The Changing Face of Multiple Sclerosis and Disease-modifying Therapies

a report by

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Introduction

For more than 200 years, multiple sclerosis (MS) had been identified as a mysterious disease with no treatment. In the last decade, the understanding of the disease has expanded dramatically and five treatments are currently US Food and Drug Administration (FDA)-approved as disease-modifying therapies (DMTs). While the pathogenesis of MS is not completely understood, environmental factors (such as infectious agents), genetics and hormonal influences, as well as an immune system dysfunction, have been implicated.1

A Reappraisal of the Definition of MS

The definition of MS as a ‘relapsing-remitting disease of myelin secondary to inflammation’ has been challenged. Currently, most MS experts believe that a combination of inflammation and ‘apoptosis/degeneration’ processes produce continual (not relapsing-remitting) disease activity in the brain, even between clinical attacks. This concept implies that, when the patient is clinically stable, brain damage continues. Most patients who present initially as relapsing-remitting MS (RRMS) therefore eventually transition to secondary progressive MS (SPMS) within 10–20 years of their initial symptoms beginning.2 Furthermore, in addition to myelin damage, axons and neurons are also destroyed, often early in the disease course.3

Some scientists have data that indicates that MS may not be a ‘disease’, but a ‘syndrome’ that comprises four distinct pathological disease processes.4 This new research complicates the MS definition but may help to explain some of the variability in drug trials.

The demonstration of early and severe damage in the central nervous system (CNS), along with early cognitive dysfunction, has led to a recommendation for early and aggressive treatments. Patients with clinically isolated syndromes (CIS) and relatively normal examinations may therefore begin therapy if they have evidence of on-going clinical or magnetic resonance imaging (MRI) activity that indicates MS.

Disease-modifying Therapies

Currently, four immunomodulating drugs and one immunosuppressive drug are approved by the FDA for the treatment of MS. Most are indicated for patients with RRMS or early SPMS with relapses. Three therapies are interferon betas (IFNβ), including Betaseron® (IFNβ-1b), along with Avonex® and Rebif® (IFNβ-1a). Copaxone® (glatiramer acetate (GA)) is also immunomodulating, but is not an interferon. Novantrone® (mitoxantrone), an anti-neoplastic drug, is the only approved immunosuppressive agent in MS.

IFNs

Betaseron and Rebif are the higher dosed IFNβs and are given subcutaneously every other day or three times per week, respectively. Avonex, the lower dosed IFNβ, is given intramuscularly once a week. All IFNs are FDA-approved for relapsing forms of MS based on clinical and MRI data. All IFNs may have side effects including injection site reactions and flu-like syndrome. Auto-injectors as well as gradual dose escalation and the use of acetaminophen or ibuprofens before each injection when the drugs are initiated have reduced these adverse events dramatically. Blood chemistry changes such as anemia, decreased white blood cell count and/or elevated liver function tests are seen occasionally, but can usually be managed without discontinuing treatment; however,

regular blood tests are recommended. IFNs may also increase the risk for depression, so precautions and aggressive treatment of depression are recommended.

Avonex and Rebif are available in pre-filled syringes that do not require mixing, but do require refrigeration. Rebif may cause occasional injection site burning, possibly secondary to the acidic pH of the solution. Betaseron is prepared with a neutral pH diluent, which requires mixing with the drug, but does not need refrigeration. Adverse events have been reduced to such a tolerable level that most patients can take any of these medications for many years with only minimal difficulties. Pharma company-sponsored nursing support programs have been another key factor in the success of adherence with these products.5

**GA**

Copaxone (GA) is a non-interferon, polypeptide comprised of four amino acids. GA is FDA-approved for RRMS based on a reduction of relapse rate over placebo in the pivotal trial. Administered daily and subcutaneously in a pre-filled syringe, GA is not associated with flu-like side effects but needs refrigeration. Occasionally, GA-treated patients will develop a systemic reaction immediately post-injection consisting of shortness of breath, tightness in the chest, palpitations, and flushing; however, no serious consequences have been reported. Skin reactions are frequent but usually mild; however, severe lipoatrophy (a dimpling of the skin from loss of subcutaneous fatty tissue) can result in discontinuation of the drug.5

**Evidence-based Medicine Evaluations of Treatment Efficacy**

As previously stated, all of these therapies are FDA-approved for MS, although the question of which is the most effective now arises. Proponents of each of the therapies promote claims of therapeutic supremacy. Independent evidence-based medicine (EBM) reviews have helped clarify these claims. The American Academy of Neurology (AAN), the MS Council and the Cochrane Committee have published independent evaluations.6–8 The AAN/MS Council recommended that all DMT therapies are better than placebo in reducing relapse rate and MRI lesions. They also concluded that the interferons have more robust data to support the claim of delaying progression of disability than Copaxone does. In addition, they reported that the higher dosed, more frequently administered interferons (Betaseron and Rebif) are probably more effective than the low dose, weekly interferon (Avonex).6 Betaseron and Rebif have not been compared directly in head to head clinical trials; however, the data from their individual class I clinical trials are similar.

The independent Cochrane Committee meta-analysis stated that the interferons are mildly to moderately effective in reducing relapses and delaying progression of disability up to two years.6 In another meta-analysis review, the Cochrane Committee concluded that the Copaxone clinical data (disability progression and relapse rate) were not robust enough to recommend its routine use in clinical practice.6 In contrast, the AAN/MS Council and the FDA support Copaxone’s use in reducing MS relapses. The Cochrane Committee also pointed out that most of the MS studies ended at two years and that no existing longer term data are scientifically rigorous. Nonetheless, long-term data on all DMTs indicate that patients who stay on medications are likely to continue to do well for years.6 Concerning safety, all of the immunomodulating drugs have substantial long-term safety data. In fact, a recent 16-year review of continuous Betaseron therapy affirms its long-term safety.5 These data are reassuring following the deaths of Tysabri-treated patients after only one to three years of therapy. In addition to independent evaluations, two class I scientific studies have compared the efficacy of high-dose interferons with low-dose weekly interferon. The first, the Independent Comparison of Interferon (INCOMIN) trial in Italy was independent of any pharmaceutical involvement and demonstrated that Betaseron was significantly more effective than Avonex in a two-year study.11 A second class I study demonstrated

10. Ebers G, Rice G et al., “16-Year Long-Term Follow-Up of Interferon Beta-1b Treatment in RRMS”, Neurology (suppl. 1) (2005);A385;P06.159.
that Rebif was clinically superior to Avonex in a six-month study with a six-month follow-up evaluation.13 This trial led to the FDA approval of Rebif.

Neutralizing Antibodies – Conflicting and Confusing Data

One of the unresolved controversies is the relevance of neutralizing antibodies (NAbs), especially with high dose interferons.13,14 The data spans the continuum from demonstrating negative effects with NAbs to positive effects with NAbs. Since the data are so conflicting and confusing, the independent review by the AAN/MS Council Clinical Practice Guidelines stated that the clinical utility of measuring NAb is uncertain. The debate is further fueled by competing pharmaceutical company interests, which have obscured clarity. The author believes that until the controversy is resolved, patients should be treated based on clinical outcomes and not on NAb tests. That is, if a patient is doing well, they should stay on therapy even if they have NAbs. Conversely, if a patient is responding sub-optimally, they should change therapy even if they have no NAbs. NAbs are also usually transient and disappear in spite of continuous interferon therapy in most patients.

Immunosuppressive Therapies

The FDA has approved Mitoxantrone (Novantrone) for the treatment of ‘worsening MS’. While clinical and MRI data are robust,15 its current use is mainly restricted to patients who have been sub-optimal responders to the DMTs previously discussed. Mitoxantrone is an anthracenedione derivative anti-neoplastic agent that is given intravenously every three months for two to three years. The clinical and MRI data are robust. While most patients tolerate the administration of the drug well, the potential risk of irreversible cardiac toxicity, amenorrhea and secondary neoplasm limit the use of Mitoxantrone. Regular cardiac evaluations for left ventricular (LV) dysfunction are recommended while on treatment. Other anti-neoplastic, immunosuppressive therapies are available and/or in clinical trials, but are not FDA-approved for MS. Azathioprine (Imuran), cyclophosphamide (Cytoxan), Methotrexate, Cladribine®, and Campath® are examples.

Other Important Considerations

Utilization of MRI

The use of MRIs in MS has facilitated earlier MS diagnosis; however, the routine use of follow-up MRIs as a surrogate marker for treatment effect is controversial. In fact, one group of MS experts did not recommend routine MRIs in following patients on DMTs. Many neurologists evaluate MRIs every one to three years as an additional screen for efficacy of treatment. The MRI remains a valuable diagnostic test for MS. In addition, the MRI aids in evaluating therapeutic efficacy in clinical trials and clinical practice. The most recent data suggest new MRI activity may be an early marker of a sub-optimal clinical response.17

Sub-optimal Treatment Response

The diagnosis and treatment of sub-optimal responses to therapy are also controversial. The question remains over what constitutes a sub-optimal response, as none of the treatments cure the disease. Increased relapse rate (especially with moderate or severe relapses), new MRI lesions, progression of disease, and cognition decline are all considered important criteria. If the diagnosis of a sub-optimal treatment response is established, the question of what is the best course of treatment arises. Increasing the drug dose and/or frequency, switching treatments, or combining treatments are options. The best course of action for a sub-optimal response is not established but may be clarified with current on-going clinical trials. For example, recent pilot data from two clinical trials in RRMS indicate that increasing the dose of Betaseron increases efficacy without reducing adherence.16

Tysabri® (Natalizumab)

Tysabri (natalizumab) is a monoclonal antibody

Recognizing the difficulty in finding a trusted source for information, the American Academy of Neurology, together with its Foundation, developed a public website, The Brain Matters (www.thebrainmatters.org/eu), to meet the information needs of patients and caregivers alike.

At The Brain Matters your patients and their families will find information quickly and easily about the causes, symptoms, and treatment of disorders that impact their lives. The Website also provides valuable links to an array of patient resources and advocacy groups.

> www.thebrainmatters.org/eu helps to demystify several neurological disorders, including:

Alzheimer’s disease  •  Brain injury  •  Dystonia
Epilepsy  •  Migraine  •  Multiple sclerosis  •  Pain
Parkinson’s disease  •  Sleep disorder  •  Stroke
The Brain Matters Website was developed with financial support from Medtronic, the Groff Foundation, and the AAN Foundation Corporate Roundtable.

> Working With Your Doctor

Patients learn about how your specialized training in neurology can help, and how to best work with you in managing their care.

> Progress Through Research

A section on clinical trials explains how patients can participate in the latest research, with a link to clinical research databases.

> Patient Story

Each disorder section contains a personal story from a patient's perspective that gives inspiration on living with a neurological disorder.
directed against the alpha-4 integrin in the class of the selective adhesion molecules (anti-very late activation (VLA)-4 monoclonal antibody) that was approved by the FDA in 2004 only to be withdrawn after fatal cases of progressive multifocal leukoencephalopathy (PML) were detected.19 Tysabri demonstrated robust clinical and MRI results in mildly affected RRMS patients over a two-year period. In an attempt to reintroduce the drug, a thorough safety analysis of all patients treated with Tysabri is under way. Its future role in the routine treatment of MS is clouded because other treatments with robust efficacy data have been proven safe after 10 or more years of experience. Unfortunately, most MS clinical trials do not represent rigorous scientific standards because of the lack of patient randomization, use of un-blinded evaluators, or lack of representative controls. Nonetheless, these so-called ‘marketing trials’ are sometimes published and create confusion for both patients and neuroscientists. The issue of efficacy has been addressed by the pivotal trials, independent evidence-based medicine (EBM) reviews and scientifically rigorous (class I) head-to-head clinical trials. The higher-dosed and more frequently administered interferons (Betaseron and Rebif) have more robust efficacy data than the weekly, low-dose IFN (Avonex) according to expert EBM reviews. As a group, the interferons have more robust efficacy data related to delaying the progression of MS disability compared with Copaxone data. Class I head-to-head clinical trials between Copaxone and IFNs are in progress. High-dose interferons are more likely to be associated with NAbs, but their clinical significance has not been established.

This situation is particularly difficult when the ‘marketing trials’ differ from the rigorous class I trial data. The question over whether 10 ‘marketing trials’ are more valuable than two class I scientific trials is pertinent. In the author’s opinion, careful scrutiny of the methodology of trials before assigning credibility to the data should be encouraged.

Summary and Conclusions

The understanding of MS has increased dramatically and DMTs have markedly improved the lives of MS patients over the past 11 years. The diagnosis can be made earlier so that treatment can begin before extensive damage has accumulated in the brain and spinal cord. The choice of treatment is a balance between efficacy, tolerability, safety, and convenience. The successful management of most side effects has improved drug tolerability so that most patients can continue on any of these drugs for many years. Newer injection protocols have made all of the drugs more convenient. All of the current immunomodulating therapies also have good long-term safety data.

As the understanding of the disease increases every year, new treatments are being proposed and many new studies are in progress. These new treatments are likely to continue to improve the disease course of MS patients.

The treating physician’s responsibility is to educate the patient on the class I clinical trials, the EBM reviews of treatment, potential tolerability and safety issues as well as the physician’s clinical perspective and experience. The patient’s value system completes the decision-making process. Close communications between healthcare professionals, the patient, and the family, plus a focus on minimizing side effects and increasing adherence, have helped with the success of all of the treatments in the long-term. In addition to treatments with DMTs, the aggressive management of MS symptoms (fatigue, spasticity, pain, etc.) and an integrated rehabilitation/ psychosocial supportive approach has dramatically increased the quality of life for MS patients in recent years. As the understanding of the disease increases every year, new treatments are being proposed and many new studies are in progress. These new treatments are likely to continue to improve the disease course of MS patients.