Multiple Sclerosis: New Goals, New Therapies, and New Challenges in Patient Management

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Aims and Organization

Essential reviews that bridge the gap between primary literature and your daily practice

Purpose

Current Opinion in Neurology is one of 24 Current Opinion journals that aims to help clinicians and researchers keep up-to-date in a systematic way with the vast amount of information published in neurology.

- **Current Opinion in Neurology** guides you through the literature with Review articles by the world’s experts in oncology written in clear, concise, and accessible language.
- Expert commentary and on the most interesting and relevant papers published in neurology.
- Comprehensive references and bibliographies providing a ready resource.
- Search-enabled full-text web site.

Editorial Expertise

Current Opinion in Neurology benefits from four levels of editorial participation:

- Editors-in-Chief, Richard SJ Frackowiak and Deputy Editor, John Mazziotta.
- Editorial Board comprised of neurologists from around the world.
- Section Editors, appointed by the Editor-in-Chief and Deputy Editor, who are chosen for their expertise.
- Reviewers, nominated by the Section Editors, are leading authorities on each of the relevant topics.

Methods

Current Opinion in Neurology is published bimonthly:

- Each issue contains approximately 114 pages.
- The field of neurology is divided into 14 sections, each of which is reviewed once a year.
- Each section is assigned to one or two Section Editors, leading authorities in that area, who identify for review the most important topics at that time.

Issue Contents

Each issue contains the following types of information:

- Review articles: concise, up-to-date articles written by specialists who provide a personal perspective and overview of the developments in the field over the previous year.
- Annotated references: the authors’ reference lists offer personal commentary so that you can put the information into context with the text of the article and with the other references.
- Current world literature: the end of each issue contains a complete bibliography of all the papers published in the previous year. For easy reference, the list of papers is organized by subject area.
- Annual contents and cumulative indices: the last issue of each volume of Current Opinion in Neurology includes a table of contents for the year, as well as cumulative indices organized by both subject and author, so that you can easily identify the source of information you need.

Scanning the Literature

- The journals selected for scanning for Current Opinion in Neurology are chosen by the Editor-in-Chief and Deputy Editor for their relevance and importance to the field.
- The list, published at the end of the current world literature section, is reviewed and regularly updated by the Editor-in-Chief, Deputy Editor and Editorial Board to ensure that the journals scanned are representative of the field in significance, timeliness, and accuracy.

In Summary

Current Opinion in Neurology bridges the gap between the primary literature and your daily practice.

- It guides you through the vast amount of literature published each month, pointing you to the information that is most relevant, keeping you up-to-date with personal commentary from the world’s authorities in neurology.
- It provides you with comprehensive, well organized reference lists and bibliographies for use throughout the year.
MULTIPLE SCLEROSIS: NEW GOALS, NEW THERAPIES, AND NEW CHALLENGES IN PATIENT MANAGEMENT

Guest Editor: Aaron E. Miller, MD

Release date: 14 March 2012
Expiration date: 14 March 2013

Faculty:
Edward J. Fox, MD, PhD
Gavin Giovannoni, MBBCCh, PhD, FCP (Neurol.), FRCP, FRCPath
Robert W. Rhoades, PhD

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Jointly sponsored by
Supported by an educational grant from

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This activity is supported by an educational grant from Genzyme, a Sanofi Company
Target Audience
This activity has been designed to meet the educational needs of physicians, registered nurses and other clinicians involved in the management of patients with multiple sclerosis.

Release date: 14 March 2012
Expiration date: 14 March 2013
Estimated time to complete activity: 1.0 hour

Statement of Need/Program Overview
Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system with clinical manifestations of demyelination, axonal loss, neuronal death, and gliosis. It is a lifelong disease that, once diagnosed, requires ongoing treatment. Newer therapies have significantly changed the potential benefit of treatment for patients with MS, and clinicians require education to increase awareness of potential advances in treatment. While potentially providing improved efficacy, education is needed as some new treatments may require careful consideration in patient selection and monitoring. As persons with MS vary across a wide range of parameters, their treatment should be individualized to meet their specific characteristics and needs. The papers comprising this supplement are designed to meet the needs of healthcare providers who care for people with MS by summarizing the benefits and risks of both established and emerging therapies and highlighting best practices in partnering with patients in selection of specific therapies and overall disease management.

Educational Objectives
After completing this activity, the participant should be better able to:

• Discuss MS management options with the potential to delay disease progression
• Describe MS management options with the potential to improve adherence
• Evaluate emerging data on investigational treatment options and novel therapies for patients with RRMS
• Identify patients at increased risk for adverse events with new MS therapies and manage such events if they occur
• Develop individualized treatment goals and interventions based on patient characteristics
• For registered nurses: Provide appropriate care and counsel for patients and their families

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Robert W. Rhoades, PhD
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<tr>
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<tr>
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Treatment of relapsing-remitting multiple sclerosis: current approaches and unmet needs

Aaron E. Miller and Robert W. Rhoades

Purpose of review
The aim of this review is to summarize unmet needs for patients with multiple sclerosis (MS). It is important to understand the current status of these patients and both the benefits and limitations of the most commonly used MS treatments as new medications with the potential to simplify therapy and improve outcomes may soon be available.

Recent findings
Current treatments for MS decrease the frequency of relapses and slow progressive disability. However, nearly all of these medications require frequent administration, and some patients also experience side effects. In some patients, adherence to MS treatment may be less than optimal. This may be associated with increased risk for relapses and hospitalizations and higher cost of care.

Summary
Healthcare providers involved in the treatment of MS must be aware of the unmet needs of their patients and intervene as needed to improve adherence and/or modify treatment regimens to optimize outcomes.

Keywords
adherence, cost, quality of life

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune, inflammatory, demyelinating disease that attacks the central nervous system (CNS) [1]. MS generally takes one of four clinical courses: a relapsing-remitting course characterized by unpredictable exacerbations of existing symptoms or appearance of new symptoms [relapsing-remitting MS (RRMS)]; an initially relapsing-remitting course that ultimately becomes steadily progressive (secondary progressive MS); a form that is progressive from the onset without relapses (primary progressive MS); and rarely a course that is progressive from onset but is then punctuated by relapses (progressive-relapsing MS) [2]. Approximately, 85% of patients initially manifest a relapsing-remitting course, with 10–15% demonstrating the primary progressive form [1]. This article reviews the epidemiology of MS, societal cost and patient burden associated with MS, the benefits and limitations of current therapies, and unmet patient needs. This article complements a recent review that focuses on advances in MS therapy and predictions regarding treatment by 2020 [3].

EPIDEMIOLOGY OF MULTIPLE SCLEROSIS

MS affects about 400,000 people in the United States and approximately 2.5 million people worldwide [1]. The disease affects persons of all ages, but symptoms are most likely to appear in individuals 20–50 years of age [4]. The prevalence of MS in women is approximately two to three times that in men [1].

SOCIETAL COST OF MULTIPLE SCLEROSIS

It has been estimated that the total direct and indirect costs of MS in the United States is $28 billion each year [4]. A recent evaluation of healthcare costs

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Curr Opin Neurol 2012, 25 (suppl 1):S4–S10
for 1411 newly diagnosed patients with MS vs. 7055 healthy controls indicated that MS patients were significantly more likely to be hospitalized (15.2 vs. 4.3%), have at least one emergency department visit (25.5 vs. 12.2%) and at least one visit for physical, occupational, or speech therapy (23.7 vs. 9.9%) over a 1-year follow-up period. The mean overall annual cost of care for a patient with MS was $18,829 vs. 4038 for a healthy control individual, excluding MS treatment drugs [5].

Both the direct and indirect costs of MS increase dramatically as the disease progresses. The annual cost for a patient with an Expanded Disability Status Score (EDSS) of 0.2–2.5 was $5740; and the respective values for patients with scores of 3.0–5.5, 6.0–7.5, and 8.0–9.5 were $11,114, $26,365, and $46,366, respectively (Fig. 1) [6]. Another survey carried out in the United States indicated that the total annual per patient cost of MS was $47,215 with 53% attributed to direct medical and nonmedical costs, 37% to production losses, and 10% to informal care [7].

The high productivity losses for patients with MS result in large measure from the very high unemployment rate in this group. A cross-sectional and longitudinal investigation of work loss in 8867 patients with MS indicated that 56–58% of them were not employed and that unemployment was associated with a progressive disease course, longer symptom duration, and greater level of disability. Specific problems in mobility, hand function, fatigue, and cognitive performance were also associated with increased risk for unemployment [8].

The high cost of MS has significant effects on patients and their families. A survey of 983 working-age patients with MS in the United States indicated that 16.4% had considerable difficulty paying for healthcare, 27.4% put off or postponed seeking needed healthcare because of costs, and 26.6% reported considerable worries about affording such basic necessities as food, utilities, and housing [9]. Results from another survey of 411 MS patients indicated that 37% had experienced a decline in their standard of living since being diagnosed with the disease [10].

### PATIENT BURDEN

The lesions of MS can occur in many parts of the CNS and result in a wide range of symptoms including fatigue, visual impairment, vertigo, and sensory impairment [11,12]. MS may be a devastating disorder with progressive accumulations of motor, sensory, and cognitive disabilities and impaired quality of life (QOL) [13–18].

Interpersonal relationships and social functioning are also greatly impaired in patients with MS. Results from a cohort of 371 patients with RRMS or progressive MS indicated that about one-fourth of those with relapsing-remitting disease and over 70% of those with progressive disease were separated or divorced following their diagnosis. Both friendship and other family relationships were also affected by the disease [19]. Loneliness is often a poorly recognized component of the experience of MS that may result from changes in social networks that occur during the course of chronic illness. A survey of 659 women with MS indicated that more than 50% felt lonely, and this was significantly associated with low levels of social support, increased social demands of illness, higher functional limitation, and lower perceived health status [20].

MS exacts significant physical, psychological, and economic tolls on patients’ families and caregivers, and this burden rises as the disease progresses and the patients’ conditions worsen. Caregivers may spend as much as 3.5 h per day aiding patients with MS and this assistance is viewed as essential for 70% of patients [21,22]. As the MS patient’s disease progresses, ability for self-care declines and the increasing requirement for daily assistance can take a rising physical and economic toll on caregivers.
Worsening MS in the patient has been shown to be correlated with declining physical and mental health in the caregiver [24]. The impact of MS on caregiver QOL has been demonstrated in a survey of 445 MS patients and their caregivers. Care giving was associated with significant reductions in mental health, vitality, and general health scores for caregivers vs. a normative control group. Patient Beck Depression Inventory score was a significant predictor of almost all caregiver SF-36 dimension scores; and EDSS, disease duration and course, and patient therapeutic characteristics also predicted declines in some dimensions of caregiver QOL [25]. Results from another survey showed that the distress for caregivers also increased with the emergence of cognitive and psychiatric conditions in the patient in addition to decline in EDSSs [26]. Evidence also indicates that MS is associated with increased mortality and shortened lifespan. Results from a cohort of 878 patients with MS indicated that median survival after diagnosis was 41 vs. 49 years for otherwise-matched patients without MS. The standardized mortality ratio was increased 2.7 fold in the MS patients vs. the control individuals [27]. A review of results from multiple studies indicated that patients with MS lose 5–10 years of life [28].

**DISEASE-MODIFYING THERAPY FOR MULTIPLE SCLEROSIS**

At present, no cure exists for MS and the goals of treatment are to arrest or slow the progression of disability, decrease relapse rate, manage symptoms, slow subclinical disease progression demonstrated by imaging techniques (e.g., MRI), and maintain or slow subclinical disease progression as measured by EDSSs [34]. Results from another survey showed that the distress for caregivers also increased with the emergence of cognitive and psychiatric conditions in the patient in addition to decline in EDSSs [26].

Evidence also indicates that MS is associated with increased mortality and shortened lifespan. Results from a cohort of 878 patients with MS indicated that median survival after diagnosis was 41 vs. 49 years for otherwise-matched patients without MS. The standardized mortality ratio was increased 2.7 fold in the MS patients vs. the control individuals [27]. A review of results from multiple studies indicated that patients with MS lose 5–10 years of life [28].

**UNMET NEEDS IN PATIENTS WITH MULTIPLE SCLEROSIS**

Although the agents described in the preceding section have all been shown to decrease the risk for relapse and slow disease progression in patients with RRMS, stopping or even reversing disability progression remains an unmet need in many patients [42–45]. Further, MS is a heterogeneous disease and some patients may not respond adequately to treatment for reasons that remain to be elucidated [46,47].

Adverse events associated with medical treatment can negatively impact adherence to therapy across a wide range of chronic diseases and this is also the case with MS. Adverse events noted for IFN-βs include injection site reactions, flu-like symptoms, and depression [48]. The most common systemic adverse event observed in patients taking IFN-βs is flu-like symptoms. These symptoms are most common during the first few months of treatment. They usually appear 2–6 h after injection and resolve within 24 h [49]. Injection site reactions are relatively common with all the agents delivered by subcutaneous injection, but occur less often for the IFN-β-1a preparation delivered via i.m. injection [48]. Liver function abnormalities have been noted in patients taking all IFN-βs and in patients receiving fingolimod [45,50]. Results from one clinical trial indicated that i.m. IFN-β-1a was associated with a significantly lower incidence of abnormal liver function test results than subcutaneous IFN-β-1a (9 vs. 18%, \( P = 0.002 \)) [36]. Natalizumab is generally well tolerated, but is associated with a small risk for the development of potentially fatal progressive multifocal leukoencephalopathy (PML), an
Table 1. Summary of prospective, randomized, head-to-head trials of disease-modifying therapies for RRMS

<table>
<thead>
<tr>
<th>Author (study)</th>
<th>Comparison and study duration</th>
<th>Annualized relapse rate</th>
<th>Relapse free (%)</th>
<th>Disease progression (%)</th>
<th>Change in EDSS (mean)</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Durelli et al. [35], (INCOMIN)</td>
<td>IFN β-1a i.m. 30 μg QW (n = 92) vs. IFN β-1b SC 250 μg EOD (n = 96) 24 months</td>
<td>0.7 vs. 0.5 (P = 0.03)</td>
<td>36 vs. 51 (P = 0.03)</td>
<td>30 vs. 13 (P = 0.005)</td>
<td>0.54 vs. 0.13 (P &lt; 0.004)</td>
<td>Unblinded for clinical outcomes; MRI-blinded assessment.</td>
</tr>
<tr>
<td>Panitch et al. [36], (EVIDENCE)</td>
<td>IFN β-1a i.m. 30 μg QW (n = 338) vs. IFN β-1a SC 44 μg TIW (n = 339) 48 weeks</td>
<td>0.65 vs. 0.54 (P = 0.09)</td>
<td>52 vs. 62 (P = 0.009)</td>
<td>14 vs. 13 (NS)</td>
<td>ND</td>
<td>Treating physicians and patients unblinded to treatment; evaluation physicians and MRI examiners blinded to treatment and outcomes.</td>
</tr>
<tr>
<td>Etemadifar et al. [37]</td>
<td>IFN β-1a i.m. 30 μg QW (n = 30) vs. IFN β-1b SC 250 μg EOD (n = 30) vs. IFN β-1a SC 44 μg TIW (n = 30) 24 months</td>
<td>1.2 vs. 0.7 vs. 0.6 (P &lt; 0.001) for each vs. baseline</td>
<td>20 vs. 43 vs. 57 (P &lt; 0.05)</td>
<td>ND</td>
<td>−0.1 (NS) vs. −0.7 (P &lt; 0.05) vs. −0.3 (P &lt; 0.05)</td>
<td>Single center. Evaluating physician blinded; patients unblinded to treatment allocation. No MRI data reported.</td>
</tr>
<tr>
<td>Koch-Henriksen et al. [38], (DMSSG)</td>
<td>IFN β-1a SC 22 μg QW (n = 143) vs. IFN β-1b SC 250 μg EOD (n = 158) 24 months</td>
<td>0.70 vs. 0.71 (NS)</td>
<td>ND</td>
<td>25 vs. 21 (NS)</td>
<td>ND</td>
<td>Physicians and patients unblinded; MRI-blinded assessment. IFN β-1a dosage was 22 μg weekly administered SC.</td>
</tr>
<tr>
<td>O’Connor et al. [39], (BEYOND)</td>
<td>GA SC 20 mg QD (n = 448) vs. IFN β-1b SC 250 μg EOD (n = 887) vs. IFN β-1b SC 500 μg EOD (n = 899) 24 months</td>
<td>0.34 vs. 0.36 vs. 0.33 (NS)b</td>
<td>59 vs. 58 vs. 60 (NS)b</td>
<td>69 vs. 77 vs. 84 (NS)b</td>
<td>ND</td>
<td>MRI favored both doses of IFN β-1b vs. GA for change in T2 lesion volume and cumulative new T2 lesions, (P &lt; 0.05 for all).</td>
</tr>
<tr>
<td>Mikol et al. [40], (REGARD)</td>
<td>GA SC 20 mg QD (n = 378) vs. IFN β-1a SC 44 μg TIW (n = 386) 36 weeks</td>
<td>0.29 vs. 0.30 (NS)</td>
<td>62 vs. 62 (NS)</td>
<td>8.7 vs. 11.7 (NS)</td>
<td>ND</td>
<td>Physicians and patients unblinded to treatment; evaluating physicians and MRI evaluations blinded.</td>
</tr>
<tr>
<td>Cadavid et al. [41], (BECOME)</td>
<td>GA SC 20 mg QD (n = 39) vs. IFN β-1b SC 250 μg EOD (n = 36) 24 months</td>
<td>0.33 vs. 0.37 (NS)</td>
<td>72 vs. 53 (P value not reported)</td>
<td>ND</td>
<td>ND</td>
<td>Physicians and patients unblinded to treatment.</td>
</tr>
</tbody>
</table>

DMSSG, Danish Multiple Sclerosis Study Group; EDSS, Expanded Disability Status Scale; EOD, every other day; GA, glatiramer acetate; HR, hazard ratio; i.m., intramuscular; IFN, interferon; ND, not determined; NS, not significant; QD, once per day; QW, once per week; SC, subcutaneous; TIW, three times per week.

bAt the time of this trial it was thought that IFN β-1a 22 μg would have equivalent efficacy whether administered subcutaneously or intramuscularly.

bNot statistically significant for either IFN β-1b dose vs. GA or for comparison of 250 vs. 500 μg doses of IFN β-1b.
opportunistic infection of the brain from reactivation of polyomavirus JC. Although the risk of PML with natalizumab is a concern, the ability to identify patients at risk has advanced with the findings that antibody to JC virus (JCV) and prior immunosuppressive therapy are associated with a significantly increased risk for PML in patients receiving natalizumab [51]. A serologic test for antibody to JC virus can identify patients who are seropositive and at elevated risk of PML [52]. Risk of PML can be stratified by JCV antibody status and immunosuppressive use and quantified by duration of natalizumab exposure. Current models estimated PML risks to range from 0.1 per 1000 for those JCV-antibody negative with no prior immunosuppressive use to 8.1 per 1000 in those JCV-antibody positive with prior immunosuppressive use and over 2 years of natalizumab exposure [53].

Women with MS who wish to become pregnant and/or breastfeed also need options that will permit them to stay on treatment; and a need remains for therapies that are approved for use during pregnancy and during breastfeeding. Fortunately, the risk for relapses is decreased during pregnancy, but is increased postpartum [54].

ADHERENCE TO DISEASE-MODIFYING THERAPIES IN PATIENTS WITH MULTIPLE SCLEROSIS

A variety of different measures have been used to quantify how well a patient follows a prescribed treatment regimen. Adherence to therapy is defined as the percentage of prescribed medication taken, and persistence is defined as continuing to take prescribed drugs [55].

Failures of persistence with and adherence to disease-modifying therapy are both important problems for patients with MS. Results from one study indicated that one-third of patients taking IFN-β interrupted treatment for more than 1 month over 5 years of follow-up and that more than 9% discontinued within 6 months [56]. Results from a more recent study of 6680 MS patients receiving disease-modifying treatments indicated that those taking i.m. IFN-β-1a possessed their medication for 77% of the days observed vs. 70% for subcutaneous IFN-β-1b, 72% for glatiramer acetate, and 74% for subcutaneous IFN-β-1a [57]. Time to nonpersistence with i.m. IFN-β-1a and subcutaneous IFN-β-1a is shown in Fig. 2. The time for 50% of patients to stop treatment was about 600 days after the index prescription [57]. Results from another study of 358 patients with MS whose healthcare claims were evaluated for 1 year indicated persistence rates of 85% for i.m. IFN-β-1a, 42.9% for subcutaneous IFN-β-1b, 42.7% for glatiramer acetate, and 45% for subcutaneous IFN-β-1a [58].

Patients with MS cite many different reasons for discontinuing treatment. The most common reasons for interrupting therapy among patients taking IFN-β are perceived lack of efficacy (30%), injection site reactions (12%), flu-like symptoms (10%), depression (9%), headache (8%), liver function test abnormalities (7%), and fatigue (6%) [55]. Requirement for injection has also been noted as a barrier to adherence in patients with MS taking disease-modifying therapy [59].

There is no published information about adherence to treatment with either natalizumab or fingolimod outside the setting of controlled clinical trials. However, patients who discontinue natalizumab may experience an aggressive return of disease activity shortly after discontinuation that is believed to reflect immune system reconstitution [60].

Poor adherence to disease-modifying therapy for MS patients is associated with both poorer treatment outcomes and increased cost of care. Results from a retrospective cohort study of 1606 MS patients indicated that those who were adherent to treatment (medication possession on ≥85% of days prescribed) had significantly lower risk for relapses [risk ratio = 0.89; 95% confidence interval (CI) = 0.81–0.97], emergency department visits (risk ratio = 0.78; 95% CI = 0.61–0.99), and hospitalizations (risk ratio = 0.79; 95% CI = 0.65–0.98) vs. nonadherent patients [61]. Results from a second study that included 2446 patients with MS prescribed disease-modifying therapy indicated that...
59.6% were adherent to treatment (defined as possessing medication on ≥80% of days prescribed). Adherent patients were significantly less likely than nonadherent patients to have MS-related hospitalization [odds ratio (OR) = 0.63, 95% CI = 0.47–0.83] or MS relapses (OR = 0.71, 95% CI = 0.59–0.85). The average cost of care for the adherent patients was $3380 vs. 4348 for those who were nonadherent (P = 0.003) [62**].

**CONCLUSION**

MS is a progressive and highly debilitating disease that results in high burdens for both individual patients and society. Current disease-modifying therapies for MS are effective for decreasing relapses and slowing progression, but a need for interventions that can completely arrest or even reverse progressive disability in these patients, remains.

Clinicians should consider treatment goals and carefully evaluate benefits of and patient adherence to current therapy. Goal assessment and individualization of therapy should include consideration of current disease activity and disability, patient lifestyle and expected longevity, patient’s preference for route of treatment administration, patient’s ability to self-treat or need for therapy to be delivered by a healthcare professional, and reproductive status and expectations.

**Acknowledgements**

None.

**Conflicts of interest**

A.E.M. has received consulting fees from Acorda, Avanir, Biogen Idec, BioMarin, Chelsea Therapeutics, Daichi Sankyo, EMD Serono, Glaxo, Merck Serono, Novartis, Nuron Biotech, Ono, LA-SER and Sanofi-aventis; fees for non-CME/CE services directly from a commercial interest or their agents (eg, speakers’ bureaus) from Acorda, Biogen Idec, EMD Serono, Pfizer, and Teva; and contracted research support from Acorda, Biogen Idec, Genentech, Genzyme, Novartis, Roche, Sanofi-aventis, and Teva. R.R. has no conflict of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- **of outstanding interest


New goals in MS treatment


This article summarizes adherence and persistence to disease-modifying treatments among patients with MS, and identifies beneficial outcomes associated with better adherence.


New treatments and treatment goals for patients with relapsing-remitting multiple sclerosis

Edward J. Fox and Robert W. Rhoades

Purpose of review
The aims of this article are to review emerging therapies for multiple sclerosis (MS) and to consider new approaches to assessment and achievement of treatment success in patients with this disease.

Recent findings
A number of disease-modifying therapies for MS, including oral agents, are in advanced development and likely to be available soon. Fingolimod has been approved recently by the US Food and Drug Administration. Agents in development include alemtuzumab, BG-12, daclizumab, teriflunomide, laquinimod, and B-cell-targeted monoclonal antibodies ocrelizumab and ofatumumab. The advent of emerging efficacious therapies has set the stage for re-evaluation of treatment goals for patients with MS. Freedom from disease, defined by the absence of relapses, disability progression, and radiologic evidence of disease activity, is increasingly seen as the measure of treatment success.

Summary
New MS treatments may provide the basis for aggressive early intervention in patients with MS and intensification of treatment when disease is not controlled. The availability of therapies that can achieve higher treatment goals may significantly improve long-term outcomes for MS patients.

Keywords
alemtuzumab, BG-12, daclizumab, fingolimod, freedom from disease, laquinimod, multiple sclerosis, ocrelizumab, ofatumumab, teriflunomide

INTRODUCTION
Patients with relapsing-remitting multiple sclerosis (RRMS) most often receive disease-modifying therapy with interferon (IFN)-β or glatiramer acetate [1]. These agents are relatively safe and well tolerated and their efficacy is supported by results from large randomized controlled clinical trials [1]. Relapses and disability progression may still occur in patients receiving disease-modifying therapy, and there is an unmet need for new treatment alternatives with the potential to improve outcomes in patients with RRMS [1]. The need for new therapies is underscored by the need to ‘raise the bar’ for treatment success in patients with RRMS. Until recently, treatments for RRMS were considered effective if they partially decreased the annual relapse rate (ARR) and slowed the accumulation of physical disability on the Expanded Disability Status Scale (EDSS) score, and this is reflected in the indication for all currently available MS therapies [1]. Advances in MS therapies should not only delay progression but provide freedom from disease, which has been defined as freedom from gadolinium-enhancing T1 or new T2 lesions detected by MRI, freedom from relapses, and the absence of disability progression [2].

Recently approved or investigational agents in advanced development have the potential to significantly improve outcomes for patients with RRMS. This review summarizes results from clinical studies of these medications and considers their potential place in clinical practice.

NEW DISEASE MODIFYING AGENTS FOR MULTIPLE SCLEROSIS
Several agents for disease modification in MS are in advanced development and may soon be available. Additionally, agents previously approved for other
indication are being evaluated for safety and efficacy in MS.

Fingolimod

Fingolimod is an oral sphingosine 1-phosphate (S1P) receptor modulator approved for the treatment of MS in 2010 in North America and 2011 in Europe. It is phosphorylated by sphingosine kinase to the active form, which binds with high affinity to S1P receptors (S1PR), of which five subtypes are present on various cells and tissues [3]. Binding of phosphorylated fingolimod results in internalization and degradation of the receptor and downregulation of S1PR mRNA. With the resulting decrease in S1PR on the cell surface, lymphocyte egress from lymphoid tissues into the periphery is inhibited [4]. This action is associated with decreased lymphocyte levels in the blood and cerebrospinal fluid (CSF) and reduced risk for inflammatory events characteristic of MS pathogenesis [5]. Fingolimod significantly reduces progression of experimental autoimmune encephalomyelitis (EAE) in experimental models, but effectiveness is lost in mice with S1PR defects in S1P1 and S1P3 [6,7]. The pleiotropic influences of S1P receptors in the immune and central nervous systems may be attributable to a combination of anti-inflammatory and neuroprotective effects.

Efficacy

Phase 3 clinical trial results with fingolimod have demonstrated efficacy in patients with RRMS. The 12-month, double-blind TRANSFORMS study randomized 1292 patients with RRMS and a history of at least one relapse to oral fingolimod (0.5 or 1.25 mg/day) or intramuscular (i.m.) IFN-β-1a (30 µg/week). The ARR was 0.16 for 0.5 mg/day fingolimod, 0.20 for 1.25 mg/day fingolimod, and 0.33 for IFN-β-1a (P < 0.001 for each fingolimod dose vs. IFN-β-1a). Patients in the fingolimod groups had significantly fewer new or enlarged hyperintense T2 lesions and gadolinium-enhancing T1 lesions at 12 months compared with those who received IFN-β-1a (all P < 0.05). There were no significant differences among groups with respect to EDSS scores [8]. A 1-year extension of TRANSFORMS compared patients randomized to 0.5 or 1.25 mg daily fingolimod who remained on these regimens with those who received IFN-β-1a in the core study and were randomized to one of the two fingolimod doses in the extension phase. During this period, investigators knew that participants were receiving fingolimod but doses remained blinded. Results showed the sustained efficacy of fingolimod for the study outcome measures [9]. Patients switched from IFN-β-1a to 0.5 mg/day fingolimod had a reduction in ARR (from 0.31 to 0.22; P = 0.049) and those switched to fingolimod 1.25 mg/day also had a significant decrease in ARR (from 0.29 to 0.18; P = 0.024). After switching to fingolimod, numbers of new or newly enlarging T2 and gadolinium-enhancing T1 lesions were significantly decreased compared with the previous 12 months of IFN-β-1a therapy (P < 0.0001 for T2 lesions at both doses; P = 0.002 for T1 lesions for 0.5 mg/day fingolimod and P = 0.011 for T1 gadolinium-enhancing lesions with 1.25 mg/day fingolimod) [9].

The phase 3 FREEDOMS trial was a 24-month, double-blind, randomized study that included 1272 patients with EDSS scores of 0–5.5, and at least one relapse in the previous year or at least two relapses in the previous 2 years [10]. Patients were randomized to 0.5 mg/day fingolimod, 1.25 mg/day fingolimod, or placebo. The ARR was 0.18 for 0.5 mg/day fingolimod, 0.16 for 1.25 mg/day fingolimod, and 0.40 for placebo (P < 0.001 for each dose vs. placebo). Fingolimod also decreased the risk for disability progression [hazard ratio = 0.70; 95% confidence interval (CI) = 0.52–0.96] for 0.5 mg/day fingolimod and (hazard ratio = 0.68; 95% CI = 0.50–0.93) for 1.25 mg/day fingolimod vs. placebo, respectively. Both fingolimod doses were associated with a significant decrease in the number of new or enlarged T2 lesions, the number of gadolinium-enhancing lesions, change in volume of hypointense T1 lesions, and brain-volume loss (P < 0.001 for all comparisons at 24 months) [10].
Safety

In the placebo-controlled phase 3 trial, lower respiratory tract infections were more common with fingolimod than with placebo (9.6–11.4% for fingolimod compared with 6% for placebo) [10]. Seven patients receiving fingolimod 1.25 mg were diagnosed with macular edema. Increases in alanine aminotransferase occurred in 8.5–12.5% of patients in the fingolimod treatment group compared with 1.7% in the placebo group, but returned to the normal range [10]. In the TRANSFORMS trial, herpesvirus infections were diagnosed in 23 patients in the 1.25 mg/day group (5.5%), nine patients in the 0.5 mg/day group (2.1%), and 12 patients in the placebo group (2.8%). There were two deaths in patients treated with 1.25 mg/day fingolimod, one due to disseminated primary varicella zoster infection and the other from herpes simplex encephalitis [8*].

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody against CD52, a glycoprotein antigen found on the surface of mature lymphocytes and monocytes. CD52 is absent from platelets, erythroid and myeloid cells, and hematopoietic stem cells. In transgenic mice expressing human CD52, alemtuzumab depletes peripheral blood lymphocytes with a lesser effect in lymphoid organs [11]. Alemtuzumab has also been shown to induce production of neurotrophic factors in reconstituted autoreactive T cells [12].

Efficacy

Alemtuzumab was studied in CAMMS223, a 3-year, phase 2, rater-blinded trial. CAMMS223 included 334 patients with RRMS, disease duration 3 years or less, and EDSS 3 or less, who were randomized to subcutaneous (SC) IFN-β-1a (44 μg three times per week) or annual intravenous (i.v.) cycles of alemtuzumab (12 mg/day for 5 days initially and for 3 days a year after) vs. subcutaneous IFN-β-1a (44 μg three times per week) in 581 patients with RRMS who had not received prior disease-modifying therapy. Results from this study showed that alemtuzumab treatment resulted in a 55% reduction in relapse rate vs. IFN-β-1a over 2 years (P < 0.0001). At 2 years, 8% of patients who received alemtuzumab and 11% of those treated with IFN-β-1a had a sustained increase in EDSS scores (P = 0.22) [15].

CARE-MS II is currently comparing alemtuzumab with IFN-β-1a subcutaneous in patients with RRMS who relapsed on prior therapy. The initial analysis of results in 840 patients showed a 49% reduction in relapse rate in patients receiving alemtuzumab 12 mg, compared with IFN-β-1a subcutaneous (P < 0.0001) [16]. The coprimary endpoint showed a 42% reduction in the risk of sustained disability measured by EDSS (P = 0.008).

Safety

In the CAMMS223 trial, adverse events in the alemtuzumab vs. IFN-β-1a subcutaneous groups included thyroid disorders (23 vs. 3%), immune thrombocytopenic purpura (ITP) (3 vs. 1%), and infections (66 vs. 47) [13]. In September 2005, the data and safety monitoring board (DSMB) recommended suspension of the alemtuzumab arm after three patients developed ITP, one of whom died. Safety and efficacy assessments proceeded during the suspension, and those randomized to IFN-β-1a subcutaneous continued treatment. A program was established for the effective identification and management of ITP, and the DSMB lifted the alemtuzumab dosing suspension in May 2007 [13].

In CARE MS-1, no patient receiving alemtuzumab withdrew from the trial due to an adverse event. Eighteen percent of alemtuzumab-treated patients developed an autoimmune thyroid-related
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adverse event and 0.8% developed ITP during the 2 year study [15]. Infections were reported more frequently in alemtuzumab-treated patients than in patients receiving IFN-β-1a subcutaneous-treated patients (67 vs. 46%). Infusion associated reactions were common in alemtuzumab-treated patients, but were typically controlled with concomitant medications.

There is evidence that the autoimmunity observed in MS patients receiving alemtuzumab may be driven by interleukin (IL)-21. Patients who developed secondary autoimmunity during treatment with alemtuzumab in the CAMMS223 study had more than two-fold greater levels of serum IL-21 at baseline than those who did not. Assesment of IL-21 may serve as a biomarker to help identify those at higher risk of developing autoimmunity [17].

BG-12 (Dimethyl Fumarate)

BG-12 is a fumaric acid ester with immunomodulatory properties. BG-12 has demonstrated benefits in animal models of EAE. Fumaric acid esters may decrease leukocyte passage through the blood–brain barrier and exert neuroprotective properties by the activation of antioxidative pathways [18].

Efficacy

DEFINE was a phase 3, randomized, double-blind, placebo-controlled, dose-comparison study of BG-12 in 1234 patients [19]. Patients with RRMS were randomized to BG-12 at a dose of either 240 mg twice a day or 240 mg three times a day, or to placebo. Both BG-12 doses were associated with a significant decrease in the proportion of patients who relapsed at 2 years compared with placebo (P < 0.0001). Both BG-12 doses were significantly superior to placebo in reducing ARR, the number of new or newly enlarging T2 hyperintense lesions, and the number of new gadolinium-enhancing lesions. BG-12 was also superior to placebo in slowing the rate of disability progression as measured by EDSS scores at 2 years [19]. The reduction in 12-week disability progression was 38 and 34% for the twice and three-times daily doses, respectively (P < 0.05 for both).

Safety

DEFINE results indicated that BG-12 had a safety profile comparable to that for placebo [19]. Results from a phase 2b study of BG-12 (120 or 240 mg three times per day) in 257 patients with RRMS indicated that adverse events occurring more often with BG-12 vs. placebo were abdominal pain, flushing, and hot flush [20]. Dosing interruptions were allowed for abnormal results of liver or renal function tests or lymphopenia, and treatment was discontinued in patients with abnormalities persisting for 4 weeks. Adverse events led to discontinuation in 8, 11, and 13% of those receiving BG-12 doses of 120 mg once daily, 120 mg three times daily, and 240 mg three times daily, respectively. Events leading to discontinuation included flushing, elevated alanine aminotransferase, nausea, diarrhea, and vomiting. There was no increased risk of infection associated with BG-12 use.

Laquinimod

Laquinimod is an immunomodulator with efficacy in MS. Although its mechanism of action is not fully understood, laquinimod has been shown to promote anti-inflammatory cytokine profiles in human peripheral blood mononuclear cells. In EAE models, laquinimod effectively reduced inflammation, demyelination, and axonal damage [21].

Efficacy

Laquinimod has been evaluated in the phase 3 ALLEGRO trial, a 2-year randomized, double-blind, placebo-controlled study that included 1106 patients with RRMS who were randomized to receive 0.6 mg laquinimod once daily or placebo. The primary outcome measure was the number of confirmed relapses. Laquinimod treatment resulted in a 23% reduction in ARR vs. placebo (P = 0.0024) and a 36% decrease in the risk for disability progression, as measured by EDSS (P = 0.0122). Treatment with laquinimod was also associated with a 33% reduction in progression of brain atrophy vs. placebo (P < 0.0001) [22].

A second phase 3 study of laquinimod, the BRAVO trial, is comparing 0.6 mg laquinimod once daily with placebo in patients with RRMS. The top-line results of BRAVO showed that the primary endpoint of reducing ARR was not reached (P = 0.075). Despite randomization, the laquinimod and placebo groups had dissimilar baseline MRI characteristics. After a preplanned sensitivity analysis adjusting for baseline MRI, laquinimod was associated with a statistically significant reduction of ARR (21.3%), of risk of disability progression on EDSS (33.5%), and of brain volume loss (27.5%) compared with placebo (all P < 0.05) [23].

Safety

In ALLEGRO, serious adverse events occurred in 22.2% of laquinimod patients and 16.2% of placebo patients. Herpesvirus infection occurred in 17 patients who received laquinimod vs. 20 patients on placebo, with cancers detected in 8 vs. six patients, respectively. The most
common adverse event that occurred more often with laquinimod vs. placebo was elevation in alanine transaminase (6.9% with laquinimod vs. 2.7% for placebo; elevations were more than three times the upper limit of normal in 4.9 and 2% of the laquinimod and placebo groups, respectively). Transaminase elevations, which were transitory, resulted in discontinuation in 13 patients receiving laquinimod and seven on placebo [22].

**Teriflunomide**

Teriflunomide is an oral reversible inhibitor of dihydroorotate dehydrogenase (DHODH), a mitochondrial membrane protein essential for pyrimidine synthesis [24]. DHODH blocks de-novo pyrimidine synthesis leading to an inhibition of the proliferation of autoreactive B and T cells. In the presence of teriflunomide, replication of hematopoietic and memory cells is preserved through metabolism of the existing pyrimidine pool. Teriflunomide has been shown to have additional activities, including modulation of immunoglobulin class switching, IL-2 production, and IL-2 receptor expression [25].

**Efficacy**

Teriflunomide (7 or 14 mg/day) was compared with placebo in a 36-week phase 2 trial in 157 patients with RRMS and 22 patients with secondary progressive MS still experiencing relapses. The mean values for the primary endpoint of combined unique active lesions per MRI scan were 0.5, 0.2, and 0.3, respectively, for placebo, 7 mg/day teriflunomide (\(P < 0.03\) vs. placebo), and 14 mg/day teriflunomide (\(P < 0.01\) vs. placebo). Patients who received teriflunomide also had significantly fewer T1-enhancing lesions or new or enlarging T2 lesions than those treated with placebo (\(P < 0.05\) all comparisons). Patients receiving teriflunomide 14 mg/day had significantly reduced T2 disease burden. The proportion of patients with increased disability by EDSS at 36 weeks was significantly lower with teriflunomide compared with placebo (7.4 vs. 21.3%, \(P < 0.04\)), a relative reduction of 69% [26]. Two phase 2 studies evaluated teriflunomide as adjunctive therapy in persons with MS [27,28]. In these studies, patients receiving glatiramer acetate (\(n = 120\)) or a β-IFN (\(n = 116\)) were randomized to add placebo or teriflunomide 7 or 14 mg daily to their current therapy. In both studies, teriflunomide had good safety and tolerability and both doses were associated with improved disease control according to reduced number and volume of T1 gadolinium-enhancing lesions, compared with placebo.

Results from the phase 3 TEMSO study demonstrated significant reduction in ARR and disability progression with teriflunomide compared with placebo. TEMSO evaluated 1088 patients with relapsing forms of MS, EDSS scores at least 5.5, and at least one relapse in the previous year or at least two relapses in the preceding 2 years. Patients were randomized to teriflunomide 7 or 14 mg/day, or placebo. The adjusted ARRs with teriflunomide 7 and 14 mg/day were 0.370 and 0.369, respectively, compared with 0.539 for placebo (\(P < 0.001\) for both comparisons) [29]. Time to first relapse was increased 24.4 and 28.1% for the 7 and 14-mg doses compared with placebo, respectively (\(P < 0.01\) for both comparisons). The 14-mg/day dose of teriflunomide was associated with a 29.8% reduction in the risk of sustained disability progression (\(P = 0.028\)).

A key prespecified endpoint of TEMSO was T2 burden of disease by MRI. Teriflunomide 7 mg/day resulted in a 39.4% reduction in T2 disease burden vs. placebo (\(P = 0.03\)); and teriflunomide 14 mg/day resulted in a 67.4% reduction (\(P < 0.001\) vs. placebo). The numbers of gadolinium-enhancing T1 lesions and unique active lesions per scan were also reduced with both teriflunomide doses vs. placebo (\(P < 0.001\) for all comparisons) [30].

Teriflunomide is also being evaluated as an adjunctive therapy in combination with IFN-β in the phase 3 TERACLES study, with estimated completion in 2014. Two additional studies are underway; TOWER and TENERE are monotherapy studies comparing teriflunomide with placebo and IFN-β-1a subcutaneous, respectively [31]. TOPIC is an ongoing phase 3 trial evaluating the efficacy and safety of once daily teriflunomide vs. placebo in patients with clinically isolated syndrome [32].

**Safety**

In the phase 2 study, serious adverse events were reported in 19 patients (seven placebo, five teriflunomide 7 mg/day, and seven teriflunomide 14 mg/day). These included elevated hepatic enzymes, hepatic dysfunction, neutropenia, rhabdomyolysis, and trigeminal neuralgia. Adverse events that appeared to occur more often with teriflunomide than placebo included nausea, paresthesia, limb pain, diarrhea, and arthralgia [26]. Teriflunomide was generally well tolerated in the TEMSO trial. Adverse events occurring at a higher rate in the teriflunomide groups vs. placebo were diarrhea, nausea, and alanine transferase increases. No serious opportunistic infections occurred in patients treated with teriflunomide [26].

**B cell depletion**

Several treatments are in development for the therapy of MS that target B cells. This therapeutic strategy is supported by observations that activated
B cells and plasma cells accumulate in MS lesions and in the CSF of patients with MS. B cells may contribute to MS pathology by production of anti-myelin autoantibodies and by regulating T cell responses via antigen presentation, cytokine release, and induction of regulatory T cells [33].

**Rituximab**

Rituximab is a chimeric monoclonal antibody that depletes CD20-positive B cells through cell-mediated and complement-dependent cytotoxic effects and promotion of apoptosis. In a phase II trial in patients with RRMS, rituximab treatment resulted in significantly decreased numbers of gadolinium-enhancing lesions vs. placebo (−91%; \( P < 0.001 \)) as well as a significantly decreased risk for relapse (20.3 vs. 40.0%, \( P = 0.04 \)) [34]. Rituximab was associated with infusion-related reactions and moderately increased risk of progressive multifocal leukoencephalopathy (PML) in patients receiving this agent for approved indications. Owing to an impending patent expiration and efficacy and safety concerns for use of rituximab in patients with MS, no phase 3 development of rituximab in MS is ongoing.

**Ocrelizumab**

Ocrelizumab is a humanized anti-CD20 monoclonal antibody that results in B cell depletion. It has been evaluated in a 48-week phase 2 study that included 220 patients with RRMS who were randomized to treatment with i.v. ocrelizumab (600 or 2000 mg for the first 24 weeks and 1000 mg for the second 24 weeks), i.m. IFN-\( \beta \)-1a (30 \( \mu \)g once weekly), or placebo. The mean number of gadolinium-enhancing lesions was reduced by 89% in the low-dose and 96% with high-dose group compared to placebo. At the end of 48 weeks of treatment, 80% of the patients who received the 600-mg dose and 72.7% of those who received the 2000/1000-mg dose were relapse-free. One patient on ocrelizumab died at 14 weeks due to brain edema after the occurrence of a systemic inflammatory response syndrome. No opportunistic infections were reported [35]. Phase 3 studies of ocrelizumab for rheumatoid arthritis and lupus were suspended when the respective DSMBs decided the risks outweighed the benefits in these patient populations [36].

Ocrelizumab is also being evaluated in ORATORIO, a 120-week, phase 3, double-blind, randomized, placebo-controlled trial in patients with primary progressive MS [37]. This trial consists of five treatment cycles of i.v. ocrelizumab 600 mg. The primary outcome measure is time to onset of sustained disability progression [34]. Two large global studies will compare ocrelizumab with IFN-\( \beta \)-1a subcutaneous (OPERA I and II) in patients with RRMS [38]. These phase 3, double-blind, double-dummy trials will assess efficacy and safety in patients randomized to ocrelizumab 600 mg i.v. every 24 weeks or IFN-\( \beta \)-1a subcutaneous three times weekly. Enrollment (\( N = 800 \)) is projected to be completed in 2012, with data reported in 2014.

**Ofatumumab**

Ofatumumab is a third anti-CD20 antibody being developed for the treatment of MS. A 24-week, phase 2 safety and pharmacokinetics study in 38 patients with RRMS indicated no dose-limiting toxicities and no unexpected safety findings. Active treatment also resulted in significant reductions in the number of gadolinium-enhancing T1 lesions and new/enlarging T2 lesions in patients treated with ofatumumab vs. placebo [39]. This agent has not yet proceeded to phase 3 development.

**Daclizumab**

Daclizumab is a humanized monoclonal antibody directed against the high-affinity IL-2 receptor. This receptor is present on activated, but not resting, T cells. Binding of IL-2 to this receptor is necessary for clonal expansion and continued viability of activated T cells [40]. Although the anti-inflammatory effects of daclizumab were believed to result from decreased T cell activation, it is not associated with significant changes in T cell or B cell numbers or the ability of T cells to proliferate. It appears that the effects of daclizumab may be related to an increase in immunoregulatory CD56\textsuperscript{bright} natural killer cells [41].

**Efficacy**

Daclizumab was evaluated for the treatment of RRMS in the phase 2 CHOICE trial. It was a double-blind placebo-controlled study in 230 patients with active disease despite IFN-\( \beta \) treatment. Patients were randomized to receive subcutaneous daclizumab 2 mg/kg every 2 weeks, subcutaneous daclizumab 1 mg/kg every 4 weeks, or placebo for 24 weeks, as an adjunct to their current IFN-\( \beta \) therapy (46% subcutaneous IFN-\( \beta \)-1a, 30% i.m. IFN-\( \beta \)-1a, and 24% subcutaneous IFN-\( \beta \)-1b). The primary endpoint was the total number of new or enlarged gadolinium-enhancing lesions detected between weeks 8 and 24. The mean number of new or enlarged gadolinium-enhancing lesions was 4.75 in the IFN-\( \beta \)-placebo group vs. 1.32 for patients who received IFN-\( \beta \) with high-dose daclizumab (\( P = 0.004 \)), and 3.58 for those treated with IFN-\( \beta \) with low-dose daclizumab (\( P = 0.51 \)).
Daclizumab is also being compared with i.m. IFN-β-1a in a phase 3 study in patients with RRMS. The estimated date for completion is 2014 [43].

SELECT is a phase 2b clinical trial that evaluated two doses of daclizumab (150 or 300 mg every 4 weeks) in 600 patients with RRMS [44]. At 1 year, daclizumab was associated with 54 and 50% reductions in AAR for the 150 and 300-mg dose groups, respectively ($P < 0.001$ vs. placebo for both doses).

**Safety**

Safety data from the CHOICE trial indicated similar rates of infection across all treatment groups. The incidence of cutaneous adverse events was higher in the combined daclizumab groups (34%) vs. placebo (27%); grade 3 cutaneous events included rash ($n = 1$) and eczema ($n = 2$) in the daclizumab group. A higher incidence of grade-3 or grade-4 infections occurred in those who received daclizumab (4.6%) vs. placebo (1.3%). Grade 3 infections occurred in 10 patients in the high-dose daclizumab group, two in the low-dose daclizumab group, and two in the placebo groups. No opportunistic infections were observed and all infections resolved with therapy [42].

**Cladribine**

Cladribine is an immunosuppressant whose active metabolite disrupts cellular metabolism, inhibits DNA synthesis and repair, and leads to apoptosis of lymphocytes [45]. Cladribine has been shown to be effective for the treatment of RRMS in the CLARITY trial [45], but concerns about sustained immunosuppression and associated cancer risk resulted in withdrawal of applications for marketing authorization in the European Union [46] and discontinuation of development in the United States [47].

**Benefits and limitations of emerging therapies for multiple sclerosis**

The availability of new therapeutic options for disease modification has the potential to expand options for persons with MS. These new therapies have the potential to redefine the goals of therapies in the context of appropriate patient selection and management strategies.

**Changing the course of disease**

A goal for the treatment of MS not yet realized for many patients is freedom from disease activity, defined as a complete absence of relapses, MRI evidence of disease activity, and progression of disability [2]. Freedom from disease activity was demonstrated for 29.5% of patients treated with natalizumab in the AFFIRM trial [2], which is a reasonable benchmark for assessment of new MS therapies. Further, 3-year results from the CAMMS223 study indicated alemtuzumab often decreased EDSS scores rather than slowing increases [13].

Changing the course of disease in patients with MS is closely linked to the concept of neuroprotection. At present, the mechanisms underlying neurodegeneration in MS and how to promote neuroprotection are not completely understood [48]. Moreover, there is no consensus on biomarkers for neuroprotection that could be evaluated in studies of MS therapies [49]. A variety of measures have been suggested as potential candidates for assessment of neuroprotection in clinical trials [50]. It has been proposed that brain volume change on serial MRI may provide a sensitive overall measure of neuroprotection in MS trials [50]. However, the use of whole-brain atrophy to assess neuroprotection lacks specificity for tissue-related processes (e.g., loss of myelin or axons and increase in glial content). Inflammation can also confound atrophy measurements [51]. Prevention of white matter atrophy may be a practical MRI measure for assessment of neuroprotective effects of MS treatments. Loss of white matter reflects axonal damage and subsequent degeneration of neuronal cell bodies and gray matter atrophy [52].

**Challenges in patient selection and monitoring**

Although potentially providing improved efficacy, new treatments for MS also present challenges in patient selection and monitoring. For example, an electrocardiogram, ophthalmologic evaluation for macular edema, assessment of pulmonary function, and liver function tests are all recommended prior to initiation of treatment with fingolimod [53]. Patients receiving alemtuzumab will also require close monitoring for autoimmunity, and it is possible that pretreatment assessment of IL-21 levels may be useful for risk stratification with this treatment [17]. Rituximab requires monitoring of neurologic function due to risk for PML in patients receiving it for its current indications [54]. This requirement may extend to any anti-B-cell antibody approved for the treatment of MS. Increasing monitoring of patients for infection or malignancy will be important for many of the new MS treatments based on safety results from phase 2 and 3 clinical trials.
CONCLUSION

The emergence of a large number of new disease-modifying treatments for MS should prompt a re-evaluation of our approaches to the long-term management of these patients. First and most importantly, we need to set a higher standard for treatment success. Freedom from disease, as defined in preceding sections, should be our target. It is likely to be achievable in many patients using newer therapies, either alone or in combination with currently approved agents. Setting a higher standard for treatment success will result in less tolerance of relapses, clinical evidence of progression, or new lesions detected on MRI. Physicians are more likely to intensify treatment as necessary to recover more control over the disease.

Early initiation of disease-modifying therapy is also an important component of advancing treatment for MS. The Multiple Sclerosis Therapy Consensus Group recommends early initiation of treatment with the goal of terminating inflammation and reducing axonal damage [55]. Early intervention with the best available therapy and a high standard for treatment success has the potential to significantly improve long-term outcomes for MS patients.

Acknowledgements

None.

Conflicts of interest

E.F. has received consulting fees from Bayer, Biogen Idec, EMD Serono, Genzyme, Novartis, Opexa, and Teva; fees for non-CME/CE services directly from a commercial entity with the best available therapy and a high standard for treatment success has the potential to significantly improve long-term outcomes for MS patients.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as: ■ of special interest ◦ of outstanding interest


A useful current review summarizing principles of neuroprotection as a consideration of current and emerging disease-modifying therapies.


Rituxan [package insert]. South San Francisco, CA; Genentech, Inc; 2011.

Individualizing treatment goals and interventions for people with MS

Gavin Giovannoni and Robert W. Rhoades

Purpose of review
The aim of this article is to consider factors that should be evaluated in the selection of therapy for people with multiple sclerosis (MS). This includes a review of current approaches to treatment selection and how to align this process with patients’ treatment goals. These issues have increased in importance with the availability of new disease-modifying therapies and will continue to do so as more novel treatments are approved.

Recent findings
The model for decision making in the management of people with MS as well as other chronic diseases has evolved from one in which medication is prescribed by the neurologist and the person is expected to comply with treatment, to one in which the neurologist and individual with MS achieve concordance with respect to both the expectations and goals of therapy and the means to achieve them. This shift has resulted in a requirement for easily understood evidence-based information about the risks and benefits of different treatment alternatives. It has been demonstrated that providing MS sufferers with such information increases effective self-management and satisfaction.

Summary
Healthcare providers involved in the treatment of MS have an increased responsibility to ensure people with this disease, their partners, and when appropriate, their families are involved in all decisions regarding care. This includes helping to select and adjust therapy on the basis of the individual MS sufferer’s characteristics and needs that are likely to evolve as the disease progresses.

Keywords
concordance, education, individualization, risk-benefit

INTRODUCTION
Multiple sclerosis (MS) is a disease in which disability progresses for many sufferers despite effective disease-modifying therapies [1,2]. It cannot be cured with current therapies. As a result, the generally accepted goals of treatment for MS sufferers are as follows: improve quality of life (QOL) by relieving symptoms caused by exacerbations and reduce the number of these events; reduce MRI activity; delay the onset of secondary progressive MS; slow or stop the course of disease progression; and minimize treatment-associated adverse events [3]. Although these overall goals are generally accepted, they also may vary substantially from one MS sufferer to another. This article focuses on MS sufferer-related, disease-related, and medication-related factors that should be considered in selection of therapy for persons with relapsing-remitting MS (RRMS). It also considers the importance of education and communication aimed at understanding MS sufferer needs, managing expectations, and establishing treatment goals in concordance with the person with MS; and the potential for this approach to improve adherence to therapy and outcomes.

PATIENT-RELATED FACTORS THAT SHOULD BE CONSIDERED IN SETTING TREATMENT GOALS
A very large number of factors should be considered in tailoring treatment for the person with MS (Fig. 1) [4]. Characteristics that may influence treatment goals and selection of therapy include age, culture,
education, duration of disease and degree of disability, desired lifestyle, work requirements, literacy and health literacy, coping skills, treatment history (e.g., inability to tolerate specific agents and/or adhere to self-injection regimens), preferences for route of drug/biologic delivery, degree of family/social support, and risk tolerance/aversion [5,6]. For example, younger and more active MS sufferers with important work/family responsibilities may want treatment with the greatest potential to slow disease progression and may be willing to accept increased risk for adverse events to achieve this goal. Older, more sedentary persons with long-standing and slowly progressing disease may be willing to accept treatments with lower efficacy in order to avoid the potential for rare, but potentially serious, adverse events.

Consideration of MS sufferer characteristics listed in the preceding paragraph may influence both the treatment selected and route of administration. For example, oral disease-modifying therapy is now available, and many persons with MS may prefer an oral drug. However, the ultimate choice of route of treatment administration should be a decision shared by the person with MS and his or her healthcare providers [7] and within national guidelines. For example, those with a high probability of poor adherence with self-treatment may benefit from a therapy delivered at specific visits in a healthcare setting. Conversely, MS sufferers who are more likely to adhere to their therapies may prefer a self-injected or oral medication.

ACHIEVING CONCORDANCE IN MULTIPLE SCLEROSIS TREATMENT

Achieving concordance with the person with MS is an important initial consideration in individualizing treatment for individuals with MS. Concordance

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**FIGURE 1.** Considerations for individualization of treatment in persons with multiple sclerosis [4].
is a very different concept from compliance to therapy. Compliance is defined as the extent to which the behavior of the individual being treated matches the prescriber’s recommendations. It implies a limited role for the person being treated in selection of therapy and in deciding whether or not to take it [8]. Adherence is defined as the extent to which the behavior of the person being treated matches agreed-upon recommendations from the prescriber. It emphasizes that he or she is free to decide whether to adhere to the neurologist’s recommendations and that failure to do so should not be a reason for blame [8]. Concordance is a broader concept that includes the consultation process, in which the neurologist and MS sufferer agree upon therapeutic decisions that incorporate their respective views and patient support for taking of medications [8,9]. The differences between the compliance and concordance approaches for prescription and taking of medication are summarized in Table 1 [8,10,11].

One of the assumptions underlying a concordance model for prescribing and taking of medications is that the MS sufferer desires involvement in these decisions [10]. Results from surveys of such individuals indicate that this is the case. One survey indicated that about 80% of MS sufferers desire autonomous roles in treatment decisions [12,13]. In another small-scale survey, Paterson et al. [14] assessed MS sufferers’ approaches to everyday self-care decision making. These investigators interviewed 21 persons with type 2 diabetes, HIV/AIDS, or MS who were identified as ‘expert self-care managers’ by their clinicians. Study results indicated that these individuals made decisions based on a large number of disease-specific elements related to timelessness, interpretation of biomarkers, interaction within a social context, the construction of health practices, and available relevant information. The MS sufferers stated that they made numerous self-care decisions every day, and that these decisions were made in view of short-term, intermediate-term, and long-term consequences [14].

**MULTIPLE SCLEROSIS SUFFERERS’ ASSESSMENTS OF DISEASE AND TREATMENT RISKS AND BENEFITS**

MS sufferers’ involvement in decisions regarding MS treatment includes making judgments about the impact of the disease and the risks and benefits of treatment. There may be substantial differences between patients’ and neurologists’ perceptions of these issues. In one study, 42 consecutive MS sufferers attending a neurology outpatient clinic completed the SF-36 and EuroQol assessments. A neurologist measured neurological impairment using the Expanded Disability Status Scale and an independent nonclinically qualified assistant administered the disability questionnaire of the Office of Population Censuses and Surveys. Study results indicated that persons with MS and clinicians disagreed on which domains of health status were most important. MS sufferers’ assessments of their physical disability using the physical functioning domain of the SF-36 were highly correlated with the clinicians’ evaluations and the nonclinical measurements. However, none of the measures of physical disability correlated with overall health-related QOL measured with EuroQol. These investigators concluded that persons with MS are less concerned than their clinicians about physical disability in their illness [15].

Persons with MS are also willing to accept significant risk to achieve their treatment goals, and they may be less risk averse than their neurologists. In one study, 651 MS sufferers chose hypothetical treatments from pairs of alternatives with varying

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**Table 1. Comparison of the compliance and concordance models [8,10,11]**

<table>
<thead>
<tr>
<th>Compliance</th>
<th>Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s behavior is consistent with the prescriber’s recommendation</td>
<td>Provider and patient formulate therapeutic decisions that incorporate their respective views to support medication taking</td>
</tr>
<tr>
<td>Aim is to enhance patient adherence to prescribed medication regimen</td>
<td>Aim is to optimize health gain from use of medications, compatible with what the patient desires and can achieve</td>
</tr>
<tr>
<td>Patient follows health professionals direction; patient may be deferential or passive</td>
<td>Agreement between the patient and provider based on shared decision making</td>
</tr>
<tr>
<td>Patient may be reluctant to voice reservations or confide in their provider about missed doses or use of complementary therapies</td>
<td>Provider respects the beliefs and wishes of the patient in determining whether, when, and how their medicine is taken; primacy of the patient’s decision is recognized</td>
</tr>
<tr>
<td>Provider gives patient minimal information about medication and may not assess patient comprehension</td>
<td>Patient is better informed and a more active participant leading to greater adherence to his or her plan</td>
</tr>
</tbody>
</table>
levels of clinical efficacy and associated risks. Study results indicated that delay in years to disability progression was the most important factor in treatment preferences. In return for decreases in relapse rates from 4 to 1 and increases in delay in progression from 3 to 5 years, persons with MS were willing to accept a 0.38% annual risk of death or disability from progressive multifocal leukoencephalopathy (PML), a 0.39% annual risk of death from liver failure, or a 0.48% annual risk of death from leukemia [16]. Another study assessed MS sufferers’ and neurologists’ perceptions of risks associated with MS therapy with natalizumab. This treatment is highly effective, but is associated with a rare, but potentially fatal opportunistic infection, PML [17,18]. In this study, 69 persons with MS receiving treatment with natalizumab and 66 neurologists received an evidence-based informational brochure about the risk of PML and were asked to fill out an evaluation sheet. After reading the information, persons with MS were significantly more likely than neurologists to continue natalizumab treatment and willing to accept higher risks of PML; 49% of neurologists would stop treatment at a PML risk of 2 : 10 000 or higher, whereas only 17% of MS sufferers would do so at that event rate [19**]. Results from another survey of risk acceptance that included results from 5446 persons with MS in the North American Research Committee on Multiple Sclerosis registry indicated that one-half of the respondents would accept a mortality risk more than 1 in 10 000 for a hypothetical MS cure [20**].

It has also been shown that MS sufferers’ prior experience with treatment significantly influences assessment of risk and benefit. In a cross-sectional study conducted between 2007 and 2009, ambulatory sufferers with RRMS and without significant depression or cognitive impairment and who had been taking an IFN-β or glatiramer acetate were asked to respond to a series of questions during a clinic visit [21**]. They were asked if they would consider switching to a new therapy with mild risk and requiring mild vigilance, a new therapy with significant risk and requiring significant vigilance, a new oral therapy with mild risk and requiring mild vigilance, and a new oral therapy with significant risk and requiring significant vigilance. MS sufferers were divided into groups based on duration of therapy (<5 years or ≥5 years), with 100 in each group. Persons with MS in both groups indicated they would favorably consider switching to new therapies that carry a mild risk and require mild vigilance or treatment monitoring, with more than 90% in each group indicating they would consider switching to a new oral therapy with mild risk requiring mild vigilance (Fig. 2). Those with longer disease duration were significantly more likely to switch to a new therapy with significant risk and requiring significant vigilance than MS sufferers with shorter treatment durations. More MS sufferers

**FIGURE 2.** Results of a survey of relapsing-remitting multiple sclerosis patients undergoing self-injected disease modifying therapy (DMT). Patients were administered standardized questionnaires to ask if they would consider switching to a new therapy that was oral or injectable and was associated with mild or severe risk and vigilance [21**].

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with longer disease duration (59%) than with shorter disease duration (31%) said they would consider switching to a new oral therapy with significant risk requiring significant vigilance. Persons with MS in both groups (70% for shorter treatment duration and 91% for longer duration) favored a reduction in disability progression over decreased relapses as a 10-year treatment outcome [21**].

All of the results reviewed in this section underscore the importance of developing, validating, and implementing tools to educate persons with MS about risk and to help align their perceptions of risk with those of their neurologists.

**HELPING PERSONS WITH MULTIPLE SCLEROSIS MAKE INFORMED TREATMENT DECISIONS**

In the concordance model, a major role of the clinician who manages persons with MS is to inform, advise, and work with them as part of a team to decide on a course of therapy that best meets their needs. Morgante et al. [22] have described approaches to helping persons with MS make better decisions about their care. The approaches are as follows:

1. Establish a collaborative, trusting relationship.
2. Be nonjudgmental (understand the MS sufferer’s perspective).
3. Explore MS sufferer’s health beliefs and values, focusing on ethnic/cultural differences (e.g., ask about previous experiences).
4. Assess the MS sufferer’s support system (family, employment, finances).
5. Identify obstacles to MS sufferer participation in decision making (e.g., cognitive limitations).
6. Clarify treatment options by explaining the risks and benefits of each therapy.
7. Identify the MS sufferer’s priorities.
8. Listen to the MS sufferer’s concerns.
9. Help the person with MS recognize and achieve personal comfort with decision making.
10. Advocate for the person with MS if his/her decision goes against the team’s consensus.
11. Help the MS sufferer implement his/her decision (e.g., navigate insurance hurdles).
12. Evaluate the outcome of the decision.
13. Realize that decision making is a continuous process.

These investigators noted that newly diagnosed MS sufferers may be compelled to make important and emotionally charged decisions regarding treatment that may be influenced by fears about the future. Clinicians should assess the individual MS sufferer’s ability and willingness to participate in the decision-making process and tailor interactions accordingly [22]. It has been suggested that education of persons with MS and shared decision making can result in improved treatment satisfaction, better communication by MS sufferers of their values to clinicians, and earlier recognition of ineffective or harmful therapies [23]. In addition, these approaches may result in risk-averse MS sufferers appropriately initiating immunomodulatory therapy early in the course of the disease [23].

In counseling individuals about treatment for MS, neurologists need to be aware of their ability to influence MS sufferers’ decisions and the potential impact of changing their opinions. One recent study investigated whether neurologists’ recommendations caused persons with MS to change their treatment selection. This investigation included 101 persons with MS who were presented with a hypothetical choice between two drugs. They selected a medication, and then received a fictitious clinician’s recommendation for the alternative choice. They then made a final choice between the two agents. Overall, 26% of the persons with MS followed the advice of their neurologist and thus chose the treatment option that differed from their initial preference. Those who followed their neurologist’s advice were less satisfied with their decision than patients who did not [24].

Engaging the person with MS in decision making regarding his or her MS treatment requires the provision of evidence-based information. This has been defined as information about relevant treatment effects communicated in absolute numbers (as absolute risk reductions and/or numbers needed to treat), preferably with the use of illustrations. Presentation of relative risk reductions should be avoided as these are not intuitively understood by MS sufferers and usually overestimate treatment effects [25]. Although absolute risk data may be more readily comprehended, they are derived from clinical trial data and patients should understand that their individual situation is unique. It has been suggested that evidence-based patient information should also focus on the most relevant outcomes for persons with MS (e.g., relapses) with less attention to surrogate measures (MRI results) [26]. These approaches to presentation of information were implemented in an education program aimed at involving MS sufferers in decisions on relapse management. In this study, 150 persons with RRMS were randomized to a single, 4-h group session on relapse management (intervention group) or a standard information leaflet (control group). The
author assumed the group session would increase decision autonomy. The primary outcome measure was the proportion of relapses treated with self-administered oral corticosteroids or no corticosteroids (oral or intravenous therapy) as an indicator of MS sufferer autonomy in treatment decision making. Study results indicated that 78% of persons with MS in the intervention group chose to treat their relapse with oral corticosteroids or no corticosteroids. This was the case for 56% of those treating relapses in the control group. Intravenous corticosteroids were administered on an inpatient or outpatient basis to 22% of MS sufferers in the intervention group vs. 44% of those in the control group. Autonomy of treatment decision making in the intervention group was also reflected by fewer visits and telephone calls to neurologists to gain assistance in managing relapses [27].

Although provision of evidence-based decision aids has gained wide acceptance, concerns have been raised about delivery of such information to persons evaluating treatments, even in highly simplified formats. It has been noted that more than one-half of adults have significant difficulty understanding or applying probabilistic and mathematical concepts and that at least 22% have only the most basic quantitative skills, such as counting; whereas another 33% can do only simple arithmetic. In addition, people may also be biased in their interpretation of risks. They may give exaggerated importance to small risks or, conversely, exhibit optimism bias and exaggerate the chance that they will be among those who benefit from treatment [28]. All of these concerns underscore the importance of the neurologist-MS sufferer interaction in assessing the risks and benefits of alternative treatments in reaching a concordant decision regarding a therapeutic regimen.

**EFFECTS OF CONCORDANCE ON ADHERENCE TO THERAPY AND TREATMENT OUTCOMES**

Although much has been written about the potential benefits of a concordance approach to treatment selection in persons with MS, there is as yet relatively little evidence from controlled studies to support this approach. However, studies of individuals with other chronic diseases that require significant decisions regarding treatment have indicated substantial benefits with this model. A study of concordance during decision making regarding HIV treatment switching and stopping in relation to patient health-related outcomes included 217 patients who completed a scale that measured concordance. Concordance was measured between the HIV patients’ and physicians’ opinions regarding the change in treatment. Higher concordance was significantly associated with better QOL, less severe and burdensome symptom experience, lower global distress index scores, fewer symptoms reported, higher CD4 cell count, and significantly greater adherence to treatment [29]. The use of a concordance model has also been shown to be effective for controlling blood pressure in individuals with diabetes. Results from a survey of 212 older persons with hypertension and diabetes who were being treated at a Veterans Administration Medical Center indicated that two communication-related factors had independent associations with blood pressure control as determined by multivariate regression analysis: endorsement of a shared decision-making style and proactive communication with one’s clinician about abnormal results of blood pressure self-monitoring. A third factor, clinicians’ use of collaborative communication when setting treatment goals, also affected hypertension via its effects on decision-making style and proactive communication [30].

Although a concordance approach to decision making has not yet been evaluated in persons being treated for MS, there is evidence that improved communication and education enhances the response to treatment. In one study, 120 newly diagnosed MS sufferers were randomly assigned to diagnosis disclosure (current practice) or current practice with an information aid that consisted of a personal interview with a neurologist using a navigable compact disc and a take-home booklet. The primary composite endpoint was a score in the highest tertile of MS knowledge and satisfaction with care questionnaires. Other endpoints were safety, treatment adherence, extra contacts/consultations, switching of care center, and changes in Hospital Anxiety and Depression Scale and Control Preference Scale scores. Study results indicated that 50% of MS sufferers who received the intervention and 13% of those in the control group achieved the primary endpoint. However, no significant treatment effects were seen on secondary outcomes [31]. A second study assessed the influence of an evidence-based patient aid on the decision to undertake MS immunotherapy in a group of 297 patients. The intervention group received the decision aid and a control group received standard information. The primary outcome measure was the match between the MS sufferer’s preferred and actual roles during consultation with the neurologist. A secondary outcome was treatment choice. There were no significant between-group differences for the primary or secondary outcome [32]. It has also been
shown that education can alter MS sufferers’ expectations regarding therapy. However, these effects are relatively modest. A study that included 99 persons with MS indicated that, before educational intervention, 57% expressed unrealistically optimistic expectations regarding reduction in attack rate, and 34% expressed unrealistically optimistic expectations regarding improvement in functional status that would result from treatment with IFN-β-1b. Education significantly altered unrealistically expectations, but 33% of the persons with MS maintained overly optimistic expectations regarding reduction in attack rate. Posteducation, unrealistic expectations of improvement in functional status were significantly related to discontinuing therapy within 6 months [33].

In contrast to the modest benefits of the interventions described in the preceding paragraph, results from other studies have indicated that support from healthcare professionals, which might be considered as a component of the concordance model, is associated with better adherence to MS therapy. Results from a study of 341 persons with RRMS who were being treated with glatiramer acetate indicated that 225 were adherent to treatment and 116 were not adherent. Logistic regression analysis revealed that MS sufferers’ perceptions that the neurologist supported taking medication as prescribed was significantly associated with adherence [34]. Similar results were reported in an evaluation of 199 persons with self-reported progressive forms of MS who were also being treated with glatiramer acetate [35].

CONCLUSION

Persons with MS vary across a wide range of parameters and their treatment should be individualized to meet their specific characteristics and needs (see Key Points). Individualized treatment may change over the course of a MS sufferer’s disease due to variability of symptoms, changes in relapse frequency, and treatment tolerability. When and how therapy should be escalated or switched should be part of the treatment plan for each person with MS. Optimal treatment regimen and route of administration also may vary across MS sufferers and over the course of their disease.

Decisions regarding whether or not to initiate treatment and the selected regimen should be made in consultation with the MS sufferer. Current approaches to optimizing therapy for persons with MS and other chronic diseases have increasingly focused on the MS sufferer as a partner in medical decision making. Studies reviewed in this article indicate that persons with MS value unbiased communication of clinical evidence to support their decision making; and there is a growing body of evidence that provision of such evidence and a concordance approach to decision making has the potential to increase MS sufferer satisfaction and possibly change behavior. As the number of options for disease-modifying therapy in MS grows, the neurologist–MS sufferer partnership in treatment decisions will become increasingly important.

Acknowledgements

None.

Conflicts of interest

G.G. has received consulting fees from Bayer-Schering Healthcare, Biogen Idec, Elan, Five Prime Therapeutics, Genzyme, Ironwood, Merck Serono, Novartis, Roche, Sanofi-aventis, Synthion BV, UCB Pharma, and Vertex; fees for non-CME/CE services directly from a commercial interest or their agents (eg, speakers’ bureaus) from Genzyme, Merck Serono, and Novartis; and contracted research support from GW Pharmaceuticals, Merck Serono, Merz, and Novartis. R.R. has no conflict of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest


Study of persons with MS receiving treatment with natalizumab and their neurologists. Results showed that persons with MS were three times more likely than neurologists to accept risks associated with natalizumab.

20. Fox R, Salt E, Alster JM, et al. Risk tolerance in MS patients: survey results from the NARCOMS registry. In: American Academy of Neurology (AAN) 63rd Annual Meeting; 9–16 April 2011; Honolulu, Hawaii. Abstract P06.057. Results from this survey of 5446 persons with MS in the North American Research Committee on Multiple Sclerosis (NARCOMS) registry indicated that one-half of respondents would accept a mortality risk more than one in 10 000 for a hypothetical MS cure.