and combined into a single group of 15,000 genes. Of these, only genes with a P value <0.05 were selected, resulting in a total of 3,200 genes for further analysis. The selected genes were then overlapped with 7,500 known proteins from the protein-protein interac-

![Figure 2. SNP GeneChip Assay](image-url)
associated with both immune and neural pathways. In addition, genetically associated by genome-wide association studies tend to have neural origins. Thus, our findings suggest that in addition to immune deregulation, susceptibility to MS may have neural development. Therefore, the question then becomes whether modules enriched in P values indicating strong association to MS occur more than would be expected by chance, and have these biological pathways been defined previously?

The next step was to refer to the Kyoto Encyclopedia of Genes and Genomes (KEGG) for a classification of all known biological pathways. We assembled our own database of genes and relating these to the known pathways. This allowed us to statistically measure the enrichment of sub-modules into each of these pathways and identify proteins related by function and those that interact physically. This, in turn, provided us with a method for prioritizing genes for further study and identifying disease-specific pathways that may be linked to susceptibility.

Our susceptibility study revealed genes for glutamate receptors that appear to be organized into a highly enriched module. These are not genes that have been found to be involved in MS susceptibility in genome-wide association studies, possibly because the individual genes do not reach the threshold of susceptibility. However, the pathway that the genes are part of is highly statistically relevant.

Our analysis also revealed genes for ephrin receptors, known to be involved in neural specification. Another group of receptors are involved in a signaling pathway involved in neural development. Thus, our findings suggest that in addition to immune deregulation, susceptibility to MS may have neural origins.

In summary, we can conclude that genes shown to be modestly associated by genome-wide association studies tend to interact in modules and pathways, and that MS appears to be associated with both immune and neural pathways. In addition, we believe that pathway analysis offers a novel and systematic method for identifying significant pathways in the population that may prove useful in stratifying individual patients.

References
One mission: MS remission

Our mission to stop a disease like multiple sclerosis requires not just a single-minded focus—but one that’s as relentless as the disease itself. That’s why at Biogen Idec and Elan, we view fighting MS as not only our job at work, but as our mission in life.
Imaging of Primary Progressive Multiple Sclerosis

David Miller, MD

Introduction

The use of imaging techniques continues to advance our knowledge of the pathological processes underlying primary progressive multiple sclerosis (PPMS), the most debilitating subtype of MS. Magnetic resonance imaging (MRI) remains the primary imaging tool for PPMS in vivo. Findings from imaging studies have shown that MRI aids in visualizing brain and spinal cord lesions, identifying markers of atrophy, and detecting pathology in the cortex and normal-appearing white matter (NAWM). In addition, MRI data from long-term studies may aid clinicians in determining the prognosis of patients newly diagnosed with PPMS.

Optical coherence tomography (OCT) has an emerging role in PPMS imaging. This technique has been widely used in measuring retinal nerve fiber layer (RNFL), which may reflect the degree of axonal loss in the optic nerves of patients with MS. Continued use of this technology is expected to contribute to current understanding of the pathological links to PPMS and other MS subtypes.

The focus of this discussion is to provide an overview of important imaging studies in PPMS. It is important to note that most published studies of PPMS include patients with an average disease duration of ten years. Because a definite diagnosis occurs after a five-year history of symptoms in most patients, it is difficult to be confident in the diagnosis, or to enroll patients with disease duration of three years or less.

Conventional MRI Imaging of the Brain and Spinal Cord

In 1990, Thompson and colleagues reported that patients with PPMS had a smaller T2 lesion load compared to patients with benign and secondary progressive multiple sclerosis (SPMS). In a separate serial study, the investigators reported that patients with PPMS had fewer new T2 lesions or lesions enhanced by gadolinium (Gd) compared to patients with SPMS.

In a more recent study, De Stefano and colleagues compared the location of brain lesions in patients with PPMS and relapsing remitting multiple sclerosis (RRMS) and reported a lower lesion load in patients with PPMS (Figure 1). In addition, lesions in the PPMS patients tended to cluster around the ventricles in contrast with the more diffuse configuration of lesions in the RRMS group.

The European imaging collaboration MAGNIMS (Magnetic Resonance Network in Multiple Sclerosis) has followed patients with PPMS clinically and with MRI since 1997. Data from an analysis of patients according to clinical presentation showed that lesion load is significantly higher in patients with non-cord versus cord presentations; approximately 2-fold higher with either T2 or T1 hypointense lesion load.

In a study of 45 patients with a mean duration of PPMS of less than 3.3 years, Thompson and colleagues used triple-dose Gd-enhanced MRI to study the effects of inflammation in early disease. The results demonstrated Gd-enhancing brain lesions in 42% of patients at baseline. Patients with enhancing lesions had a greater T2 lesion load (P = 0.008), higher brain atrophy (P = 0.012), and greater disability (EDSS, P = 0.027; MSFC, P = 0.026) compared to patients without enhancement. These findings suggest the presence of substantial inflammation in a subgroup of patients with early disease.

In an early study of 80 patients by Kidd and colleagues, MRI of the brain and spinal cord demonstrated that lesions of the spinal cord are relatively common in patients with MS. A total of 139 intrinsic lesions were identified in 59 patients (74%), and occurred more frequently in the cervical than thoracic cord. Importantly, the frequency of lesions found in patients with PPMS was no greater than that of other MS subtypes evaluated.

An over-representation of PPMS has been shown to occur in patients with clinically-defined MS, abnormal cord imaging, and normal or near normal brain MRI as demonstrated in a study of 20 patients by Thorpe and colleagues (Figure 2). Analysis of results showed that all patients had cord lesions. Of these, 11 patients were shown to have PPMS, which is significantly higher than would have occurred in a random distribution.

Conventional MRI can also demonstrate atrophy in both the brain and spinal cord of patients with PPMS. In a prospective clinical and MRI study, Ingle and colleagues followed 41 patients with PPMS for five years, assessing measures of both brain and spinal cord atrophy (Figure 3). Significant deterioration was observed in all MRI measures (P < 0.001),
Alternative MRI Imaging Techniques

Additional MRI-based techniques have reported abnormalities in WM and GM. These include reduced magnetization transfer ratio (MTR); abnormal measures of diffusion (either increased mean diffusivity or reduced fractional anisotropy as detected by diffusion tensor MRI imaging); increased T1 relaxation time; and metabolite abnormalities as detected by MRI spectroscopy. Significant reductions in GM perfusion have also been demonstrated using MR-based techniques.\textsuperscript{14, 15, 16}

Reduced MTR and increased diffusivity in the spinal cord was demonstrated by Filippi and colleagues in patients with MS.\textsuperscript{14}

Bieniek and colleagues assessed multimodal MRI measures in 43 patients with early PPMS and 37 patients with early RRMS. The measurements included five MRI pathology domains: GM tissue loss, intrinsic GM MTR abnormality, WM tissue loss, intrinsic WM MTR abnormality, and cervical cord atrophy.\textsuperscript{17}

As expected, patients in the PPMS group were older, predominately male and had more severe disability than patients in the RRMS group. Both T2 and T1 lesion loads were similar in the PPMS and RRMS groups. However, inflammatory activity of the disease, represented by Gd-enhancing lesions, was higher in RRMS patients.\textsuperscript{17}

A univariate comparison of the primary results showed significant abnormalities in atrophy of brain GM and WM and intrinsic abnormality in MTR of GM and WM in both patient groups. The only MRI domain that varied among the groups was cord atrophy, which only occurred in patients with PPMS (P = 0.007). These findings were confirmed in multivariate logistic regression analysis that demonstrated that age, gender, and cord atrophy were the only significant predictors of PPMS (Figure 5).\textsuperscript{17}

A study using magnetic resonance spectroscopic imaging (MRSI) in PPMS was reported by Sajja and colleagues. The study included 58 participants from the PROMiSe trial, drawn from four centers and followed for three years. Investigators evaluated a slab of tissue in the cerebral hemispheres and measured N-acetyl aspartate (NAA)/creatine (Cr) and choline (Cho) content, including an increase in ventricular volume (38%), and a decrease in central cerebral volume (4%) and upper cervical cord area (11%). In addition, no correlation between progressive cord atrophy and brain atrophy was observed, suggesting that these processes may be occurring independently.\textsuperscript{12}

Sastre-Garriga and colleagues investigated changes in grey matter (GM) and white matter (WM) volume using statistical parametric mapping in 31 patients with PPMS with a mean disease duration of three years. Patients were assessed at baseline and after one year. Investigators reported a 1.49% decrease in GM fraction over one year independent of lesion load (Figure 4). In addition, no net change in WM fraction was observed; however, those with high Gd-lesion loads showed a decrease over the following year.\textsuperscript{3}

Spinal cord atrophy has potential importance in predicting the progression of MS as it is indicative of axonal loss and progressive disability. In 1996, Losseff and colleagues demonstrated significant spinal cord atrophy in patients with PPMS (mean cord area of 73.1 mm\(^2\) at C2) as compared with that reported in patients with RRMS (mean cord area of 85.6 mm\(^2\) at C2). Of note, the degree of atrophy in the PPMS group was not as extensive as in patients with SPMS (mean cord area of 61.2 mm\(^2\) at C2).\textsuperscript{13}

Supplement to the International Journal of MS Care

Figure 1. Brain T2 Lesion Location

T2-weighted lesion probability maps in stereotactic space in patients with primary progressive (A) and relapsing-remitting (B) multiple sclerosis (MS). The color overlay created on top of the Montreal Neurological Institute standard brain shows the probability of each voxel containing a lesion in each patient group. The color bar denotes the probability range. In both patient groups, the areas with high probability of containing lesions were similar, mainly involving the superior and posterior regions of the corona radiata. However, the maximum local probability for lesions was higher in patients with primary progressive MS (A, red, yellow, and green areas; 45% peak probability) than in patients with relapsing-remitting MS (B, violet and blue areas; 33% peak probability). (Arch Neurol. 2008;65(2):236-243. Copyright © 2005 American Medical Association. All Rights Reserved. Reproduced with permission.)\textsuperscript{8}
TYSABRI® (natalizumab) injection

Brief summary of less serious information

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Cases of PML have been reported in patients who were recently or chronically treated with immunomodulators or immunosuppressants, as well as in patients receiving TYSABRI as monotherapy treatment (5.1).

• Because of the risk of PML, TYSABRI is available only through a special restricted distribution program called the TOUCH® Prescribing Program. Under the TOUCH® Prescribing Program only prescribers, patients, and caregivers associated with patients enrolled in the program are able to prescribe, distribute, or infuse the product. In addition, TYSABRI must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH Program (see Warnings and Precautions (5.2)).

• Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom that may be suggestive of PML. TYSABRI dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain that, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended (see Contraindications (4), Warnings and Precautions (5.2)).

1 INDICATIONS AND USAGE

1.1 Multiple Sclerosis (MS)

TYSABRI is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical relapses. This indication is based on the results of two phase III studies: a 2 year study (Study MS1) and a 4 year study (Study MS2).

Because TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability, TYSABRI is generally contraindicated in patients who have an inadequate response to, or are unable to tolerate, an alternate multiple sclerosis therapy (see Boxed Warning, Warnings and Precautions (5.3)).

Safety and efficacy in patients with chronic progressive multiple sclerosis have not been studied.

4 CONTRAINDICATIONS

• TYSABRI is contraindicated in patients who have or have had progressive multifocal leukoencephalopathy, a progressive viral infection of the brain that typically only occurs in patients who are immunocompromised, developed in three patients who were receiving TYSABRI in clinical trials. The third case occurred among 1043 patients with Crohn's disease after the patient received eight doses. Both multiple sclerosis patients who were receiving concomitant immunomodulatory therapy and the Crohn's disease patient had been treated in the past with immunomodulatory therapy.

In patients who have received prior treatment with TYSABRI, it is recommended that patients who were receiving concomitant immunomodulatory therapy be discontinued prior to treatment with TYSABRI. In patients treated with TYSABRI, the risk of developing PML increases with longer treatment duration, and for patients treated for 24 to 36 months is generally similar to the rates seen in clinical trials. There is limited experience beyond 3 years of treatment. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of treatment with TYSABRI will mitigate the disease. Ordinarily, patients receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune system function should not be treated with TYSABRI.

Because of the risk of PML, TYSABRI is available only under a special restricted distribution program, the TOUCH® Prescribing Program.

In multiple sclerosis patients, an MRI scan should be obtained prior to initiating TYSABRI treatment to evaluate if the patient is at high risk for developing progressive multifocal leukoencephalopathy (PML). In patients on TYSABRI who, based on this evaluation, are at high risk for developing PML from PML.

Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom suggestive of PML. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of gait, impaired vision, falling, or unexplained convulsions. Changes in personality and changes in thinking, memory, and orientation leading to confusion and psychosis. The progression of deficits usually leads to death or severe disability over weeks to months. Withholding TYSABRI dosing immediately at the first sign or symptom suggestive of PML.

For diagnosis of PML, an evaluation including a gadolinium-enhanced MRI scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended. There are no known interventions that can adequately treat PML if it occurs. Three sessions of plasma exchange over 5 to 8 days were shown to accelerate TYSABRI clearance in a study of 12 patients with MS who did not have PML, although in the majority of patients alpha-4 integrin receptor binding normalized. Adverse events which may occur during plasma exchange include clearing or other medications and volume shifts, which have the potential to lead to hypotension or pulmonary edema. Although plasma exchange has not been studied in TYSABRI treated patients with PML, it has been used in such patients in the postmarketing setting to remove TYSABRI more quickly from the circulation.

Immune reconstitution inflammatory syndrome (IRIS) has been reported in TYSABRI treated patients who were developing exacerbations of their multiple sclerosis. In almost all cases, IRIS occurred after plasma exchange was used to eliminate circulating TYSABRI. It presents as an unexplained clinical improvement in a patient's condition, accompanied by pathological findings (in some cases after apparent clinical improvement) and, in the case of PML, is often followed by characteristic changes in the MRI. TYSABRI has not been associated with IRIS in patients discontinuing therapeutic treatment for reasons unrelated to PML. In TYSABRI treated patients with PML, IRIS has been reported within days to weeks after plasma exchange. Monitoring for development of IRIS is recommended. If IRIS is observed, appropriate treatment of the associated inflammatory damage from PML. TYSABRI should be withheld.

5.2.4 Laboratory Test Abnormalities

TYSABRI induces increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Observed changes persist during TYSABRI exposure, but are reversible, returning to baseline levels usually within 16 weeks after the last dose. Elevations of neutrophils are not observed. TYSABRI induces mild decreases in hemoglobin levels that are frequently transient and not associated with anemia.

7.7 Immunosuppression

No data are available on the effects of vaccination in patients receiving TYSABRI. No data are available on the secondary transmission of infection by live vaccines in patients receiving TYSABRI.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The most serious adverse reactions were (see Warnings and Precautions (5.5):)

• Hypersensitivity

• Immunosuppression/Infections

The common adverse reactions (incidence ≥ 10%) were headache and fatigue in both the multiple sclerosis (MS) and Crohn’s disease (CD) studies. Other common adverse reactions (incidence ≥ 10%) in the MS studies was arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, nausea, and rash. Infections were not reported in the CD trials. The adverse reaction rate in CD of both Tysabri and placebo was low. Infections were the most common adverse reaction. The most frequently reported adverse reactions resulting in clinical intervention (i.e., discontinuation of TYSABRI) in the MS studies were urticaria (1%) and other hypersensitivity reactions (see Warnings and Precautions (5.5)).

A total of 1617 multiple sclerosis patients in controlled studies received TYSABRI, with a median duration of exposure of 28 months.
Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of TYSABRI cannot be directly compared to rates in the clinic or in other clinical trials and may not reflect the rates observed in practice. The adverse reaction information does, however, provide a basis for identifying the adverse events that appear to be related to drug use and a basis for approximating rates.

Multiple Sclerosis clinical studies

The most frequently reported serious adverse reactions in Study MS1 (see Clinical Trials) with TYSABRI were infections (3.2% versus 2.6% in placebo), including urinary tract infection (0.3% versus 0.3%) and pneumonia (0.6% versus 0%); acute hypersensitivity reactions (1.1% versus 0.3%, including anaphylaxis/anaphylactoid reaction (0.8% versus 0%)), depression (1.0% versus 0.1%, including suicidal ideation or attempt [0.6% versus 0.3%]), and convulsions (0.1% versus 0.3%). In Study MS2, serious adverse reactions of appendicitis were also more common in patients who received TYSABRI (0.9% versus 0.2% in placebo) [see Warnings and Precautions (5.4). Adverse Reactions - Inflections].

Table 1 enumerates adverse reactions and selected laboratory abnormalities that occurred in Study MS1 at an incidence of at least 1% point higher in patients treated with TYSABRI than in placebo-treated patients.

<table>
<thead>
<tr>
<th>Table 1. Adverse Reactions in Study MS1 (Monotherapy Study)</th>
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<tbody>
<tr>
<td>General Discomfort</td>
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<tr>
<td>Acute hypersensitivity reactions*</td>
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<tr>
<td>Other hypersensitivity reactions*</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Dermatitis</td>
</tr>
<tr>
<td>Psychiatric</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Urinary tract infection</td>
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<tr>
<td>Lower respiratory infection</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Menstrual disorders*</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Menstrual disorders*</td>
</tr>
<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Menstrual disorders*</td>
</tr>
<tr>
<td>Skin</td>
</tr>
<tr>
<td>Rash</td>
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<tr>
<td>Dermatitis</td>
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<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Night sweats</td>
</tr>
<tr>
<td>Menstrual disorders*</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Neurologic Disorders*</td>
</tr>
<tr>
<td>Irritable</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
</tr>
<tr>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>Urinary urgency/frequency</td>
</tr>
<tr>
<td>Injury</td>
</tr>
<tr>
<td>Limb injury NOS</td>
</tr>
<tr>
<td>Skin laceration</td>
</tr>
<tr>
<td>Thermal pains</td>
</tr>
<tr>
<td>Percentage based on female patients only.</td>
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</tbody>
</table>
*Percentage based on female patients only. |
ferent slice positioning. In that center, the assessed slab was through ventricles; in the three other centers, the slab was above the ventricles. This interesting finding highlights the many challenges facing investigators of multicenter studies.

Sastre-Garriga and colleagues measured metabolite concentrations in NAWM and cortical GM in 43 patients in the early phase of PPMS compared to healthy controls and assessed the correlations with disability score. The results showed reduced levels of total N-acetyl-aspartate \((P < 0.001)\) in cortical GM, indicative of GM neuronal and axonal damage; and high levels of myo-inositol \((P = 0.002)\) in NAWM, signifying glial proliferation. Both findings were associated with increased disability, suggesting that early GM neuronal damage and WM glial proliferation may be useful in determining clinical outcome.

Rashid and colleagues used a noncontrast technique called continuous arterial spin labeling to assess perfusion in GM and WM in various MS subtypes. Investigators reported decreased GM perfusion in patients with PPMS compared to controls. Reductions were found in cortical and deep GM, particularly in the thalamus and the caudate nucleus. Reduced GM perfusion may be indicative of reduced metabolism associated with neuronal or axonal loss.

**Prognosis**

Early results from three long-term studies using MRI measures may aid clinicians in predicting the course of PPMS.

The MAGNIMS trial was designed to investigate the predictors of long-term disability on the course of PPMS. Preliminary follow-up data from 101 patients show changes in EDSS over a ten-year period. The findings indicated improvement in disability for a small proportion of patients and a worsening of symptoms for a substantial number over ten years.

choline (Cho)/Cr in PPMS patients treated with glatiramer acetate or placebo. Results showed no significant differences in metabolic ratios between treatment groups. In addition, strong resonances indicative of mobile macromolecules, possibly lipid turnover, were detected. This striking finding has been previously reported and warrants further investigation.

It is interesting to note that one study center reported consistently different results than other centers because of different slice positioning. In that center, the assessed slab was through ventricles; in the three other centers, the slab was above the ventricles. This interesting finding highlights the many challenges facing investigators of multicenter studies.

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Predictors of progression in this cohort were primarily clinical. Male gender, short disease duration and poor timed walk test at baseline were predictors of poor outcome. An increase in EDSS in the first two years of follow up was also predictive of a poor outcome.

The only MRI predictor was reduction in brain volume over the first two years; changes in T1 or T2 lesion load were not shown to be independent predictors. Change in spinal cord area was also not predictive of prognosis; however, this finding seems counterintuitive and may be attributable to the inherent difficulty in obtaining reproducible measures of a small structure.

A study reported by Rovaris and colleagues provides 5-year outcome data for 54 PPMS patients with mean disease duration of 10 years at baseline. Of the 54 patients, 41 had progressive myelopathy. At baseline, mean patient age was 51 and mean EDSS was 5.5 (2.5-7.5). MRI was performed at baseline and follow up included conventional brain T2/T1 lesion loads, brain diffusion tensor imaging, and cervical cord 3D T1 to measure atrophy.

Analysis of 5-year follow-up data revealed only two significant predictors of outcome in this study. The first was EDSS: patients with a lower score at baseline had the worst disease progression over 5 years, a finding that contradicts data from the PROMiSe trial. The second predictor was increased GM mean diffusivity, which was directly associated with a deterioration in EDSS. Cord atrophy, lesion load, and white matter diffusivity were not predictive of disease progression.

Khaleeli and colleagues recently studied a cohort of 47 patients followed for three years (43 patients completed the study). Mean baseline patient data include age of 45 years, disease duration of 3.4 years, and EDSS of 4.5. Imaging was performed at baseline and 6 month intervals over the 3-year period and included T2 lesion load, GM volume, WM volume, GM MTR, and WM MTR.

<table>
<thead>
<tr>
<th>Variable in model</th>
<th>Odds ratio for patient being PP (vs RR)</th>
<th>95% CI (P value)</th>
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<tbody>
<tr>
<td>GMF (%)</td>
<td>0.97</td>
<td>0.67, 1.42</td>
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<tr>
<td></td>
<td></td>
<td>(0.890)</td>
</tr>
<tr>
<td>WMF (%)</td>
<td>1.15</td>
<td>0.65, 2.02</td>
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<tr>
<td></td>
<td></td>
<td>(0.634)</td>
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<tr>
<td>Mean GM MTR (pu)</td>
<td>0.75</td>
<td>0.15, 3.76</td>
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<tr>
<td></td>
<td></td>
<td>(0.724)</td>
</tr>
<tr>
<td>Mean WM MTR (pu)</td>
<td>0.48</td>
<td>0.14, 1.58</td>
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<tr>
<td></td>
<td></td>
<td>(0.226)</td>
</tr>
<tr>
<td>Cord area (mm2)</td>
<td>0.9</td>
<td>0.82, 0.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.031)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.14</td>
<td>1.04, 1.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.005)</td>
</tr>
<tr>
<td>Patient is female</td>
<td>0.13</td>
<td>0.02, 0.67</td>
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<tr>
<td></td>
<td></td>
<td>(0.014)</td>
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Figure 4. Grey Matter Atrophy Exceeds White Matter Atrophy in Early PPMS

Figure 5. Multivariate Comparison of Multimodal MRI Measures in PPMS
GMF, grey matter fraction; MTR, magnetisation transfer ratio; NAGM, normal-appearing grey matter; NAWM, normal-appearing white matter; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; WMF, white matter fraction. (Adapted with permission from BMJ Publishing Group Limited. [J Neurol Neurosurg Psychiatry, Bieniek M et al, 77(9), 1036-1039, 2006].)
Mean EDSS after three years was 6.0. Evaluation of mean GM and WM MTR showed a more rapid change in GM over the 3-year period. Multivariate analysis of EDSS progression revealed three predictors of increasing disability. These include the rate of decrease in GM MTR mean (P=0.032), peak location (P=0.008), and the rate of T2 lesion load increase (P=0.024, coefficient 0.7). Analysis of mean GM MTR and EDSS showed that GM MTR was the strongest predictor of progression over 3 years.19

Optical Coherence Tomography

Optical coherence tomography (OCT) is a technique for measuring thickness of the retinal nerve fiber layer (RNFL). Specifically, OCT provides cross-sectional imaging of internal tissue microstructure by measuring the echo time delay of backscattered infrared light and is analogous to ultrasound imaging. The RNFL is composed predominately of unmyelinated axons of retinal ganglion cells and axonal loss appears to be the primary cause of disability in MS. Accordingly, OCT has been used frequently in recent years to evaluate patients with MS.

A recent study by Henderson and colleagues employed OCT to measure RNFL thickness in 23 patients with PPMS and 27 patients with SPMS. In patients with PPMS and SPMS, mean RNFL thickness in eyes not affected by optic neuritis was reduced compared to healthy controls and this difference reached statistical significance in the SPMS group. Loss of RNFL thickness was most prominent in the temporal quadrant and was significantly greater in both patient groups compared to controls, and significantly greater in SPMS patients compared to PPMS patients. This finding may indicate a difference in the pathology underlying axonal loss in the retina in SPMS and PPMS.6

Conclusion

The use of MRI imaging techniques has demonstrated that most patients with PPMS have multifocal lesions of the brain and spinal cord. On average, the brain lesion load and activity is relatively low and spinal cord MRI lesion load is variable. There is sometimes evidence of diffuse signal abnormalities in the brain and cord, and cord and brain atrophy along with intrinsic quantitative GM and NAWM MR abnormalities are usually found. Retinal axonal loss is also observed.

Longitudinal studies have suggested that T2 lesion load and Gd-enhancing lesions in early disease are modestly predictive of increased disability. In addition, GM MTR and diffusion abnormality may indicate a poorer prognosis. General brain and cord atrophy may also have a predictive role. Finally, the current diagnostic criteria seem to be concordant with clinical diagnosis for many, but not all patients with primary progressive MS.0

References


Supplement to the International Journal of MS Care

29
NARCOMS Data and Patients with Primary Progressive Multiple Sclerosis

Kathleen Hawker, MD

Introduction

The North American Research Committee on Multiple Sclerosis (NARCOMS) has maintained a patient registry since its inception in 1993. Researchers recently analyzed data comparing Primary Progressive Multiple Sclerosis (PPMS) patients with not-PPMS patients in preparation for a presentation to the Primary Progressive Consensus Conference in February 2008. They found that on average, PPMS patients were slightly older, had been diagnosed slightly later in life, and age at onset of first symptom was also later. Disability was also assessed, and it was determined that while mobility was worse for PPMS patients, the non-PPMS group did worse in many other categories, including vision, fatigue, pain and depression. While more PPMS patients were being treated with IV steroids or mitoxantrone, non-PPMS patients received more immunological therapies. This information was self-reported and no follow-up data is yet available. It is hoped that additional data will help researchers improve understanding of this disease and result in development of more effective treatments.

NARCOMS Patient Registry

The North American Research Committee On Multiple Sclerosis (NARCOMS) Project has been underway for approximately 15 years. This initiative by the Consortium of Multiple Sclerosis Centers (CMSC) coordinates and exchanges data through multi-center research in multiple sclerosis. The goals are to share information, to rapidly further the progress of treatment, and to improve understanding of this disease. The CMSC also maintains a registry of MS patients, the largest of its kind in the world.

The NARCOMS data had not yet been evaluated specific to primary progressive MS in North America. Since the data presented are self-reported, we are not completely certain that all MS patients categorizing themselves as primary progressive (PPMS), truly are PPMS patients. These patients also self-reported any instances of relapse during the course of their disease. Although we believe that we captured mostly PPMS patients, there may be some secondary progressive MS patients in the data as well.

Assessment Parameters

Several different parameters were assessed (Table 1). When looking at race, a vast majority of patients were Caucasian, a small percentage were African American, and a very small percentage were of other ethnic backgrounds.

We divided the patients into two groups: PPMS and not-PPMS. At time of enrollment PPMS patients were slightly older, averaging 50.5 years; in the not-PPMS group the mean age was 46.9 years. Some of those not primary progressive may be secondary progressive, too, which may be driving the age up.

Of interest are the gender differences. As opposed to what has been seen in most natural history studies of a one-to-one comparison, we have a slight female predominance in this group, which may change some of our demographics and outcomes.

Both groups were highly educated. Very few patients had less than 12 years of school. An examination of some of the other important issues like employment, marital status, living arrangements, income, health insurance coverage, and even birth state as a north/south parameter in terms of how MS is acquired, found virtually no difference between the primary progressive and the relapsing-remitting groups.

Demographics were also reviewed (Table 2). The duration of disease at time of enrollment was approximately the same between the two groups. Whether this reflects the population as a whole is unclear, however. The age at the time of diagnosis was slightly older for the PPMS group. Age at first symptom is also significantly different in the two groups.

Table 1. Demographics (at time of enrollment)

<table>
<thead>
<tr>
<th></th>
<th>PPMS (n= 3,567)</th>
<th>Not-PPMS (n= 23,623)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>89.5</td>
<td>89.4</td>
</tr>
<tr>
<td>African American</td>
<td>4.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>50.5</td>
<td>46.9</td>
</tr>
<tr>
<td>Median</td>
<td>51.0</td>
<td>47.0</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>63.3</td>
<td>73.3</td>
</tr>
<tr>
<td>M</td>
<td>36.5</td>
<td>26.5</td>
</tr>
</tbody>
</table>

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Supplement to the International Journal of MS Care

Table 2. Demographics: Duration of disease, age of diagnosis and age of first symptom

<table>
<thead>
<tr>
<th>Duration of MS at Time of Enroll</th>
<th>PPMS</th>
<th>Not-PPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>9.8</td>
<td>9.9</td>
</tr>
<tr>
<td>Median</td>
<td>7.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age MS Dx;</th>
<th>PPMS</th>
<th>Not-PPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>40.8</td>
<td>36.7</td>
</tr>
<tr>
<td>Median</td>
<td>40.0</td>
<td>36.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age of First Symptom</th>
<th>PPMS</th>
<th>Not-PPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>33.3</td>
<td>28.6</td>
</tr>
<tr>
<td>Median</td>
<td>34.0</td>
<td>28.0</td>
</tr>
</tbody>
</table>

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Table 3. NARCOMS Disability Scales

<table>
<thead>
<tr>
<th></th>
<th>PPMS</th>
<th>Not-PPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility</td>
<td>Worse</td>
<td>—</td>
</tr>
<tr>
<td>Hand scale</td>
<td>—</td>
<td>Same</td>
</tr>
<tr>
<td>Vision</td>
<td>—</td>
<td>Worse</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Same</td>
<td>—</td>
</tr>
<tr>
<td>Cognitive</td>
<td>—</td>
<td>Worse</td>
</tr>
<tr>
<td>Bladder/bowel</td>
<td>Same</td>
<td>—</td>
</tr>
<tr>
<td>Sensory</td>
<td>—</td>
<td>Worse</td>
</tr>
<tr>
<td>Spasticity</td>
<td>Worse</td>
<td>—</td>
</tr>
<tr>
<td>Pain</td>
<td>—</td>
<td>Worse</td>
</tr>
<tr>
<td>Depression</td>
<td>—</td>
<td>Worse</td>
</tr>
<tr>
<td>Tremor</td>
<td>—</td>
<td>Worse</td>
</tr>
</tbody>
</table>

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symptoms was also slightly older in the primary progressive patients as opposed to the relapsing-remitting, or the not-PPMS group.

When comparing genetics between the two groups, the percent of patients with blood relatives with MS was about the same. The percentage of twins was exactly the same between the two groups. Other immunological conditions that the patients had, ranging from B12 deficiency to psoriasis to lupus to a variety of other autoimmune diseases, were almost identical between the two groups as well.

Investigators developed a disability scale on NARCOMS for a variety of different issues. Comparing the primary progressive and not-PPMS patients, the biggest issue that the PPMS group cited was mobility, which is rather intuitive, since most of these patients present with a myopathy.

Hand scale, fatigue, bowel and bladder disability were about the same between the two groups, most likely reflecting clinical presentation (Table 3). In the not-PPMS group, vision, cognition, sensory, pain, depression, and tremor were all worse in this population as compared to the PPMS population. This was an interesting outcome. It is important to note that this is enrollment data only. Follow-up questions from the NARCOMS database are not yet available.

Approximately six percent of PPMS patients and about four percent of non-PPMS patients were treated with steroids, intermittently. This information did not specify whether they were dose or pulse regimens of steroid treatment.

A small percentage of patients were treated for the progressive form of the disease with mitoxantrone. Treatment with mitoxantrone was used in 2.8% of PPMS patients compared to 1.6% of not-PPMS patients. Interestingly, 55.0% of the patients in the PPMS group had been treated with an immunological agent, ranging from interferons to glatiramer acetate to methotrexate, azathioprine, and cyclophosphamide, as compared to 71.8% of the not-PPMS cohort.

Despite the fact that there is no known treatment for PPMS, many patients are or were being treated. These figures do not include whether these were misdiagnoses or how rapidly these patients progressed, if treated. It also does not tell us who is currently being treated since these are only enrollment data. Follow-up data is not yet available.

These data seem to indicate that it is important to attempt treatment for PPMS patients to help prevent progression. It would be interesting to look at countries outside the United States, where it may be much more difficult to obtain treatment, to see if the percentage of patients treated is similar. We are looking forward to receiving more data and refining this analysis further.

References


Discussion

Dr. Timothy Vollmer: One other comment I would make is that we did actually do a validation study to look at the population of patients who said they had MS actually had MS and then the subtype reported by their primary physician by a review of medical records. The correlation between the patient-reported diagnosed MS and the records was 99 percent. But, the concordance of the patient and the physician’s interpretation of the form of MS and what the patient reported in terms of how we interpret it was very small.
Prognosis of Primary Progressive Multiple Sclerosis

Kathleen Hawker, MD

Introduction

Predictors of prognosis in patients with primary progressive multiple sclerosis (PPMS) can potentially aid clinicians in defining the patient population likely to be most responsive to treatment. This is particularly important when employing treatments with significant side effects as clinicians should restrict the use of such agents to the population of patients most likely to achieve the greatest benefit.

There are four primary components that contribute to the prognosis of a patient with PPMS. These include data from MRI, clinical assessment, cerebrospinal fluid (CSF) evaluation, and pathological evaluation.

Additional determinants of prognosis include genetic and immunological factors. Disease stage at diagnosis also influences prognosis and is a major issue in the management of PPMS, as this subtype lacks the distinct, phenotypic stages that occur in relapsing remitting multiple sclerosis (RRMS).

CSF Indicators of Progression

Investigations of CSF cytology in patients with MS have uncovered specific findings that appear to correlate with disease progression. In a study by Cepok and colleagues, a high ratio of B cells to monocytes was associated with a more rapid progression in patients with PPMS and RRMS compared to a CSF pattern characterized by a predominance of B cells.1 Avasarala and colleagues reported that an absence or low number of oligoclonal bands in the CSF at the time of diagnosis appear to be predictive of a more benign disease course.2

Investigators of the PROMiSe study assessed MRI features according to CSF and oligoclonal band status at entry in patients with PPMS. The results showed that disease burden and gadolinium (Gd)-enhancing lesions were significantly associated with a positive IgG index and the presence of oligoclonal bands in the CSF of patients with PPMS.3

MRI Predictors of Progression

The PROMiSe investigators correlated Gd-enhancing activity on entry MRI with accumulation of disability over the course of the 3-year study. Findings showed that PPMS patients with Gd-enhancing lesions at baseline had a faster disease progression compared to patients who were Gd-negative at onset.

Accumulation of disability was also stratified by plaque burden on entry MRI in patients enrolled in the PROMiSe study. Results showed that faster disease progression occurred in patients with the highest plaque burden.

Clinical Correlates of Progression

Studies of natural history, clinical outcomes, and MRI measures in patients with PPMS have identified clinical correlates of disease progression. Predictors of negative outcome include early rapid rate of progression, shorter disease duration, and manifestation of disease in three or more systems at onset.

Gender was shown to have a questionable or conflicting association to disease progression. Most studies reported no difference in disease progression between males and females; however, several reported that progression may be worse in females and PROMiSe investigators reported faster progression in a cohort of males. Of note, the issue of gender, including the potential impact of hormones on disease development, requires further study as MS is one of very few autoimmune diseases with a one-to-one male to female correlation.

The association between lower baseline EDSS and disease progression also remains unclear. While most studies report a more rapid progression in patients with lower EDSS, a higher score at entry was reported to be a predictor of progression in the PROMiSe study.

Negative predictors of association with disease progression have also been identified. These include age of onset and duration of disease. These findings suggest that patients with gray matter atrophy and positive oligoclonal bands who start progressing very rapidly within the first several years may be most amenable to treatment.

Conclusion

To date, multiple predictors of PPMS progression have been identified and include high plaque burden and the presence of Gd-enhancing MRI lesions at baseline; a high ratio of B cells to monocytes and a positive IgG index in cerebrospinal fluid; and early rapid rate of progression, shorter disease duration, and manifestation of disease in three or more systems at onset.

Future genetic and immunological studies may help identify markers specific to each MS subtype, allowing for earlier identification and treatment of patients with PPMS and a clearer understanding of pathological processes before the disease progresses to advanced stages. Theoretically, predictors of faster progression may help in defining patient populations who may respond to treatments.

References

Rehabilitation of PPMS Patients

Brian Hutchinson, PT, MSCS

Rehabilitation professionals have made great strides in providing services for patients with primary progressive multiple sclerosis (PPMS), although many gaps in services still exist. Rehabilitation can help to minimize or avoid secondary complications, maximize functional independence, manage symptoms and improve task specificity and movement. Interventions for patients with PPMS may improve a patient’s function and well-being.

The Multiple Sclerosis Association of America (MSAA) conducted a needs assessment in 2005, and then carried out a sub-analysis, focusing on MS classification. They found that, individuals with PPMS chose rehabilitation care, respite care partners, and in-home assistance—over all of the other available MSAA services—more frequently than did the relapsing-remitting patients or the secondary progressive patients.

In a Sonya Slifka Longitudinal Study analysis, 93 percent of PPMS patients reported difficulty with walking as opposed to the 48 percent of relapsing-remitting patients. Seventy-nine percent reported problems with spasticity versus just about half of those with the relapsing-remitting. Other increased symptoms reported by the primary progressive MS patients compared with the relapsing-remitting patients included greater bladder dysfunction (72.9% vs. 48.3%) and more pain (63.6% vs. 48.3%).

PPMS patients defined their disability as higher on the patient determined disease steps (PDDS) and there was also greater need for help with activities of daily living, such as bathing, dressing, and eating, as well as mobility with transfers and housework.

This study also revealed that PPMS patients were less likely to be employed than the relapsing-remitting patients. People with PPMS scored lower on the SF12 physical health scale, but there was no difference noted on the mental health scale.

Secondary Complications

Secondary complications, such as decubitis ulcers, contractures and osteoporosis, are a concern in this patient population. Research has shown that osteoporosis can be a problem, particularly with non-ambulatory patients.

Weinstock-Guttman, Gallagher, and colleagues examined a trend for lower bone mineral density (BMD) in both secondary progressive as well as primary progressive populations. In patients with limited ambulation and those confined to wheelchairs, they found that there was greater BMD reduction in the femur than in the lumbar vertebrae. Based on the study results, it is likely that sitting provides adequate weight bearing to maintain bone density in the lumbar region, but not the hip region.

The mean EDSS, in the osteoporotic group that did require assistance for ambulation, was higher than those who had the normal bone mineral density and were ambulatory, most likely without any kind of assistance (6.7 ± 1.6 vs. 4.4 ± 2.4).

A strong positive correlation between the ability to walk without assistance and bone mineral density was noted. A meta-analysis performed by Motl and colleagues revealed that individuals with PPMS had lower levels of physical activity and accumulated fewer daily steps than those with RRMS. Unfortunately, for those professionals who purport healthy living, there was also a correlation between increases in body mass index (BMI) and bone mineral density. Those with greater cardiovascular risk might actually be at a decreased risk for osteoporosis or osteopenia.

In addition, little information exists, and few studies have examined intervention from a rehabilitation standpoint and the effect on activity limitations and participation restrictions. Some of these studies are quite old, utilizing disability and handicap measures, and more investigation needs to be conducted in the area of primary progressive MS and rehabilitation to determine with greater certainty which interventions can make the greatest difference.

Inpatient vs. Outpatient Rehabilitation

In 1997, Freeman, Langdon, and colleagues, investigated the impact of inpatient rehabilitation. Over a six-week period, they found that there was virtually no change in the EDSS following inpatient rehabilitation. On average, individuals were in that inpatient program for 23 days.

There was a reduction in disability as measured by the functional independence measure or FIM, except for the ambulation component. This result is predictable based on how FIM is measured. To make a one-point change, a patient would have to increase his or her ambulation approximately 30 to 35 meters. To see that change in that short a period of time is not expected from an ambulation standpoint. Overall, however, there was reduced disability up to six months, as measured by the FIM, as well as reduction in handicap, as identified by the London Handicap Scale.

Fifty of those 66 patients were followed over a year at three month intervals, and as noted in the follow-up study there...
continued to be a reduction in disability, again, except for ambulation, and a reduction in handicap up to six months, although there was a decline in neurologic status, measured by the EDSS.

**Symptom Management – Spasticity**

Rehab professionals are called upon to manage a variety of symptoms in patients with PPMS, from fatigue to pain. Spasticity is often the primary physical symptom that therapists see in this population. For spasticity management in both occupational and physical therapy, one of the key areas of concentration is elongation of the target tissues. There are many available treatments including oral medications, injections and intrathecal baclofen for the management of spasticity. However, the addition of physical and occupational therapy is extremely important in gaining the optimal functional outcome.

Some methods in use for elongation of tissues include positioning, casting or splinting. A stretching program is almost always a useful component and incorporating a sustained low load stretch yields the best results. Mobilization techniques, particularly for those who have shortening of the joint capsules, may be necessary. The idea is to utilize all of the techniques including splinting, casts, wedges or other devices, as well as positioning, in conjunction with medical interventions to improve tissue length and ultimately function.

There are a number of tools used in providing proper alignment. Splinting is an important tool used by rehab professionals and dynamic splinting is becoming a more prevalent method for providing low load stretches. It is critical to ensure appropriate fitting for patients that are recommended for this type of intervention. Therefore, a rehabilitation therapist should be included in fitting and adjustment.

**Rehabilitation for Pain**

Pain management is an issue PPMS patients must confront on many levels. Generally the referral or the recommendations to rehab are for those who have more mechanical types of pains, secondary to problems with their gait or problems with other types of movement (Table 1). Rehab interventions should be designed to get to the ‘root of the problem’ and address correction or compensation of movement dysfunction to decrease any overuse syndromes or mechanical problems.

Again, this may utilize or require the use of adaptive aids, whether it is ambulatory or otherwise. It requires an exercise program to improve muscular imbalances. Functional bracing may be considered, as well as modalities for pain management such as heat, ice or electrical stimulation. Importantly, care partner training needs to be included. Many times therapists see care partners coming to them with injuries secondary to improper assistance with transfers or activities of daily living.

**Gait Training**

Gait training is a big component of physical therapists’ training and education. Research in other neurological disease populations look at body weight supported treadmill training (BWSTT). Efforts such as leg gait training can be helpful in improving the overall function, and improving a patient’s ability and efficiency with gait, using these interventions.

Another pilot study, conducted by Giesser, Beres-Jones, and colleagues, examined four severely disabled (EDSS 7.0-7.5) MS patients who participated in BWSTT. Subjects demonstrated improvements in muscle strength, spasticity, endurance, balance, walking speed and quality of life at the end of the training sessions.

Research strongly suggests that BWSTT has beneficial effects on walking speed, stride parameters and endurance. However, research has not clearly demonstrated the intensity and duration of BWSTT needed to result in improvement in walking. Structured speed-dependent treadmill (SST) resulted in improved overground walking speed compared to conventional gait training.

For re-training and improving overall motor control in MS patients, rehab professionals are exploring this type of treadmill intervention. More research is needed in the area of BWSTT in MS. There is also additional work examining robotics for gait training in the MS population. Preliminary information that is available is positive.

**Task Specificity**

Another important area to consider is task specificity. Patients appreciate looking at ways in which they can improve their overall function or their ability to perform a particular task. Often they are very frustrated because they have been through other types of rehabilitation programs that have addressed or sought to improve strength or range of motion, but were not really geared towards a specific goal or a specific task.

Current research by Nudo and Kleim, has shown the importance of task specificity and motor skills acquisition in behavioral neurology recovery after damage to critical motor areas. The key to improvement of function is repetition and task specificity, a basic concept for improving motor control.

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**Table 1. Rehabilitation of pain secondary to movement dysfunction (mechanical)**

- Training of movement (e.g. gait, transfers)
- Exercise
- Bracing
- Localized ice or heat
- Care partner training

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Some of the remunerative approaches may include techniques like visual compensatory strategies. Vestibular rehabilitation may be used for balance retraining or improving overall balance. Assistive devices are one of the most important components to improve overall safety. Methods of increasing sensory input, while often challenging, can also be helpful. For example, if a patient has a loss of sensation in the bottom of their feet, efforts are made to improve the feedback that they are receiving.

The goal is to try to help patients maximize independence and to be as functional as possible. Increasing their ability, often from an ambulatory standpoint, is the main objective.

Other Interventions

Other interventions include approaches such as endurance training. The goal here is to look at ways in which a person’s function and their overall health can be maintained, while decreasing the effects of fatigue as much as possible, particularly as it relates to de-conditioning. Individuals with neurological conditions need to work on increasing cardiovascular and muscular endurance to help improve function with daily activities.

Individualized seating systems and standing equipment are important considerations for those who are primarily wheelchair dependent. Pressure mapping can be helpful in assessing the patient’s seating system and determining areas of greater risk for skin breakdown. Standing equipment is an extremely important component, particularly for osteoporosis or osteopenia. This can be a very beneficial program for many people, especially those with progressive forms of MS. Other assistive devices might include those for gait, orthotics, bathroom equipment, assisted technology or augmentative communication.

At times, reassessment of equipment needs is important. For example, if a patient’s spasticity has been successfully decreased, it is critical to reassess the patient’s equipment needs and to look at the patient as essentially a new patient. Some equipment may be recommended for the first time while other interventions may need to be altered or eliminated. Improved nutrition may lead to significant weight gain for some patients, necessitating changes to a variety of equipment. Conversely, weight loss secondary to problems with swallowing or poor nutrition may require changes, also. Major changes in equipment should probably not be made if the patient’s condition is not yet stable.

After assessing for appropriateness of adaptive and assistive devices, it is important to educate the patient on their options, whether it’s manual vs. power mobility or bilateral vs. unilateral support. In addition, reimbursement is an important issue in the area of adaptive/assistive equipment. Many times there are specific qualifications required for adaptive equipment and letters of medical necessity are needed to justify the equipment.

Summary

Rehabilitation is an important component in the management of individuals with progressive MS. Surveys and analyses show that people with progressive MS are less physically active than those with relapsing-remitting MS.

Rehab interventions have been shown to improve function and well-being. Rehab can also play an important role in reducing care partner stress through education. Additional assistance with activities of daily living and mobility can be improved through rehab interventions. Early interventions may decrease the risk of co-morbidities secondary to decreased activity. For PPMS patients, an emphasis on rehabilitation, in-home assistance, and respite care are critical to improved quality of life.

References

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Supplement to the International Journal of MS Care
Modern-day clinicians have traditionally overestimated the relationship between cognitive dysfunction and physical disability in MS. Cognitive function has been found to correlate poorly to measures of physical and sensory disability such as Expanded Disability Status Scale (EDSS) score and disease duration. Correlations in the moderate range have been found with Magnetic Resonance Imaging (MRI) parameters, including T2 lesion burden, magnetization transfer ratio, brain atrophy, and other MRI markers.

In a study by Rao, 100 patients with MS were evaluated; 52 were cognitively intact and 48 were cognitively impaired. The study demonstrated that cognitive dysfunction affected many aspects of daily life as assessed by the Environmental Status Scale (ESS). In this study, the presence of cognitive dysfunction was significantly related to employment status. Also, the need for personal assistance was greater among those with cognitive impairments, and the patient’s participation in social activities was more limited.

Few Long Term Cognitive Changes Seen in PPMS Patients
There have been far fewer studies of cognition on primary progressive MS (PPMS) than on relapsing or secondary progressive MS. Camp’s study analyzed verbal memory at baseline, at year one, and at year two. They found that over time, the mean cognitive scores assessing aspects of verbal memory, including long-term storage, consistent long-term retrieval, and delayed recall were very similar. They concluded there were few changes over time in verbal memory.

Other aspects of cognitive function in the aforementioned study similarly showed little change over time. The Symbol Digit Modalities Test, a simple, five-minute test that measures cognitive processing speed and the Paced Auditory Serial Addition Test (PASAT), a measure of auditory processing speed and working memory, also showed no changes over time. The PASAT was administered with two different speeds of stimulus presentation, and the findings in this study were similar for both the three-second stimulus presentation rate and the two-second rate.

In addition to the above findings, verbal fluency, verbal reasoning skills and depression were evaluated. Depression severity was not clinically significant and remained relatively consistent over time. Verbal fluency and verbal reasoning skills remained stable as well.

Camp observed that those patients who had any moderate or severe cognitive deficit at baseline, continued to worsen. Once progression reached a certain threshold, the disability milestones were reached more quickly. This was similar to a study by Kujala that showed that even the presence of mild deterioration of cognitive function at baseline was associated with progressive decline prospectively.

Some Disparities in Processing Observed
Another study by Denney looked at cognitive dysfunction in primary progressive, relapsing remitting, and healthy controls. No difference was found in mean scores, when just the mean scores were compared among groups.

However, when additional multivariate modeling was done, investigators found differences between groups on the Tower of London test. This test assesses the initial planning time that the patient takes before they make their first move, or respond to a set of problems. They found that PPMS patients had significantly greater disparity in initial planning time compared with the healthy controls.

The relapsing remitting and the primary progressive groups started out in a similar way. As the problem type became more complex, the relapsing remitting group did the poorest, with the primary progressive group performing in the middle.

Similar results were found by Kraus and his colleagues using the Stroop Test. They assessed several cognitive functions, including attention and word reading in a 60-second period. There were differences between the MS and healthy control groups in performance on this test, reflecting poorer complex attention in MS. Interestingly, interaction effects were present, with the primary progressive group performing better than the relapsing remitting group, and the healthy control groups consistently performing the best.

Mood Disorders and Cognitive Function Link
There have been a number of studies that have demonstrated increased risk for major depressive disorders and suicidal behavior in MS populations. The link between suicidality and...
MS was found to be seven and a half times greater than for the general population. Additionally, the lifetime prevalence of major depressive episodes has been shown to significantly increase in MS. Bipolar disorder may be higher in MS patients as well.

We also know that mood disorders have been found to correlate with cognitive dysfunction in multiple sclerosis, especially emotional dysregulation and disconnection or imbalance of perceived and displayed emotions. A study by Montel and Bungener shows primary progressive MS patients having less depression than relapsing-remitting (RRMS) or secondary progressive (SPMS) patients. This investigation used ANOVA modeling to demonstrate that RRMS and SPMS groups had significantly more depression than did the primary progressive group. PPMS patients also had less sadness, less irritability, less feelings of loss of control, and less psychic anxiety than the other groups; total anxiety scores were all lower in the PPMS group than in the SPMS and the RRMS groups. It may be that inflammatory events associated with relapsing MS may predispose these groups more to depression than PPMS patients, which have demonstrated fewer inflammatory markers on MRI.

**Summary**

Very little is known about treatments of cognitive dysfunction in any type of MS. Patients can be treated symptomatically, via disease modifying agents, stimulants, cholinesterase inhibitors, glutamate modifiers, and through cognitive rehabilitation. There are significant gaps in our knowledge related to cognitive function in MS patients, and how to slow or halt the decline. Understanding which treatment or combination of therapies is appropriate, and at what time, is key to understanding the entire dimension of this disability. Although some research is currently underway, new and more accurate studies of treatment need to be developed, particularly focused on PPMS patients. More research is also needed in depression, anxiety, and other mood disorders, to ensure that MS patients enjoy optimal quality of life.

**References**


**Discussion**

**Question:** Have you looked at cognition in correlation to PPMS patient age?

**Dr. Fred Foley:** There haven’t been any good neuro-psych studies done on aging MS patients and looking at an older cohort and seeing some of the neuro-psych studies of MS patients indicate profiles, patterns of cognitive changes, that look like an aging brain but at a much younger age.

**Dr. Andrew Goodman:** Patients with relapsing form always report more cognitive problems than patients with PPMS.

**Dr. Fred Foley:** That’s interesting. Ralph Benedict did a study attempting to find a valid self-report of cognitive dysfunction in MS. And it was a difficult project because self-reports of cognitive dysfunction in MS are confounded by depression.

Ultimately in this test construction project, he found an instrument that was more highly associated with significant others being able to detect cognitive changes in MS. But, MS patients themselves could not detect cognitive changes.

And he came up with an algorithm for scoring it that had very good specificity for the MS self-report group whereby you would either screen them for cognitive changes or depression, because then they would tend to have one or the other. But, that’s a big problem in self-reports of cognitive changes in MS. You have to account for depression.

**Dr. Andrew Goodman:** It’s just curious that there’s not really a lot of difference in the self report of depression and self reports of cognition.

**Dr. Howard Weiner:** Do you think there’s a cognitive test that you would recommend specific for the type of dysfunction you’re seeing, primary progressive versus other non-primary progressive MS?

**Dr. Fred Foley:** I think we have to avoid looking at only mean differences on single tests and we should look at clusters of tests, or cognitive patterns that may be able to discriminate between groups. If we have to go to a more subtle way of looking at that, I think we have to learn more about this data. This literature is extremely sparse in terms of what is happening cognitively in primary progressive MS and how different that may be from other types of MS.

The literature indicates that the processing speed in PPMS is a little bit better than secondary progressive or relapsing forms of MS. So, if I had to summarize the findings, it would really be in the processing speed arena.

**Dr. Howard Weiner:** My point is, if neuropsychological testing were going to be used, say a secondary outcome in a trial of primary progressive MS should be used, is that the PASAT?

**Dr. Fred Foley:** Well, it’s a good question. For example, using different scoring approaches on the PASAT may yield greater sensitivity to detecting changes. Looking at dyads or strings of correct responses, or looking at decreases in response accuracy over the 60 responses may be a better approach. Nonetheless, we still have much to learn about PPMS and cognition, as well as the optimal ways of detecting changes.
Clinical Trials in Primary Progressive Multiple Sclerosis

Daniel Pelletier, MD

Introduction

There are currently no approved treatments for primary progressive multiple sclerosis (PPMS); however, several investigative agents have been evaluated in four randomized controlled clinical trials (RCT) conducted within the last several years. Two trials evaluated beta interferon, a third assessed glatiramer acetate (PROMiSe trial), and the final trial focused on mitoxantrone therapy. Following is a brief review of each RCT.

Phase II RCT of Intramuscular Beta Interferon in PPMS

The first trial was a single center, double blind, placebo-controlled study of interferon beta-1a in 50 patients with PPMS. Patients were randomized to weekly intramuscular injections of 30 µg (n=15), 60 µg (n=15), or placebo (n=20) for 2 years.

This trial was designed based on this assumption of 67% progression over 2 years. The primary endpoint was time to sustained progression of disability for 3 months, defined as an increase of 1.0 point in patients with a baseline Expanded Disability Status Scale (EDSS) Score ≤ 5.0, or an increase of 0.5 point for patients with a baseline EDSS score > 5.5.

Secondary clinical endpoints included the timed 10-meter walk and the nine hole peg test (9-HPT). Secondary MRI outcomes include T2-weighted and T1-weighted brain lesion loads, cervical atrophy, cerebral and ventricular volume.

A total of 49 patients completed the two year study and analysis of the primary endpoint demonstrated no significant difference between the placebo and either treatment group. Of note, 48% of patients progressed as measured by the primary endpoint.

Patients treated with interferon beta-1a 30 µg had a lower rate of accumulation of T2 lesion load compared to the placebo group (p = 0.025). No effects on brain and cervical atrophy measures were observed.

These findings suggest that future studies of PPMS should be at least 2 years in duration, with an expected rate of progression of less than 67%. In addition, the sample size should be larger if conventional clinical or volumetric MRI outcomes including brain atrophy or cervical atrophy are to be evaluated.

Phase II RCT of Subcutaneous Beta Interferon in PPMS

This was a randomized placebo-controlled single center study of interferon beta-1b administered subcutaneously in 73 patients. There were 49 patients with PPMS and 24 patients with transitional MS, a progressive form of the disease characterized by the occurrence of a single attack prior to or during the progressive phase. Patients were randomized to subcutaneous interferon beta-1b 8 MIU or placebo every other day for 2 years.

The primary endpoint was time to sustained progression for 6 months. Sustained progression was defined as increases ≥ 1.0 and ≥ 0.5 on the EDSS for 6 months in patients with baseline scores of ≤ 5.0 and ≥ 5.5, respectively.

The results showed no significant differences in the time to 6-month progression between the treatment and placebo groups, although the proportion of patients with progression was lower in the patients on interferon beta-1b (27.8% versus 37.8%). Significant improvements in the MS functional composite (MSFC) score, T2 and T1 lesion volumes and number of new T2 lesions at 24 months were observed in the interferon beta-1b group relative to placebo. No impact on brain and cervical atrophy measures was observed.

These two studies with interferon beta were not associated with a significant reduction in disease progression. However, improvements in MSFC score and MRI outcome measures suggest that treatment with interferon beta may have beneficial effects in patients with PPMS.

Phase III RCT of Subcutaneous Glatiramer Acetate in PPMS (PROMiSe)

The PROMiSe study is the largest double-blind, placebo-controlled trial of patients with PPMS to date. This phase III randomized 3-year trial evaluated glatiramer acetate (GA) in 943 patients with PPMS.

This study was unique in that investigators enrolled patients within two strata of disability: patients with relatively low baseline EDSS scores of 3.0 to 5.0; and those with higher EDSS scores of 5.5 to 6.5.

The objective was to enroll 40% of patients in the low EDSS group with an expectation that 50% of patients would...
progress each year with a mean time to progression of 1.44 years; and 60% in the high EDSS group with the expectation that 20% of patients would progress each year with a mean time to progression of 4.48 years.

The primary endpoint was time to confirmed sustained progression for 3 months, defined as an increase of ≥1 point in patients with baseline EDSS scores of 3.0 to 5.0; or an increase of ≥0.5 points in patients with baseline EDSS scores of 5.5 to 6.5.3

Secondary endpoints included the proportion of progression-free patients, changes in baseline from mean EDSS and MSFC scores, change in number and volume of brain lesions on MRI, number of gadolinium (Gd)-enhanced lesions, volume of T1 hypointense lesions as a percentage of FLAIR-defined lesion burden, and brain atrophy.3

Importantly, trial investigators did not enroll the percentages expected in the EDSS group in the low ranges (40%) or the EDSS group in high ranges (60%); the actual proportions were 54% and 46%, respectively. This was designed to be a 3-year study based on calculations of the low and high EDSS ranges, with two interim analyses. During the second interim analysis (year 2), the data safety monitoring board decided to terminate the study when it was determined that the primary endpoint could not be met.3

The delay in time to sustained disease progression for 3 months in patients treated with glatiramer acetate compared with placebo was not statistically significant (Hazard Ratio, 0.87[95% CI, 0.71-1.07]; p=0.1753). Fewer GA-treated patients experienced sustained progression vs. the placebo group, but again, the differences did not reach statistical significance (GA-treated patients, 39.6% vs placebo treated patients, 45.2%).3

Post-hoc sensitivity analysis was performed in male patients to see if possible treatment differences could be discerned. The results showed that compared to placebo, there was a significant delay to sustained progression of disability in male patients treated with GA (Hazard Ratio, 0.71[95% CI, 0.53-0.95]; p =0.0193). Analysis comparing the percentage of progression-free patients in the treatment group (61.6%) to placebo (49.1%) also reached statistical significance (Hazard Ratio, 0.71[95% CI, 0.51-0.98]; p =0.039).3

Analysis of mean number of Gd-enhanced lesions demonstrated that the mean change from baseline was significantly lower (p = 0.0022) in the treatment group compared to placebo during the first year (Figure 1A). Analysis of mean T2 lesion volume change (Figure 1B) revealed smaller progressions in the GA group; however, the differences were only statistically significant in the second year (p= 0.0026).3

The results of the PROMiSe study suggest that PPMS studies should be at least 2 years in duration: with 3 years for phase III trials. In addition, if natural history data are used to derive sample size, a lower rate of progression and possible placebo effect should be expected; 50% progression on EDSS per year does not appear to be realistic in PPMS trials.

It is important to note that study investigators designed this trial with two EDSS ranges instead of one and a trend was observed. It may also be important to use outcome measures of 20% increase from baseline in timed tests such as the 9-hole peg test or 25-foot walk. Again, investigators detected a trend. These findings suggest that alternative primary endpoints

![Figure 1. Intention to Treat Analysis: MRI Data](https://example.com/figure1)
and additional outcome measures should be considered when designing clinical trials.\textsuperscript{3}

Results of this trial also suggest that predictors of increased risk of EDSS progression include positive cerebrospinal fluid (CSF), male gender, and higher baseline EDSS.\textsuperscript{3}

**Phase II RCT of i.v. Mitoxantrone in PPMS**

The fourth study is a double-blind, two-year multicenter randomized placebo-controlled trial of i.v. mitoxantrone (12 mg/m\(^2\) every 3 months) in 62 patients with PPMS. This study stands apart from the others discussed above in that all enrolled patients were required to be cerebro-spinal fluid (CSF) positive (2 or more oligoclonal bands, or increased IgG index or synthesis). The age of patients in the study was 18-65 years with an EDSS score between 3.0 and 6.5.\textsuperscript{4}

The primary endpoint of the study is sustained treatment failure on mitoxantrone versus placebo (assuming a 65% failure rate at one year) for 3 months using combined outcome measure of disability including worsening of EDSS, defined as $\geq 1.0$ points for patients with entry EDSS 3.0 to 5.0 or $\geq 0.5$ points for patients with entry EDSS of 5.5 to 6.5; or worsening of $\geq 20\%$ from baseline on best performance of 2 consecutive 9-hole peg test scores obtained with either hand.\textsuperscript{5}

Secondary endpoints include comparison of the proportions of treatment failures; comparison of change in z-scores of 9-hole peg test and 25-foot timed walk; and comparison of time to sustained 20\% increase on 9 hole peg test or 25-foot timed walk. Secondary MRI outcomes include measurements of T2 and T1 lesion volumes and brain atrophy.\textsuperscript{5}

Analysis of the primary endpoint, time to sustained treatment failure at 3 months, showed no significant benefit of treatment over placebo (p=0.38).\textsuperscript{5}

In addition, there was no significant benefit of treatment vs. placebo on secondary clinical endpoints. Analysis of time to sustained progression over 3 months as measured by EDSS demonstrated no significant difference between the groups. Similar analyses show no effect on 9-HPT. Trial results to date indicate no effect of mitoxantrone treatment on clinical outcomes. Statistical analysis of MRI data is not yet completed.\textsuperscript{5}

**Conclusion**

Clinical investigations of the primary progressive subtype of MS are confounded by a number of variables, including the fact that PPMS is, like MS itself, characterized by heterogeneity. Variables among the study population include mean lesion volume, ranging from very low to very high; the proportion of patients with Gd-enhancing lesions; and the presence or absence of cognitive impairment or positive CSF. In addition, study patients may experience attacks during the trial, leading to a change in diagnosis from PPMS to progressive-relapsing MS.

The real “nightmare” of clinical trial investigators relates to study design utilizing, often small, pre-existing natural history cohorts and evolving PPMS diagnostic definitions. The investigators look at the best available data before they design the study, but recruitment and clinical worsening are not as expected. In such cohorts, disability progression is often slower than anticipated, leading to erroneous expectations of treatment response.

How can these issues be avoided? Potential solutions include using the most current natural history dataset and definition of PPMS available for trial design, increasing the sensitivity of clinical and MRI outcome measures, and setting a suitable point to stop a study for interim analysis. Another option is to select patients with characteristics predictive of rapid disease progression, such as male gender, high EDSS, and positive CSF; however, the concern then becomes finding enough patients to enroll in the study and generalizing the results to all PPMS patients.

The resolution of these and other issues related to the clinical study of patients with PPMS is critical in advancing our knowledge of this complex disease and improving clinical care for affected individuals. o

**References**

Presentation of Group I Discussion

Discussion Leader: Paul O’Connor, MD

Dr. Paul O’Connor: We were charged with answering the following questions. First, is PPMS treatable? A minority of our group would use the detection of enhancing lesions on MRI as a trigger to use immunomodulatory therapy of one sort or another; interferon, glatiramer acetate and possibly steroids, possibly other immunosuppressive agents. We’ll come to that in a second.

We all agreed that in exceptional cases, for example a younger patient with very rapid progression of disability or an MRI with many enhancing lesions (many defined as a greater than five and certainly numbers like 10 or 15 were mentioned, not just one or two) so, many enhancing lesions or a young patient with very rapid progression in those situations, we would be inclined to treat with immunomodulatory therapies. And the therapies, again, could include anything from interferon to glatiramer acetate.

But, for these kinds of rapidly worsening patients, there is much more discussion of agents like mitoxantrone, cyclophosphamide, possibly natalizumab and possibly rituximab. So, as always in medicine, treatment has to be individualized to the patient and their circumstances.

Dr. Sean Pittock: Just a couple of points. I think if this potentially is going to be used by some as a guideline, if we’re going to say that a minority considered using immunomodulatory medications in the setting of a patient with primary progressive MS and enhancing lesions, whether or not we should give a sense of the number of enhancing lesions. If you’ve got one enhancing lesion or if you’ve got four enhancing lesions, that information might be helpful.

The other point would be that you don’t want to come across as being ageist. We all agreed about (being aggressive in) the younger patient. Should we add something like especially in the younger patient because, I suppose if you’re an older patient and you have five enhancing lesions and you have a rapid decline, you would probably consider it in those patients. Because, we tend to talk more about the younger patients because we want to be more aggressive, but we don’t want to exclude (older patients) necessarily.

Dr. Paul O’Connor: We don’t want to exclude them. We wouldn’t want to invite in older patients, I don’t think, to get high-dose cyclophosphamide or mitoxantrone unless they really look like they’re going to benefit from it.

Dr. Sean Pittock: Again, it’s only in the sighting of a very active looking MRI and a very rapid aggressive course.

Dr. Daniel Pelletier: Well, I think that the problem lies in our definition of primary progressive MS.

Dr. Kathleen Hawker: One of the interesting points we brought up in our group, and I think we’ll get into it, is talking about the neurobiology of the immune system in different age groups.

There is obviously a different immune reaction because these are older patients that cannot mount the severe inflammatory response as younger patients. Is this why we see the more aggressive disease typically in younger patients rather than in older patients?

Dr. Paul O’Connor: Yes

Dr. Kathleen Hawker: So, is this, actually, not necessarily totally disease related, but related to an aging phenomenon that we see in many other aspects, that older people cannot mount these large degrees of inflammation. This is why primary progressive MS looks the way it does as opposed to it being categorized as a different disease?

Dr. Paul O’Connor: It could be that age actually confounds everything here, and maybe gender a bit, too, is that men mount less vigorous autoimmune responses. And PPMS is equally common in men and women.

Dr. Kathleen Hawker: If you extrapolate out from the Queens Square data, there’s about 50 percent of patients who have gd lesions on their scans, at least early on. So, we’re saying, “Would you treat—would you do triple-dose gd? Would you scan people more frequently, early on?”

Dr. Paul O’Connor: So, this is coming up in terms of our monitoring.

Dr. David Miller: I think one thing that has emerged from that study is that there’s the caveat that triple-dose gadolinium was used. But, that probably doesn’t affect overall the number of patients that are active.

I think the important point about that study (Queens Square) was a clinically unusual group because they all had disease duration as five years. I think it might be the only study where the whole group had a short disease duration. The mean was three years.

There is a suggestion that they were more severe patients, as picking up the worst, the most rapidly progressing, and so they are diagnosed early. But, whatever reason, if you see someone with PPMS with short disease duration, there is a higher chance they will have active inflammation.
We felt that MRI would be used for the CNS. The rationale here is that, in progressive disease, immunomodulatory agents, especially those that penetrate we will find out in a few months. We discussed other treatment?

If the spine has not been imaged or if there is clinical evidence to make you think that some alternate diagnosis, like a neoplasm, is brewing in the picture, or when the patient is deteriorating unexpectedly quickly, which we put in to touch on the case of the very aggressively worsening patient.

So, MRI in this population was not something that we would recommend on an annual basis with a PPMS patient once the diagnosis is firmly established.

In terms of monitoring, we felt monitor clinically with ancillary lab testing as indicated, bladder ultrasound as an example. We did feel that there is overlooked need for doing more bone mineral densitometry tests in this population of middle-aged individuals, many of whom have impaired ambulation and in whom the rate of osteopenia, osteoporosis is actually quite high and tends to be overlooked. They tend to only be tested if they’re postmenopausal or if they’ve been on a lot of steroids, whereas, in fact, many in the population, as mentioned, are osteopenia or osteoporotic, and this is a very treatable condition.

We also mentioned vitamin D monitoring, as with all MS patients, because it tends to be low surprisingly frequently in this group.

The next question was, what is the future of PPMS treatment? And of course, number one may be rituximab. We will find out in a few months. We discussed other immunomodulatory agents, especially those that penetrate the CNS. The rationale here is that, in progressive disease, the disease has really taken root in the central nervous system, and eradicating it from the periphery doesn’t seem to take it out of the CNS.

In fact, if you look at the pathology of bone marrow transplant cases where the patient has died, and this is covered in a paper by Metz in Brain last year, in patients who have been transplanted and who had aggressive disease, the brain is jammed with microglia and macrophages even though the peripheral immune system has been completely wiped out.

So, it seems that, in aggressive disease and in long-standing disease, you need to get something into the CNS to more or less eradicate the unwanted activity that’s going on there.

I guess you could call it inhibiting the inflammation from the innate immune system, whose arm is the macrophages and microglial, and which is not greatly affected with conventional immunosuppressive drugs that we use in MS.

Now, what drugs do penetrate the CNS? Well, I don’t think rituximab penetrates into the CNS, but in small amounts, right? Most monoclonal antibodies have a hard time getting by the blood-brain barrier.

I believe fingolimod does penetrate into the CNS, and it is a putative treatment for PPMS. It’s just going to be a trial in PPMS. So, that’s something to think about as a potential future therapy.

A neuroprotective agent would be nice. We don’t have any yet, but we’re still looking. We have them, but only insofar as anti-inflammation causes neuroprotection.

A combination induction and maintenance therapy was mentioned in connection with treating PPMS. We feel this is an idea in general which should be used in the treatment of MS across the spectrum of disease types rather than treating patients in a weak way, but in a chronic fashion.

Remyelinating agents, again, we’d like to have.

Growth hormone was also mentioned. No data on this subject. But, you do hear anecdotal stories of people who are not actually sick who take growth hormone who report feeling much better. So, something to think about, an area where more research needs to be done on a symptomatic basis in MS patients.

As always, the approach in treating MS needs to be multifaceted. That means different drugs, different modalities of treatments, and not just drugs but rehab, neuro-psych and needs to fairly aggressive, with treating early being the motto.

And that actually is the end of the summary of our discussion. Thank you.
Presentation of Group II Discussion

Discussion Leader: Jeffrey Cohen, MD

Dr. Jeffrey Cohen: We framed our discussion largely around considerations for designing future trials in primary progressive MS. Although having done that, I think we largely touched on all the same topics that you just heard from Paul. So, I’m not going to recapitulate everything that you just said, but rather highlight our main conclusions and places where we may have differed from what you concluded.

We started our discussion with some general points, which are the fundamental issues we’ve been grappling with this weekend, which include whether primary progressive MS and relapsing forms of MS represent fundamentally different disease processes or just represent different ends of the spectrum of the same disease, in other words, patients that exhibit different features to greater or lesser extents.

A related issue is whether the mechanisms of progression in primary progressive MS are the same as occur in other forms of purely progressive MS, such as late secondary progressive MS without relapses.

And then third, it still remains unclear what the basic mechanism of the gradual progression is in those purely progressive forms of MS. We didn’t solve those questions, and I guess that’s probably what Dr. Vollmer is going to talk about.

So, we went through the various aspects that one would have to consider in designing future clinical trials. The first question would be what treatments to try, and we had similar discussions (as compared to Group I).

So, it has become fashionable to consider the gradual progression in purely progressive MS as being degenerative, in other words suggesting that it’s non-inflammatory mediated. However, it was pointed out in our group, as in yours, that there are several lines of evidence of continued inflammatory mechanisms in purely progressive MS, although the nature of that is different than what we’re used to describing in the relapsing forms of MS. In other words, the mechanisms look to be predominantly involving innate immunity.

As a result, it’s not surprising that the sorts of agents that are effective in relapsing forms of MS are not effective in purely progressive MS, suggesting that we need to test other things. So, we are also anxiously awaiting the rituximab results in our group, and noted that a study of fingolimod is about to get started in primary progressive MS.

But, unless those pan out, future therapies that are immunologically oriented would probably have to be targeted versus innate mechanisms rather than adaptive immune mechanisms.

Again, there has been a lot of discussion of the potential utility of neuroprotective agents, although at this point we don’t really know what those would be, and similarly, repair mechanisms.

And then finally, as you discussed in your group, other restorative approaches such as potassium channel blockers, and rehabilitation approaches will be important to test and to formally demonstrate their benefit.

In terms of design, one has to be careful to distinguish whether you’re talking about a phase two early proof of concept study or a phase three definitive pivotal design. And really at this point, based on the number of meetings I’ve had the pleasure of attending, discussing the ways of doing neuroprotective or regenerative approach strategies, early studies in that.

And to address that question, it really remains problematic how to design a small proof of concept study to test something that is either neuroprotective or regenerative or, in the case of primary progressive MS, something that would not be expected to have a prominent effect on relapses or in a disease setting which you could not follow relapses or enhancements on MRI.

In contrast, even though there are some issues, I think we have a pretty good feel for how to do a phase III pivotal trial in primary progressive MS.

In terms of outcome measures, we do have several clinical outcome measures now, with which we have substantial experience. We know how to estimate sample size and duration, although we’ve been somewhat overly optimistic in many of our recent trials. We know how to implement those endpoints from a practical point of view in multi-center trials. We know how to analyze them statistically. We have a fairly good sense of how to do a phase III pivotal trial in primary progressive MS.

And in terms of MRI, we also discussed how one would do that. The standard MRI measures, as we noted, are feasible and may show some benefit. In other words, there are a small number of enhancements in trials and relapsing in primary progressive MS. There is lesion activity.

However, the relevance of those to the disease is less than in relapsing MS. Brain atrophy was noted to be a good com-

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promise between sensitivity and prior validation and feasibility, although it has a relatively gradual course.

And then, we focused some attention on newer methods that were discussed earlier in the day, including diffusion tensor imaging and tractography, magnetization transfer imaging and, in particular, gray matter atrophy. Those measures seem to be relevant and are increasingly being validated, but there are substantial practical and feasibility issues in implementing those in multi-center clinical trials.

In particular, we discussed that gray matter atrophy, which appears to be very attractive as an endpoint, had substantial practical issues.

We also discussed that novel imaging approaches may be of interest in primary progressive MS, in particular ways of imaging the innate immune mechanisms that appear to be important, such as microglial imaging or macrophage imaging.

One would also want to include other outcome measures that would be important such as the potential utility of OCT, issues regarding cognitive function in MS in general and in primary progressive MS in particular, and patients’ self-report on health status and quality of life.

The next issue was, how would one select studies for this trial? We noted that there were a number of factors that seemed to suggest increased risk of progression. And those include shorter disease duration, a younger age, male sex, pre-study worsening on clinical outcomes. In particular, the MSS looks like it may be a useful thing to incorporate into trials. Other elements to include are intrathecal antibody production, abnormal gray matter diffusivity and magnetization transfer.

We hoped that some of the genetics and antigenic array studies that were talked about, which seemed to be very promising, will help us select patients that are likely to maintain a primary progressive course and likely to have active disease in the course of a trial. But, those are, at this point, not ready.

And then, to distinguish that, one would also want to have factors that would increase the likelihood that the patients in the trial would respond to the treatment being tested. And these factors, at this point, are largely unknown, but in part overlap some of the same factors that predict activity including, at least from some of the trials, male sex, younger age, shorter disease duration, and the presence of intrathecal antibody production.

In general, we noted that many of these features are aspects of primary progressive disease that point towards a relapsing disease type phenotype. So, it just illustrates that our definition of this disease is largely empiric. And the things that we’re looking for in regard to success in treatment, as you discussed in your group, are the things that make the person not having typical primary progressive MS as we conceive it.

Now, just a few words about the presence of intrathecal antibody production. We noted that, in fact, we lumped together IgG index and oligoclonal bands and perhaps free kappa light chains as demonstrating this. But, at this point, we really don’t know whether those three factors have different meanings. That study has really not been done.

But, the purposes of testing for and demonstrating the presence of intrathecal antibody production in primary progressive MS would be, first of all, it increases the diagnostic likelihood that the person in fact has multiple sclerosis. There are several lines of evidence that suggest that it increases the risk of worsening. And then, finally, it may increase the likelihood of response to therapy.

And in general, I think our group supported at least analyzing CSF, although we had some disagreement about whether one should require CSF to be analyzed for a trial, and/or whether one should require the presence of intrathecal antibody production. It would be a tradeoff of utility versus practicality.

We were asked to answer, whether there is an early inflammatory phase in primary progressive MS that then evolves to a less or different inflammatory phase, as in relapsing forms of MS. Even though there are some lines of evidence that suggest that, we really couldn’t answer the question.

Nevertheless, I think the general conclusion was that early treatment would be desirable, particularly if the mechanisms evolve to become less responsive to therapy. Even if the mechanisms don’t evolve, they may be more ingrained later on. And then, third, earlier in the disease, people have less permanent tissue damage and are more likely to benefit.

That led to our final question, which was the desirability of early diagnosis. And there are many clinical trials that have illustrated that there is a prolonged interval between the onset of symptoms in retrospect and the diagnosis longer than in relapsing forms of the disease. And there are several obstacles to diagnosis, which include its insidious subtle onset and progression; the fact that the symptoms, initially, may not be recognized as being neurological; and the fact that the MRI changes are less prominent. And there is a somewhat broader potential differential diagnosis than there is for typical relapsing remitting MS.

Dr. David Miller: If someone has a progressive, cerebellar type of brainstem syndrome, it’s probably worth always doing cord imaging.

Dr. Jeffrey Cohen: I think probably somewhere in the outcome, we need to emphasize that cord imaging is particularly important in primary patients in whom you’re considering primary progressive MS.

Dr. Paul O’Connor: Thank you for your discussion and presentation, Jeff.
Introduction

Are secondary progressive multiple sclerosis (SPMS) and primary progressive multiple sclerosis (PPMS) the same disease? This is a challenging question and one that gives rise to a broader inquiry: do PPMS, SPMS, progressive-relapsing MS (PRMS) and relapsing-remitting MS (RRMS) represent separate diseases or various points on a spectrum of a single disease called MS? The current diagnostic categories, or subtypes, of MS, provide information pertaining to the prognosis and treatment of the disease although it is unclear if they tell us anything about its underlying cause or biology. The answers to these questions have important implications for patient education, treatment, and study design.

A current hypothesis states that MS is a mixture of different diseases with overlapping phenotypes and the null hypothesis is that MS is a single disease with variable phenotypic expressions secondary to background genetic and environmental factors. The following will examine which of the two hypotheses is best supported by current data.

The Role of the Immune System in MS Pathophysiology

The current theory of MS postulates that the disease is driven by memory Th-1 cells present in the circulation generated by epitope mimicry that periodically migrate into the brain, are presented with central nervous system (CNS) antigens thus cross-recognizing CNS antigens stimulating the now auto-reactive T-cells, unleashing a cascade of events that includes recruitment of macrophages, microglia, dendritic cells, and B-cells thus initiating an auto-aggressive attack on the CNS.

The T-cell is a central player because it can receive antigens from a variety of cell types, including antigen-presenting B cells. Surface immunoglobulins allow specific B cells to recognize and process corresponding antigens for presentation to T cells. This process is highly effective; B cells being much more efficient as antigen-presenting cells (APCs) than macrophages and dendritic cells for their target antigens.1

The persistence of these highly efficient B cells in the inflamed CNS of a patient with MS may drive the disease process to a substantially greater extent than do other antigen-presenting cells. There is no antigen specific memory T-cell population in the human CNS that is relatively stable over large periods of time, unlike B-cell populations in the MS brain which produce the same isotype and the same idiotype of antibody for years, and possibly decades.2

This suggests that the driving force behind MS may be a T-cell/B-cell pair, in which T-cells and B-cells interact and support each other in a vicious cycle that triggers a cascade of events and the recruitment of other effector mechanisms and leads to a burst of information that we detect as gadolinium-enhancing disease.3 Further, this scenario suggests that if the B cell populations resident in the CNS are producing antibodies directed to CNS antigens, then they can activate naive T cells crossing the blood brain barrier nonspecifically (such as during a systemic infectious event) and promote them down a memory T cell pathway such that autoaggressive T cell populations in MS are intermittently being generated in the CNS. This would explain the relationship between systemic infectious events and subsequent relapses in MS and the lack of clinical or MRI efficacy in studies done to date with anti-CD3 and anti-CD4 monoclonal antibodies.

Primary and Secondary Neurodegeneration in MS

Neurodegeneration in MS could be either a direct consequence of the inflammatory attack on the CNS (secondary neurodegeneration) or it could be an independent process not dependent on ongoing inflammation (primary neurodegeneration). In the case of secondary neurodegeneration, theoretically, a highly effective immunological therapy would also ultimately halt the neurodegenerative aspects of MS.
Therefore, other than the effects of aging, a fully effective local immunotherapy may be curative from the standpoint of disease progression.

Axonal loss may be due to several pathological processes. The inflammatory attack mediates cell-mediated cytotoxicity, antibody-mediated cytotoxicity, tumor necrosis factor (TNF) toxicity, changes in calcium fluxes and glutamate toxicity, all of which can directly transect axons or lead to secondary neuronal loss. Uregulation of TNF and iNOS in activated astrocytes and glia cells most likely plays a role in ongoing neuronal death.4

There also are some indirect effects of inflammation that appear to persist after the T-cell/B-cell process has stabilized and damage to the nervous system may activate a series of secondary causes of axonal loss.

The initial loss of myelin that is characteristic of this disease may eliminate the vital trophic interactions between myelin and axon and ongoing axonal death has been shown to occur in dysmyelinating models in animals.5 Related to the loss of the myelin sheath may be a delay in both fast and slow axonal transport. This slowed movement of structural proteins from the cell's soma to the synapse, particularly in axons connecting pyramidal neurons in the cortex to the lumbar motor neuron pool, may eventually interrupt the integral function of the synapse, and due to a loss of the synaptic connection, the neuron and its network of interconnecting neurons may be deleted from the CNS.6

The axonal loss can be compounded by the naturally occurring loss of neurons and neuronal function occurring during the normal aging process.7 In the healthy nervous system, there appears to be substantial redundancy and reserve capacity but in MS the reserve capacity in the brain and spinal cord is overwhelmed by ongoing subclinical inflammatory injury characteristic of MS, causing a premature deterioration in neurological functioning due to lack of adequate neuronal numbers and connectivity to support the needed cortical remodeling and adaptation that appears to be the major mechanism for recovery of function in MS and preservation of function in early MS and ultimately the aging nervous system.

Although remyelination clearly occurs in the early phase of MS, ultimately chronic MS plaques are characterized by persistently demyelinated axons. Studies of dystrophic axons in chronic MS demonstrated a lack of remyelination despite the presence of premyelinating oligodendrocytes in the lesion.8

Finally, genetic variations can affect an individual's ability to repair the brain. Thus multiple processes secondary to the inflammatory attack on the CNS may drive progression, inflammation, neuronal loss and demyelination leading to a loss of normal neuronal function as well as a failure of remyelination. Thus, the most effective approach to alter these secondary processes is most likely to halt the immune attack on the CNS in MS as early in the course of the disease as possible.

**Early Progression in MS**

The processes underlying progression in MS are set in motion years before the patient is declared progressive. Studies have shown a decrease in cerebral N-acetylaspargtate (NAA) to creatine (CR) levels, an index of axon integrity on magnetic resonance spectroscopy; magnetization transfer ratios (MTR) are decreased and significant clinical atrophy is noted in the gray matter of MS patients with early disease (CIS and RRMS) as compared to normal controls.9

Similar changes such as increases in normal appearing white matter (NAWM) and normal appearing gray matter (NAGM) T1- relaxation times (RT) mean and peak location, and significant decreases in NAWM and NAGM peak height have been observed in patients with early PPMS, suggesting that a process of progression is occurring throughout the CNS from the onset.10

The changes seen on various forms of imaging may represent a subclinical inflammatory attack on the nervous system in the majority of early disease, indeed less then 10% of gadolinium enhancing lesions are associated with new clinical signs. The subclinical lesions affect multiple areas in the central nervous systems, and since most systems have built-in redundancy, compensatory mechanisms are set in motion. Over time, as these mechanisms fail, a gradual loss of function will occur in multiple systems and become clinically evident. The adaptive processes that occur in response to the disease are ongoing and most likely will mask symptoms early on in the course. Thus, progressive disease may follow a loss in the adaptive potential of the brain to mask the subclinical disease activity. If one considers that in both PPMS and SPMS extensive portions of the cortex and white matter are injured, it seems intuitive that eventually the brain will no longer have sufficient neuronal reserve to recover from the continuous inflammatory assaults.11 The effect on some systems may be more apparent, based on the outcome and the tool used to assess the patient. Once this point is reached, treatment will have only a modest effect as we cannot fundamentally change the course of this disease.

**PPMS: Is it a Distinct Entity?**

Several clinical characteristics believed to distinguish RRMS/SPMS from PPMS include age of onset, sex ratio, reported level of cognitive dysfunction, and presence of motor symptoms at initial presentation. However, based on data from the North American Research Committee On Multiple Sclerosis (NARCOMS) Project, both the PPMS and SPMS patients progressively get worse over time, with little difference between the groups, and by the seventh and eighth decades,
most were using canes or bilateral support. Bladder dysfunction was shown to slowly worsen with age in both groups, suggestive of the presence of a spinal cord process consistent within each subgroup. Fatigue increased at an earlier age in all groups, then remained relatively stable over the course of the disease. Depression was increased at an early age in patients with PPMS and SPMS and cognitive dysfunction followed a similar course; increasing early and remaining relatively stable over time with a slightly higher incidence in the SPMS group. The only symptom that showed a significantly higher level of disability in SPMS than PPMS was visual dysfunction, although the magnitude of differences between the groups was relatively small.

Other Factors

There may be several genetic factors that distinguish PPMS from SPMS. It has been reported in small studies that IL-7 receptor mRNA expression in blood is decreased in PPMS compared to secondary progressive or relapsing disease and DR6 associated with DR2 haplotype may be more common in PPMS.

Immunological characteristics such as higher levels of E selectin and anti-ganglioside (GM3 and GQ1b) antibodies in PPMS may also distinguish the two forms of MS. PPMS may have less reactivity to PLP 184-209 and less inflammatory infiltrate in the CNS. However the studies are small, have not been reproduced and some studies reporting other abnormalities (serum anti-glycan antibodies) are contradictory in nature.

Other studies examined serum levels of adhesion molecules and immune cytokines associated with inflammation in patients with PPMS and SPMS, and found similar levels in both groups. These findings confirm the existence of an inflammatory component in both PPMS and SPMS.

The theory that PPMS is not an inflammatory disease is based on differences in gadolinium-enhancing lesions and total burden of disease detected in MRI studies. However, this theory is not supported by data; studies of the blood and CSF indicate that the same biology underlies both PPMS and SPMS, although possibly with quantitative differences. The observed variations are consistent with analyses of two different ends of the same disease spectrum, modified by factors such as genetics, age, and environment that alter the phenotype, rather than two distinct diseases.

This theory may be explained by the variations in the clinical manifestations of MS, which are to be expected even if the disease represents a single entity. To illustrate, we can assume that the brain and spinal cord encompass 85% and 15% of the CNS, respectively. Now consider a population of 100 patients with MS, each with 20 T2 lesions. What is the statistical variation in the number of spinal cord lesions in that population? If the lesions were randomly distributed, less than 5% of the patients in this population would have 6 or more lesions, which potentially represents the patients most likely to experience disease progression.

The next simulation uses Poisson distribution to determine the probability that a patient would remain free of an acute clinical relapse despite the presence of ongoing inflammatory disease as represented by various lesion loads. This model employed an average rate of lesion accumulation ranging from 5 to 15 per year, with a threshold for relapse of 20 T2 lesions in any one year, with an objective of determining the percentage of patients who would be relapse-free in 10 years. Based on these criteria, all patients in the first decade are relapse-free because none reach the target threshold. When the average rate of lesion accumulation over 10 years reaches 8 lesions, the percentage of relapse-free patients begins to decline.

Do varying rates of lesion accumulation between patients explain the pattern of clinical relapses and the onset of progressive disease over time? Assuming that new lesions forming in the brain have a certain probability of being clinically apparent at a given time as an acute relapse, a large proportion of patients might live for several decades without a relapse or remain relapse-free simply because of the stochastic nature of the lesions and their relation to clinical symptoms of a relapse. Accordingly, the fact that some patients have primary progressive disease and others are aggressively relapsing-remitting in phenotype does not confirm the presence of two distinct diseases but could be a consequence of varying rates and locations of lesion accumulation.

Four factors appear to determine whether an individual lesion leads to acute or chronic symptoms. The first is the frequency at which patients develop new lesions; the more lesions they accumulate, the more likely they are to present with clinically evident disease because there is a greater likelihood over time of involvement of a clinically eloquent area of the CNS. The second is the aggressiveness of the inflammatory process (e.g. how destructive is it to axons and neurons), and the third is the inherent ability of the nervous system to repair itself. The fourth is early involvement of eloquent areas since serial MRI studies demonstrate that previously injured areas in the MS brain are the preferred target for future inflammatory events, a process possibly due to up regulation of adhesion molecules in the associated vasculature.

Thus, the patient with frequent, highly destructive lesions in eloquent areas in a patient with a CNS that has very little ability to repair itself, will have the most aggressive disease. Conversely, the patient with relatively few, less destructive lesions localized in the deep cerebral white matter and a CNS with a good ability to repair itself may never develop significant disability over time.
Conclusion

The findings presented suggest the following model for MS. First and most importantly, MS is probably a single disease, but with various phenotypes. Simply stated, this disease starts at a young age and progresses into old age. Younger patients are more likely to have relapses and older patients are more likely to be progressive. This may be explained by early subclinical disease destroying the cognitive reserve that underlays the cortical remodeling that masks early disease but ultimately fails due to neuronal loss.

Inflammation may decline over time. Neurodegenerative changes, present from the beginning, are masked during the early phase by recovery processes that adapt to ongoing injury as well as neural redundancy. Over time, a loss of neural reserves occurs that results in the onset of progressive disability. Therefore, acute inflammation predominates early in the disease; with superimposed clinical relapses occurring dependent on the degree of inflammation, while progression is minimal early in the disease and increases over time, clinically predominating later in the course of the disease in all clinical subtypes.

To date, the bulk of the data suggest that PPMS patients are going to respond in a similar way to treatment regimens as compared to SPMS patients. While the above model cannot be proven, it offers a fair representation of the data.

The issue then becomes whether it is appropriate for us to continue to treat primary progressive disease as a process that is distinct from secondary progressive disease. If not, then clinical trials could include both primary progressive and secondary progressive patients, with an analysis stratified on the clinical subtype and the degree of inflammation seen on the MRI findings, which could substantially decrease costs for the clinical subtype and the degree of inflammation seen on secondary progressive patients, with an analysis stratified on then clinical trials could include both primary progressive and that is distinct from secondary progressive disease. If not, to continue to treat primary progressive disease as a process be proven, it offers a fair representation of the data.

References

Controversies in PPMS with Timothy Vollmer, MD—Discussion

Timothy L. Vollmer, MD, FAAN

DISCLAIMER: The following discussion has been edited by the co-chairs, Drs. Kathleen Hawker and Paul O’Connor.

Dr. Anne Cross: I’ll suggest not necessarily alternative, but just additional factors that might play in here in, which is how much repair capacity there is? For example, how many oligo precursors are there? How much remyelination occurs? Because in looking at human MS autopsies, some patients have a lot of remyelination and others don’t. And denuded axons supposedly are more vulnerable to all these toxic factors in the milieu, so that may also play a role as well as.

Dr. Tim Vollmer: Yes, I agree with you. And I need to add that to the list of factors related to progression, because that would be a resistance factor. And this would probably be a good thought as to actually building another table of things that resist progression versus those things that actually promote progression.

Dr. Amit Bar-Or: I like the idea of perhaps we can be more efficient if we consider the pros and cons of lumping together PPMS and SPMS in trials. Although, do we, as of today, think of relapsing-remitting MS as one pathophysiology that we want to target, or do we recognize that there may be different patients with relapsing remitting MS who would benefit from different focused immune therapies, depending perhaps on their stage of disease, of relapsing remitting on the predominant problem that they have, and so on.

And if we think of a consensus statement regarding PPMS and SPMS, or recognize perhaps that in PPMS there may also be heterogeneity? Just like we would recognize in RMS, it’s not entirely homogeneous.

Dr. Tim Vollmer: No, I don’t agree with you. The assumption that you’re making is that, because somebody has gadolinium-enhancing disease that indicates they have a different biology. And in the literature I read, of the patients who have primary progressive disease had gadolinium-enhancing disease were the ones most likely to have gadolinium-enhancing disease and follow-up scans, so, from your standpoint, yes. But, the assumption then that they are more likely to represent a distinct group from those who do not have gadolinium enhancement ignores two things. One is that gadolinium enhancement is just the tip of the iceberg. The lack of gadolinium enhancement doesn’t mean there’s inflammation. It means there’s not enough blood-barrier breakdown in that particular sequence for us to pick it up. And the evidence, as you know, is triple-dose gd or MT enhanced gd or delayed gd, so that we can move down.

The second point then that they are more likely to represent a distinct group from those who do not have gadolinium enhancement ignores two things. One is that gadolinium enhancement is just the tip of the iceberg. The lack of gadolinium enhancement doesn’t mean there’s inflammation. It means there’s not enough blood-barrier breakdown in that particular sequence for us to pick it up. And the evidence, as you know, is triple-dose gd or MT enhanced gd or delayed gd, so that we can move down.

The second point is that, in the studies looking at immune markers in blood and CSF in primary progressive and secondary progressive, they don’t identify any differences.

Dr. Amit Bar-Or: They don’t identify average differences. So, again, I’m curious as to whether those in whom there were differences, 40 percent, are the ones who also have the tendency for more gd, etc., and you’re nonetheless left with a
potentially substantial portion of the PPMS who do not have all of those inflammatory markers.

Now, I’m also quite comfortable with calling it all the same disease from a nosological point of view. But, at the end of the day, we’re interested in therapeutics that are going to be best for those individual patients. And if there is a subgroup of people that we can all comfortably say are PPMS, that you’re going to treat this way versus that way, that is an important distinction to make.

**Dr. Tim Vollmer:** Yes. And I think we’re saying the same thing, is that they’re—even though I’m being rather dogmatic here to make a point, the reality is, is that what I see as MS in the clinic does include some patients—not very many, but some patients that really look like they have a different disease. We need to work that out.

These are the patients with very small ditzels scattered throughout their brain, negative CSF for bands, and yet meet the other criteria and we don’t have a vascular cause and other things. So, it’s not that we may not find that there’s a different biological process, a different disease that we currently call MS, but the data would suggest it’s actually not the majority. It would be the exception, not the rule.

Having said that, I agree with you, just like any other disease, that the therapy that you might want to use may not depend on the fact that they have X diagnosis, but where are they at in the course of that? What other concomitant illnesses are there? What other factors are there?

So, yes, we may want to stratify patients based on clinical characteristics for a study, but I think that right now stratify them based on the nomenclature that we use, which was based on a survey, doesn’t make a whole lot of sense.

Stratifying them based on the fact that we think that they have no reserve capacity and are going to progress because of these secondary changes, and treating them, specifically looking at outcome, I think that probably does make sense comparing them to, say, patients with early relapsing disease where an anti-inflammatory therapy may itself be sufficient. You may not need anything else. We know from clinical work that most patients, not all patients, but most patients when they present to us will already have had evidence of some attacks in the brain. The brain will be abnormal. That makes it the easiest ones to see.

Is there a group that continues to have gadolinium enhancing lesions, or are these transitional patients that have less gd that are going into a later phase?

It will make a huge difference when we plan trials because, obviously if we have the late stage of a later disease, it may be less amenable to some treatments whereas, if we get them in the transitional phase, we may be able to alter things.

**Dr. David Miller:** I think it will certainly be interesting to follow-up with these patients and see if one can identify individual trends in groups. Although, one of the rather striking things in following individual patient imaging is how things fluctuate over time. And, people can have an active year with quite a lot of disease, and then two years of very little, and then become active again.

So, that complicates the analysis because of this considerable in-trial subject variability that’s going on underlies the disease. And I guess that also reflects our clinical experience of patients’ disease as well.

I think as a general observation in terms of MRI activity measures, gd-enhancing lesions, big increases in lesion load, is that it tends to correlate well clinically, fairly consistent years being in a relapsing phase of the disease, whether it’s relapsing remitting or relapsing secondary progressive.

And where, on the other hand, you see much less in the way of activity is in non-relapsing secondary progressive MS and in well established long disease duration primary progressive MS.

So, I would tend to make this split more between whether someone is in a relapsing phase of the disease.

**Dr. Tim Vollmer:** Thinking about that, this particular process, we talked about the development of that intracranial persistent inflammatory process.

Maybe in primary progressive, what we’re seeing is just that this is occurring earlier with relatively little of this, that, early on, they develop this intrinsic slowly progressive process. And that’s why we don’t see the gadolinium enhancement or the bursting activity. And it will be interesting to look at that from a pathological standpoint. It certainly would be consistent with your reports of early changes diffusely in the patients.

I think that this is just like type 1 diabetes, in that the expression of the disease can be buffeted by quite a few different things. It doesn’t necessarily mean that the initiating event is fundamentally different. It may be, but it doesn’t necessarily mean that.

And my only point being is that, when we think about it right now, my sense is we’re actually slowing our progress and harming our patients potentially by stratifying the patient’s diagnosis automatically.

So, I would have argued that, in the rituximab study, that it would have made as much sense to enroll the secondary progressive patients as the primary progressive patients there, power it up enough to do a subset analysis to stratify to get to that point.

**Dr. Paul O’Connor:** So, Tim, what do you think of the notion that people with PPMS are simply those people who have MS who don’t have a vigorous enough autoimmune tendency to mount relapses in the early years when they latently have the disease?

**Dr. Tim Vollmer:** Yes, my sense is that the relapses are related to this particular immune process, is that those auto
reactive cells that you keep identifying in the peripheral blood migrate across a specific place. They set off a cascade of events and get this bursting inflammation that can be relatively dramatic, if it’s in a critical area. So, a pathway that’s relatively focused, then it can have a big impact on one’s system and become obvious, optic nerve, spinal cord, motor, etc.

But, most of the lesions that are down in the deep white matter, in that area, fibers from different systems are all mixed together there. So, any given lesion on the periventricular white matter is not likely to be clinically that apparent because it’s going to affect a large number of systems to a relatively small degree.

So, again, I think, it’s location, location, location for that, but it’s this process, not this one that’s causing the relapses.

Dr. Paul O’Connor: Right. But, if you’re not prone immunologically to have a big bursting attack you may not feel anything.

Dr. Tim Vollmer: Yes, exactly. And it may be that the exact nature of this, for example the presence of complement-fixing antibodies or possibly the amount of cytotoxicity that the cells can mediate in the brain may be important. So, if that were the case, you can have variations in that.

Some patients that don’t have complement-fixing antibodies or don’t have a particularly aggressive cytotoxic attack, and so this would be relatively unapparent, but it would still lead to this, ultimately, and this then would become the dominant pattern for them.

Dr. Sean Pittock: Tim, I’ll ask two questions: one maybe you can’t know in advance are who will be drug responders and non-responders in studies and whether that has any relevance to discretion of whether that if we can get that information, would that be helpful? And two, can you comment on the issue of pathologic heterogeneity.

Dr. Tim Vollmer: Well, in terms of the drug responders—non-responders, I think the term non-responders is a difficult one. Partial responders or inadequate responders might be a better way to think about them.

In terms of the variation in pathology, again, I don’t know. But, just like with the Guillain-Barre scenario, the pre-existence of anti-ganglioside antibodies that otherwise are not pathogenic in and of themselves have a dramatic impact on the phenotypic presentation of AIDP when it occurs in those patients.

So, there’s no reason why that couldn’t be the case here, and that those patients that we see that have type two pathology, for example, it might not just be because of the attack on the nervous system, but because of their environmental effects and antibodies or T-cell reactivities they’ve developed elsewhere.

Now, I don’t happen to think epitope mimicry is the basis for MS. But, epitope mimicry could certainly modify the expression of MS, even if it was initiated by an intra-blood-brain barrier primary event.

Dr. Andrew Goodman: Tim, I think this hypothesis (on Dr. Vollmer’s slide) seems to me does largely account for a lot of the spectrum of variation that we see for almost everybody with MS.

But, I’m still not sure. I may agree with you that we are, perhaps limited by these categories. But, I still have the question that non-relapsing MS may be a better category.

But, I’m just wondering whether there still isn’t a small group of people, perhaps mostly men, fifth decade and on, for the kind of myelopathic disease that doesn’t fit. Is that not the same as the non-relapsing version of the classic MS?

Dr. Tim Vollmer: There may be rare groups, and maybe the proteomics and genomic approaches are the way to sort those out with appropriately designed groups.

Dr. Andrew Goodman: It’s 25 years ago that Steve Hauser and Howard Weiner published their paper on cyclophosphamide in what was called chronic progressive MS. And they made the point that the key thing was to identify people in this transitional phase and hit them hard with ACTH, actually, and cyclophosphamide, and that was the key to preventing the progressive phase of MS.

Dr. Kathleen Hawker: If you take a look at families where you have relapsing-remitting and primary progressive, is there an age of onset difference in the primary-progressive in those groups?

Dr. Paul O’Connor: So, we have some of the Canadian database and if it’s within a family, the age of onset is associated with the type of MS. So, if it’s relapsing-remitting, it begins in the 20s and 30s. But within the same family, if it’s primary progressive, it would be into their 40s or 50s.

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