A New Era of Therapy in Multiple Sclerosis: Balancing the Options and Challenges Ahead

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Abstract The recent explosion in regulatory approvals of disease-modifying medications for patients with relapsing-remitting multiple sclerosis makes the choice of therapy increasingly complicated. It is not yet known which medication is best for particular patients or at specific points of the disease process. Based on nearly two decades of experience with beta interferons, early intervention clearly modifies the disease course; however, no current treatment has been shown to prevent or reverse disability accumulation in the long term. At two Biogen Idec–sponsored symposiums held during the 2013 Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), experts discussed available tools to help clinicians and patients make these decisions and the evidence supporting new and future therapeutic options.

Multiple sclerosis (MS) is an inflammatory, demyelinating disease defined by lesions in the central nervous system (CNS) that are disseminated in time and space. The disease course is heterogeneous and characterized by a symptomatic spectrum ranging from relapsing-remitting episodes of disability to the development of progressive disease.

This article reviews currently available disease-modifying therapies approved for relapsing-remitting MS (RRMS) in the context of current experience and evidence for intervention, and it offers tools for clinicians and patients who are navigating the therapeutic options. It is based upon presentations delivered at two industry-sponsored symposiums held during the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Copenhagen.

A DIVERSE MENU FOR TREATING RRMS

The Tried and True

Twenty years of experience have shown that the treatment of RRMS with interferon beta is safe, delays disability, reduces mortality, and delays conversion from clinically isolated syndrome to RRMS.\(^1\)\(^2\) Figure 1 summarizes the clinical development of this immunomodulatory agent in RRMS over the past 25 years.\(^3\)

The mechanism of action of interferon beta in patients with MS is unknown, but it may cause a shift to anti-inflammatory cytokines and prevent leukocytes from crossing the blood-brain barrier.\(^4\) Table 1 summarizes the currently available formulations of interferon beta, along with administration options, adverse effects, and the pivotal clinical trials that evaluated each formulation.

Ongoing trials are striving to improve the efficacy of interferon beta therapy and patient adherence to this treatment. ADVANCE is a phase 3, randomized, controlled trial comparing administration of subcutaneous (SC) pegylated interferon (peginterferon) beta-1a every 2 or 4 weeks with placebo. Pegylation, the addition of polyethylene glycol (PEG), increases the potency and half-life of interferon beta and decreases its immunogenicity.\(^5\) At 1 year, there was a significant decrease in the annualized relapse rate, number of gadolinium-enhancing lesions, and production of neutralizing antibodies among treated patients, suggesting that peginterferon beta will be an attractive and effective alternative to current formulations.\(^6\) Elsewhere in this issue of The Neurology Report, Dr. Sona Narula summarizes the key data from year 1 of the ADVANCE study.

The other injectable option, glatiramer acetate, is a copolymer comprising glutamic acid, lysine, alanine, and tyrosine, which originally was designed to mimic myelin basic protein and induce experimental autoimmune encephalitis (EAE); instead, it ameliorated disease in both animal models\(^7\) and humans.\(^8\) The mechanism of action is not completely clear; however, much like the interferon-beta treatments, glatiramer acetate may cause a shift toward anti-inflammatory cytokines. Many years of experience has proven that glatiramer acetate is also a safe and effective treatment of RRMS that delays the conversion from a clinically isolated syndrome to RRMS (Table 1).

Mitoxantrone is a type II topoisomerase inhibitor that is approved for RRMS in Europe.\(^9\)\(^10\) It is an exciting option as it is the only anti-inflammatory agent that may be effective against primary progressive MS.\(^11\) Table 1 summarizes the challenges associated with the use of glatiramer acetate.

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Figure 1: Timeline of development of interferon beta over the past 25 years. RRMS = relapsing-remitting multiple sclerosis; CIS = clinically isolated syndrome; SC = subcutaneous; IM = intramuscular; IFN β-1a = interferon beta-1a; IFN β-1b = interferon beta-1b; NF = new formulation (serum free); IFNB MS = Interferon Beta in Multiple Sclerosis; MSCRG = Multiple Sclerosis Collaborative Research Group; PRISMS = Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis; CHAMPS = Controlled High-Risk Avonex Multiple Sclerosis Prevention Study; ETOMS = Early Treatment of Multiple Sclerosis; BENEFIT = Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment; REFLEx = Rebif Flexible Dosing in Early Multiple Sclerosis; EU = European Union. Adapted from Calabresi.3

TARGETED IMMUNOMODULATION

Natalizumab

Natalizumab is the most potent therapeutic option available for treating RRMS, but it also carries the highest risk (Table 1). This monoclonal antibody binds α-4 integrin on activated T cells; this interaction prevents these cells from binding with VCAM1 on endothelial cells of the blood-brain barrier, thereby blocking entry into the CNS.10

Figure 2,11 a summary timeline of natalizumab development milestones, highlights the accelerated approval of the drug and its eventual withdrawal from the market after three patients developed progressive multifocal leukoencephalopathy (PML).12 Fortunately, it is now possible to stratify patient risk for developing PML based on the presence of anti-JC virus antibodies as a marker of prior infection, prior or current immunosuppression, and duration of natalizumab treatment (Figure 3).13

The ability to stratify risk for PML is critical. Post hoc analyses of the AFFIRM and SENTINEL trials continued to show the significant efficacy of natalizumab, not only in reducing the relapse rate and disease activity, as found on magnetic resonance imaging (MRI), but also in effecting remission (or "disease-free activity" by both clinical and radiologic measures) in some patients.14,15

Interestingly, patients having an Expanded Disability Status Scale (EDSS) score < 3 were more likely to return to baseline after a relapse on natalizumab than were those with an EDSS score > 3, suggesting that this is a critical threshold for repair reserve.16 These results set the stage for a new standard for treatment-outcome goals and primary endpoints for future clinical trials.

Fingolimod

Fingolimod, another potent immunomodulator, was the first approved oral drug for RRMS (Table 1). Fingolimod binds to sphingosine-1-phosphate (S1P) receptors on lymphocytes, sequestering these cells in lymphatic tissue so that they may not access the CNS.17 Fingolimod was significantly more effective than was interferon beta-1a for reducing annualized relapse rates and disease activity on MRI.18 However, this therapy requires more baseline and continued monitoring, given the risk of skin neoplasm, macular edema, bradycardia, and infection related to its use (Table 1).

Teriflunomide

Teriflunomide was the next oral immunomodulator to be approved (Table 1).19 Its prodrug form, leflunomide, is an effective treatment for another autoimmune disorder, rheumatoid arthritis.
Teriflunomide inhibits dihydroorotate dehydrogenase, preventing de novo pyrimidine nucleotide synthesis, which may suppress the effector function of activated lymphocytes; however, it is not clear whether this mechanism is responsible for its efficacy in autoimmune disease. Treatment with teriflunomide showed a modest effect versus placebo in reducing the annualized relapse rate (Table 1) and was at least equivalent to interferon beta-1a.19,21

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration</th>
<th>Major and minor adverse events</th>
<th>Pivotal clinical trial evidence*</th>
</tr>
</thead>
</table>
| Interferon beta-1b        | SC injection every other day | • Pyrexia  
• Depression  
• Injection-site reactions  
• Neutralizing antibodies  
• Hematologic, thyroid, and liver abnormalities | IFNB MS Group37 (1993)  
CIS: BENEFIT36 (2006) |
| Interferon beta-1a        | IM or SC pen injection once a week | • Pyrexia  
• Depression  
• Injection-site reactions  
• Neutralizing antibodies  
• Hematologic, thyroid, and liver abnormalities | MSCRGA39 (1996): ↓ Annualized relapse rate versus placebo (0.61 vs 0.90)  
CIS: CHAMPS40 (2000) |
| Interferon beta-1a        | SC injection 3 times weekly | • Pyrexia  
• Depression  
• Injection-site reactions  
• Neutralizing antibodies  
• Hematologic, thyroid, and liver abnormalities | PRISMS41 (1998): ~30% ↓ in relapse rate compared with placebo  
CIS: ETOMS42 (2001) and REFLEX43 (2012) |
| Glatiramer acetate        | Daily SC injection | • Injection-site reactions or lipoatrophy  
• Post-injection flushing reaction | CP1MSSG45 (1995): ↓ Annualized relapse rate versus placebo (0.59 vs 0.84)  
REGARD46 (2008)  
CIS: PrecISE47 (2009) |
| Mitoxantrone              | IV infusion every 3 months | • Congestive heart failure  
• Leukemia, lymphoma  
• Lymphopenia, neutropenia  
• Liver dysfunction  
• Discolored urine  
• Alopecia  
• Nausea  
• Congenital defects | Edan et al44 (1997)  
MIMS45 (2002): ↓ Annualized relapse rate versus placebo (0.35 vs 1.02) |
| fingolimod                | PO once daily | • Bradycardia/AV block (first-dose monitoring)  
• Macular edema  
• Infection (disseminated zoster, HSV encephalitis)  
• Transaminitis  
• Skin cancer | TRANSFORMS48 (2010): ↓ Annualized relapse rate versus interferon beta-1b (~0.20 vs 0.30)  
FREEDOMS49 (2010): ↓ Annualized relapse rate versus placebo (~0.17 vs 0.40) |
| Natalizumab               | Monthly IV infusion | • PML (requires JC virus antibody testing and risk stratification)  
• Neutralizing antibodies  
• Infection  
• Allergic reaction | AFFIRM50 (2006): ↓ Annualized relapse rate versus placebo (0.26 vs 0.81)  
SENTINEL1 (2008): ↓ Annualized relapse rate versus placebo (0.34 vs 0.75) |
| Teriflunomide             | PO once daily | • Infection (check PPD prior to starting)  
• Transaminitis  
• Gastrointestinal symptoms (nausea)  
• Alopecia  
• Peripheral neuropathy  
• Pregnancy Category X | TEMSO51 (2011): ↓ Annualized relapse rate versus placebo (0.37 vs 0.54) |
| Dimethyl fumarate         | PO twice daily | • Flushing  
• Gastrointestinal symptoms (nausea, diarrhea)  
• Lymphopenia  
• Proteinuria | DEFINE52 (2012): ↓ Annualized relapse rate versus placebo (~0.18 vs 0.36)  
CONFIRM53 (2011): ↓ Annualized relapse rate versus placebo (~0.21 vs 0.4), but similar to that of glatiramer acetate |

Abbreviations: SC = subcutaneous; MS = multiple sclerosis; IM = intramuscular; IV = intravenous; PO = orally; AV = atrioventricular; HSV = herpes simplex virus; PML = progressive multifocal leukoencephalopathy; PPD = purified protein derivative.

* Pivotal randomized controlled trials leading to approval or showing efficacy in delaying conversion from clinically isolated syndrome (CIS) to relapsing-remitting multiple sclerosis. Results are noted for the trials that report annualized relapse rates. For further information on these therapies, please consult the full prescribing information and a recent review on safety monitoring."
from a phase 3 clinical trial showed that dimethyl fumarate is at least as good as glatiramer acetate in reducing the annualized MS relapse rate. Further such head-to-head comparisons will likely guide treatment decisions in the future. In an ongoing, long-term safety extension study known as ENDORSE, efficacy has been sustained, and there have been no new or worse safety events than those originally reported in the DEFINE and CONFIRM trials (Table 1).

Other Drugs

Other immunomodulating, disease-modifying drugs currently in development or being tested in ongoing phase 3 clinical trials include laquinimod, rituximab, and alemtuzumab.22,23,25

CURRENT TREATMENT CHALLENGES: IN NEED OF A TREATMENT ALGORITHM

These many treatment options and their potential for causing significant adverse events are making RRMS management increasingly complex, but some tools and lines of evidence are available to clinicians to guide management.26

First, early identification and initiation of therapy may improve the course of RRMS. The currently available therapies outlined here target immune activity, which is more active early in the course of disease and is evident by the number of relapses that occur and the accumulation of gadolinium-enhancing lesions on MRI.27 With the modified 2010 McDonald criteria for diagnosis of RRMS, it is now possible to diagnose and intervene earlier in the disease course. However, this shift means that newly diagnosed patients are not directly comparable to those treated in the original clinical trials; instead, they may be more similar to a subgroup of patients from these early trials who had a clinically isolated syndrome. In addition, the patients recruited to modern trials will not be directly comparable to those participating in the original trials. This heterogeneity is evident in Table 1, in which the reported annualized relapse rate in the placebo arm of many of the seminal trials ranged from 0.3 to 1.02.

Second, certain patient characteristics are associated with more aggressive disease than others. These factors include relapse severity, degree of recovery, gender, race, age, and disease activity on MRI and are summarized in Table 2. Patients with these more aggressive characteristics probably should be treated with more highly effective therapies earlier in their disease course.

To initiate therapy, the clinician and the patient together must make treatment decisions based on prognosis, treatment goals, patient preference, and analysis of benefit and risk of the options. The clinician can navigate the currently available first-line therapies (interferon beta or glatiramer acetate) and second-line therapies (all others) or rank them as low, moderate, and highly effective. Over time, and with further head-to-head clinical trials, it may be easier to develop a universal algorithm for treatment initiation. In the meantime, the clinician and patient should balance treatment goals (eg, reduction of relapses vs freedom from disease) with potential adverse events.

Once patients are on therapy, response must be aggressively monitored with follow-up MRI and reports of relapse occurrence to determine whether disability is accumulating or adverse effects or neutralizing bodies are developing. At this point, we have limited tools to characterize and follow disease severity. They include the EDSS score, accumulation of MRI lesion burden, and clinical report of relapse. The modified Rio Score is an evidence-based algorithm that incor-
FIGURE 3     Estimates of the incidence of progressive multifocal leukoencephalopathy (PML) among patients with multiple sclerosis treated in the postmarketing setting with natalizumab, stratified according to prior or no prior use of immunosuppressants and duration of natalizumab treatment (A) and according to positive or negative status with respect to anti-JC virus antibodies, prior or no prior use of immunosuppressants, and duration of natalizumab treatment (B). Adapted from Bloomgren et al.13

porates all three of these tools; this tool accurately predicted responders from the PRISMS patient population.30 Future biomarkers of response to therapy such as brain atrophy on imaging studies and analyses of cerebrospinal fluid (CSF) and serum markers, as well as tools that can consistently identify physical and cognitive changes over time, are needed.

■ PROGRESSION IN MS: AN UNMET NEED

Despite these exciting new therapeutic choices for patients with RRMS, there is still no disease-modifying intervention for the progressive form of the disease. The basic pathogenic mechanisms underlying brain atrophy in MS are unknown, and many questions remain unanswered: Is progression a primary neurodegenerative disease occurring simultaneously with demyelination? Is neuronal loss secondary to loss of oligodendrocytes? What role does the immune response play in progressive disease?

Anti–LINGO-1 Antibodies

One disease-modifying therapy currently in development, anti-LINGO-1 antibodies, specifically targets remyelination in MS lesions. The goal is to protect axons in MS lesions through remyelination, potential prevention of axonal degeneration, and amelioration of the progressive form of the disease.

LINGO-1 is a leucine-rich repeat transmembrane domain protein initially identified by Mi and colleagues as a novel component of the Nogo receptor complex involved in blocking CNS axon regeneration.31 LINGO-1 expression is restricted to the CNS and is found in neurons, oligodendrocytes, and oligodendrocyte precursor cells (OPCs).32 Genetic deletion or antibody-mediated blocking of
LINGO-1 has demonstrated that it is a negative regulator of both oligodendrocyte differentiation and myelination in vitro and slice culture. Given that blocking LINGO-1 with anti–LINGO-1 antibody led to OPC differentiation, remyelination, and improvement in functional recovery in several mouse models of demyelination, and that chronic MS lesions contained premyelinating oligodendrocytes, anti–LINGO-1 antibody appears to be an excellent candidate for treatment in MS.

A phase 1 study sponsored by Biogen Idec involving intravenous administration of anti–LINGO-1 antibodies to both healthy controls and patients with RRMS and secondary progressive MS provided evidence of the safety of this therapeutic approach, and CSF was collected at concentrations predicted to be efficacious. Two phase 2 trials currently are enrolling patients with RRMS and relapsing secondary progressive MS (SYNERGY) or a first episode of optic neuritis (RENEW).

### CONCLUSION

This is an exciting time to be treating patients with RRMS, as many options are available to alter the course of disease. Further clinical studies that directly compare therapies or that identify tools and biomarkers for predicting and evaluating response to therapy are needed before evidence-based algorithms for management of this disease can be developed. In addition, understanding the pathogenesis of progression in MS and identifying novel approaches for neuroprotection and prevention of disability are important future goals.

### REFERENCES


3. Calabresi P. Reinventing MS care—evolution: advancing interferons for people with MS. Presented at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); October 2–5, 2013; Copenhagen, Denmark.


16. Giovanacci G. Reintroducing MS care—evolution: silencing the disease from the start. Presented at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); October 2–5, 2013; Copenhagen, Denmark.


24. Montalban X. Reinventing MS care—revolution: defending the brain. Presented at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); October 2–5, 2013; Copenhagen, Denmark.


### TABLE 2

Factors Linked to a Higher Risk of More Aggressive Disease in Patients with Multiple Sclerosis at Diagnosis

<table>
<thead>
<tr>
<th>Relapse severity</th>
<th>Magnetic resonance imaging</th>
<th>Incomplete recovery from relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>• One moderate or severe attack</td>
<td>• Two gadolinium-enhancing/new T2 lesions or more than two T1 hypertense lesions</td>
<td>• Two spinal cord lesions</td>
</tr>
<tr>
<td>• Need for corticosteroids and/or hospitalization</td>
<td>• Brain atrophy</td>
<td>• Brain atrophy</td>
</tr>
<tr>
<td>• Severe effect on activities of daily living</td>
<td></td>
<td>Older age</td>
</tr>
<tr>
<td>• Effect on more than one functional system</td>
<td></td>
<td>Male gender</td>
</tr>
<tr>
<td>• Severe involvement of motor function/cerebellum/brainstem</td>
<td></td>
<td>African-American ethnicity</td>
</tr>
</tbody>
</table>

Adapted, with permission, from Freedman et al.20
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36. Sandrock A. Reinventing MS care—revolution: the future is repair. Presented at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); October 2–5, 2013; Copenhagen, Denmark.


