Balancing Early Aggression Against Risk of Progression in Multiple Sclerosis

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ABSTRACT: Multiple sclerosis is a chronic demyelinating disease characterized by focal and diffuse inflammation of the central nervous system resulting in significant physical and cognitive disabilities. Disease-modifying therapies targeting the dysfunctional immune response are most effective in the first few years after disease onset, indicating that there is a limited time window for therapy to influence the disease course. No evidence of disease activity is emerging as a new standard for treatment response and may be associated with improved long-term disability outcomes. An aggressive management strategy, including earlier use of more potent immunomodulatory agents and close monitoring of the clinical and radiologic response to treatment, is recommended to minimize early brain volume loss and slow the progression of physical and cognitive impairments in patients with relapsing-remitting multiple sclerosis.

RÉSUMÉ: **Équilibre entre le traitement agressif précoce et le risque de progression de la maladie dans la sclérose en plaques.** La sclérose en plaques est une maladie démyélinisante chronique caractérisée par une inflammation focale et diffuse du système nerveux central entraînant des déficits physiques et cognitifs importants. Les traitements modificateurs de la maladie, qui ciblent la réponse immunitaire dysfonctionnelle, sont plus efficaces dans les premières années de la maladie indiquant qu'il y a une fenêtre de temps limitée au cours de laquelle l'évolution de la maladie peut être influencée par ce traitement. L'absence d'évidence d'activité de la maladie est de plus en plus considérée comme étant le nouveau standard de réponse au traitement et peut être associée à une amélioration des résultats quant à l'invalidité à long terme. Une stratégie de traitement agressive, incluant une utilisation plus précoce d'agents immunomodulateurs plus puissants et une surveillance étroite de la réponse clinique et radiologique au traitement, est recommandée afin de minimiser la perte de volume cérébral précoce et ralentir la progression des déficits physiques et cognitifs chez les patients atteints de la forme cyclique de la sclérose en plaques.

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating disease commonly ascribed to abnormal activation of autoaggressive T cells that cross the blood-brain barrier into the central nervous system (CNS) and result in demyelination and axonal loss. However, there is a growing recognition of more widespread immune dysregulation and tissue damage throughout the CNS, underscoring the need for early, more effective intervention to slow the progression of physical and cognitive deficits.

In addition to the focal demyelinating lesions noted by Charcot,[1] imaging studies have demonstrated widespread inflammation and tissue damage throughout the normal-appearing white (NAWM) and gray matter (NAGM).[2,3] Histopathological changes can occur in gray matter (GM) in the absence of focal white matter (WM) lesions, suggesting that GM and WM pathology may be independent.[4] Moreover, diffuse inflammation associated with astrocytic and microglial activation is evident both in NAWM and NAGM.[5,6] It remains unclear if activation of innate immune processes is a primary event or is secondary to T-cell activation. Diffuse inflammation is more pronounced in progressive forms of MS,[7,8] which may indicate secondary activation of the innate immune response and herald the onset of

disability progression,[9] in which neurodegeneration resulting from inflammation predominates over focal inflammatory processes. In support of this is the finding that diffuse axonal loss occurs independently of demyelination and is poorly correlated with focal WM lesion burden.[10] As such, both diffuse axonal injury and tissue loss in demyelinated plaques appear to contribute to global brain atrophy.[11]

An accelerated rate of brain atrophy on MRI is already evident early in the disease course, even in clinically isolated syndrome (CIS) and the early relapsing-remitting phases of MS.[12-14] Of particular importance to the progression of physical and cognitive disability is the rate of GM atrophy, which has been reported to be about threefold higher in CIS patients converting to

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relapsing-remitting MS (RRMS), and 14-fold higher in secondary-progressive MS (SPMS) compared with healthy controls.[15]

Cognitive impairment can be detected at the earliest disease phases, affecting patients with CIS and radiologically isolated syndrome, defined as incidental WM pathology without clinical evidence of demyelination.[16-19] The prevalence of cognitive impairment in MS has been estimated to be as high as 68% in early MS, increasing to 81% later.[20] The earliest and most commonly affected domain is information processing speed, with additional deficits in memory, visual-spatial processing, and language.[21] Cognitive impairment has a profound impact on patients' quality of life,[22] participation in activities of daily living,[23] and employment.[24] Deterioration in cognitive function has been correlated with neuropathological findings such as brain atrophy,[25] lesion volume,[26] and cortical lesions.[27] GM atrophy is reportedly the most important predictor of long-term disability and cognitive impairment.[28] In support of this, a recent analysis of early MS patients found significantly lower scores on magnetization transfer imaging in cognitively impaired subjects compared with those without cognitive impairment.[29] There were no differences in lesion load between the two groups, suggesting that early cognitive impairment may be due primarily to diffuse loss of brain tissue integrity rather than WM lesions.

CLINICAL COURSE OF MS

MS is diagnosed in accordance with the International Panel's revised 2010 criteria.[30] Three phenotypes have been characterized, based on clinical and radiological findings, history, and disease course: CIS, RRMS, and progressive disease with accumulation of disability from onset (primary-progressive MS; PPMS) or after an initial relapsing course (SPMS).[31] CIS, RRMS, and progressive disease (PPMS and SPMS) may be further described as active or not active. Disability is evaluated with the Expanded Disability Status Scale (EDSS) on a scale of 0 (no disability) to 10 (death).[32] It is important to note that, because EDSS is heavily weighted to ambulation, cognitive impairment may be underrepresented with this disability measure.

Natural history studies indicate that the median time from onset of RRMS to an EDSS score of 4 (moderate disability but fully ambulatory), 6 (requiring the use of a cane), and 7 (requiring a wheelchair) is approximately 8, 20, and 30 years, respectively.[33,34] In pediatric-onset MS, the median time to reach these milestones is longer (approximately 20, 29, and 37 years), but typically occurs when the patient is about 10 years younger compared than those with adult-onset MS.[35]

The development of SPMS occurs in adults about 20 years after onset[36] and is diagnosed retrospectively based on accumulating disability and a declining relapse frequency. Although worsening disability occurs at an earlier stage in PPMS, it is often diagnosed when individuals are older, so that EDSS milestones are typically reached at approximately the same age in PPMS and SPMS.[37,38] With the onset of the progressive phase, neurological decline occurs at the same rate in patients, independent of their initial presentation.[33]

MS is associated with significant morbidity and an estimated 1.7 increased risk of all-cause mortality compared to age-matched controls.[39] An analysis of patients registered at MS clinics in British Columbia reported a median survival of 78.6 years for women and 74.3 years for men (standardized mortality ratio, 2.89), or about 6 fewer years compared with the general population.[40] The main causes of early mortality are conditions associated with impaired mobility and neurological dysfunction, such as infections and pulmonary and cardiovascular disease.[41,42]

TIME WINDOW FOR INTERVENTION

MS has historically been viewed as a focal inflammatory disease primarily resulting from T-cell activation, and the disease-modifying therapies (DMTs) used in RRMS primarily affect different aspects of immune dysregulation. The therapeutic goals focused on reducing disease activity, as demonstrated by a reduction in relapse frequency and accrual of new lesions on MRI, and slowing the worsening of short-term disability as assessed by EDSS. Because DMTs primarily target the inflammatory component of the disease, there is an urgency to initiate and optimize therapy within the first few years of diagnosis to obtain the most benefit from treatment.

Early in the disease course, worsening disability is largely attributable to relapse-related residual neurological deficits.[43,44] As a result, the number of relapses in untreated patients in the first 2 years postdiagnosis provides an indication of disability risk, but has limited prognostic value thereafter because of the reduction in relapse frequency that occurs as part of the natural history.[45,46] One observation is that any relapse in the first 5 years postdiagnosis increases the risk of reaching EDSS 6 over the short term (hazard ratio, 1.48).[47] Also important is worsening disability in the first 5 years after diagnosis, which is predictive of later disability.[48] An important goal of treatment is the prevention of short-term surrogates of progression, such as accumulation of disability confirmed at 3 or 6 months. This "EDSS progression" is better characterized as sustained accumulation of disability confirmed after a specified number of months, to distinguish it from "progression," a term now reserved for the progressive phase of MS.[31]

A limitation of natural history database analyses is that prognostic factors may not be predictive of progression in a treated population. Consequently, efforts have been made to identify clinical and radiological predictors of an inadequate treatment response to enable clinicians to manage suboptimally responding patients more promptly.

Analyses of patients treated with interferon-β have shown that ongoing MRI activity, as evidenced by new gadolinium-enhancing T1-weighted or new/enlarging T2-weighted lesions, is predictive of worsening disability.[49] The presence of one new T2 lesion in the year after initiating an interferon-β agent has been associated with a 10-fold increase in the risk of sustained EDSS worsening (>1 point confirmed at 6 months) during the 4.8-year follow-up.[50]

MRI and relapse criteria have been combined to calculate a modified Rio score for predicting an inadequate response to interferon-β.[51] Patients are scored from 0 to 3 according to the number of new T2 lesions (>four lesions = 1 point) and relapses (one relapse = 1, two relapses = 2). Sormani et al calculated that at 4 years, the risk of worsening by ≥1 EDSS point was 32%, 42%, and 50% with scores of 0, 1, and 2 or 3, respectively. Applied to the dataset of patients treated with subcutaneous interferon-β-1a in the Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) trial,[52] 59.5% of treated patients had >42% risk of worsening disability after 1 year of treatment,[51] suggesting that many interferon-treated patients will experience a suboptimal

therapeutic response. These observations were extended in a larger meta-analysis of 40 trials of CIS, RRMS, and SPMS, which found a significant association between disease activity (annualized relapse rate, T2 lesion count and volume) during treatment and worsening disability.[53]

A further impetus to early, effective treatment is the high rate of cognitive impairment in CIS and MS, which may occur before the onset of symptomatic disease.[54] Data from a recent long-term study suggested that there may be a 5-year window after diagnosis, during which reducing disease activity and limiting neurological disability with treatment may decrease cognitive impairment.[54]

EVOLUTION IN THE STANDARD OF CARE

Two decades of DMT use have demonstrated that first-generation injectable therapies have a modest effect on short-term measures of disease activity in RRMS (recently reviewed by Michel et al[55]). Of greater importance to morbidity and patient quality of life is the impact of treatment on long-term disability progression, but here the findings are mixed. Long-term follow-ups of pivotal trials for interferon-β and glatiramer acetate (GA) have generally reported lower rates of progression to SPMS and less disability, but interpretation of these data is limited by the high proportion of dropouts and that these are uncontrolled observational data.

In the 15-year follow-up of the US GA trial, in the subgroup of 100 patients receiving ongoing therapy (mean drug exposure, 13.6 years), EDSS was stable or improved in 57%, but 39% reached EDSS ≥4 and 35% transitioned to SPMS.[56] When the modified intention-to-treat cohort (n = 232) was stratified by baseline EDSS score, 61% of patients with greater disability at onset reached EDSS ≥4 after a mean of 8.6 years. A meta-analysis found no significant effect of GA on disability.[57] In accordance with this lack of effect, GA is not clinically indicated for the reduction of disability progression.[58]

In the 8-year follow-up of the PRISMS trial of subcutaneous interferon-β-1a, there appeared to be some benefit with respect to EDSS progression with earlier versus delayed treatment.[59] However, only 49% of the original cohort remained on therapy. Similarly, in a single-center study of patients treated with intramuscular interferon-β-1a for 15 years, ongoing treatment also appeared to be associated with less disability, but the analysis was based on only one-third of the original cohort.[60]

The 16-year follow-up of the pivotal trial of interferon-β-1b was able to obtain data for a majority of the original study population.[61] Patients who started treatment earlier with the higher dose of interferon-β-1b obtained no added benefit with respect to MRI or disability outcomes compared with those initially randomized to placebo. As in the GA trial, long-term disability outcomes were highly dependent on disease severity at baseline.[62] A separate analysis at 21 years of follow-up reported a survival advantage with long-term interferon-β-1b exposure.[63] In contrast, a retrospective analysis of patients in the British Columbia database of MS patients found that interferon-β-1b use was not associated with a reduction in progression of disability compared to untreated contemporary or historical controls.[64]

As noted previously, it is hypothesized that T-cell activation in the periphery and reactivation in the CNS are the primary immunologic events, which then lead to innate immune activation in the CNS, diffuse inflammation throughout the NAWM and NAGM, neurodegeneration, and progressive tissue loss. This is the rationale for treatments targeting different aspects of this process of T-cell activation and migration into the CNS. Accordingly, it may be inferred that the potential long-term benefits of this approach cannot be fully achieved with the limited efficacy of first-generation DMTs and that more aggressive strategies need to be considered. Moreover, because genetic and environmental factors are known to influence the etiopathology of MS, the availability of a broader range of therapies could enable a more individualized approach to patient care, and the selection of an agent that will achieve a better degree of disease control.

Some support for a more aggressive approach can be obtained from studies of rapidly evolving RRMS or progressive MS treated with lymphoablation and stem cell transplantation (SCT). SCT has been shown to produce a rapid and sustained reduction in CNS inflammatory activity, and stabilization or improvement in disability scores.[65-67] A recent study reported structural and functional improvements in the optic nerve post-SCT in SPMS patients.[68] However, some patients will experience slowly worsening disability despite profound suppression of inflammatory disease activity,[69,70] which may be attributed to neurodegenerative mechanisms that may be somewhat independent of inflammation, a differing pathobiology in some subsets of patients, genetic and/or environmental modulators of disease activity, or other factors.

With the development of a broader range of DMTs, there is an opportunity for clinicians to individualize therapy to achieve a more robust response. This in turn has led to a need for more stringent criteria for therapeutic response, as reflected in the emerging treatment goal of "no evidence of disease activity." This is generally defined with the three metrics of no relapses, no gadolinium-enhancing T1 lesions or new/enlarging T2 lesions, and no EDSS progression confirmed at 3 or 6 months (no evidence of disease activity [NEDA]-3). NEDA-3 was first used in a post-hoc analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) dataset, which determined that 37% of patients treated with natalizumab achieved NEDA-3 compared with 7% with placebo at 2 years.[71] Subsequent analyses have reported that about one-third of patients can also achieve NEDA-3 at 2 years with agents such as fingolimod and alemtuzumab (Table 1).[72-74] Even higher NEDA-3 rates may be achievable in younger patients, as suggested by a recent analysis of fingolimod phase III trials.[78]

NEDA-3 provides an indication of the efficacy of treatments in suppressing focal inflammatory disease activity, but does not capture the full impact of therapy on the neurodegenerative component of MS. Individual measures need to be standardized (e.g. worsening disability confirmed at 3 or 6 months), and extensions of various clinical studies will help to determine the predictive value of NEDA-3 for long-term disability outcomes. A further limitation is that early in the disease course, NEDA-3 results largely reflect an absence of radiologic activity, and traditional MRI markers of disease activity (gadolinium-enhancing T1 or new/enlarging T2 lesions) are known to be only weakly correlated with long-term disability.[79]

The addition of measures that reflect ongoing tissue loss, such as brain atrophy rates, new hypointense T1 lesions ("black

holes"), and magnetization transfer ratio, may provide a more robust evaluation of treatment response and help to refine the predictive value of NEDA for physical and cognitive outcomes. For example, a longitudinal MRI study found that the proportion of patients with cognitive impairment doubled over the 2-year observation period, from 26.4% at baseline to 52.8% at 24 months.[80] By the end of the study, there was a significant correlation between brain parenchymal volume and cognitive impairment as well as brain atrophy and EDSS change. This loss of brain volume cannot be regained, underscoring the importance of early, effective treatment to minimize cognitive deterioration.

In healthy controls, the rate of brain volume loss is estimated at −0.1% to −0.3% per annum,[81] so a cutoff of −0.4%/year has been proposed for the metric of NEDA-3 + atrophy (NEDA-4).[81] Using this value, Kappos et al reported a > fourfold higher

likelihood of achieving NEDA-4 with fingolimod vs placebo at 2 years (odds ratio = 4.41, p < 0.0001).[82] NEDA-4 analyses have not yet been reported for other DMTs.

Evidence of ongoing disease activity during treatment, as demonstrated by the failure to achieve NEDA-3, should prompt a review of the current regimen with the view to selecting a treatment that may provide improved efficacy or tolerability. The addition of brain volume change in NEDA-4 further refines the efficacy evaluation by incorporating a measure of the underlying pathophysiology of MS that is predictive of physical and cognitive outcomes. Brain atrophy measures are now routinely obtained at some specialized MS centers, and their use may become part of the standard of care in the next few years. However, the optimal method of MRI acquisition (e.g. whole-brain, GM atrophy) and atrophy quantification (e.g. brain parenchymal

Table 1: Rates of NEDA-3* at 2 years with newer disease-modifying agents

Trial	Free of relapses, %	Free of EDSS progression, %†	Free of clinical disease activity, %‡	Free of MRI activity, %	NEDA, %¶
AFFIRM[71]					
Natalizumab	71	84	64	58	37
Placebo	43	72	39	14	7
FREEDOMS[72]					
Fingolimod	70.4	82	62	—	33
Placebo	46	76	42	—	13
DEFINE[75]					
DMF BID	76	86	69	45	28
DMF TID	77	85	69	39	26
Placebo	58	78	49	27	15
CONFIRM[76]					
DMF BID	74	89	69	24	18
DMF TID	78	89	73	29	20
GA	70	86	66	21	12
Placebo	61	86	57	11	7
TEMSO[77]					
Teri 7 mg	58	81	49	32	18
Teri 14 mg	61	83	53	40	23
Placebo	49	76	43	25	14
CARE MS-I[73]					
Alemtuzumab	78	92	74	—	39
Interferon-β-1a	60	89	56	—	27
CARE MS-II[74]					
Alemtuzumab	65	87	60	—	32
Interferon-β-1a	47	79	41%	—	14

*NEDA, no evidence of disease activity, Formerly called disease activity-free.
†3-month confirmed disability progression (except for CARE-MS studies).
‡No relapses + no EDSS progression.
¶No relapses, no EDSS progression, no Gd + T1, and no new/enlarged T2 lesions.
AFFIRM, Natalizumab (Antegren) Safety and Efficacy in Relapsing Remitting Multiple Sclerosis; BID, twice daily; CARE-MS, Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis; CONFIRM, Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis; DEFINE, The Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS; FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis; GA, glatiramer acetate; TEMSO, Teriflunomide Multiple Sclerosis Oral; Teri, teriflunomide, TID, three times daily. Note: comparisons cannot be made across trials because of differences in study design, patient characteristics, and different criteria used to define NEDA-3.

fraction, Structural Image Evaluation, using Normalisation, of Atrophy [SIENA]), with correction for various confounders such as hydration status, drug/alcohol use, and comorbidities in individual patients, has not been fully determined. Emerging technologies, such as optical coherence tomography of retinal nerve fiber layer thickness as a measure of axonal degeneration,[83] may also be useful in assessing the extent and progression of WM and GM atrophy.

CLINICAL MANAGEMENT

An aggressive treatment strategy is not merely a matter of adopting a "zero tolerance" approach to ongoing disease activity and escalating treatment accordingly. Rather, aggressive management also requires more frequent clinical and radiological assessments to allow for early detection of suboptimal response, and identification of factors, such as poor tolerability and adherence, that may contribute to treatment failure.

Close monitoring is playing an increasingly important role in patient management because of the risk of serious adverse events. A 6-hour observation period at first dose is required with fingolimod because of its potential effects on heart rate, blood pressure, and cardiac conduction. The frequency of second-degree atrioventricular block or higher is estimated to be about 1%, and about 4% to 6% in patients with a preexisting cardiac condition.[84] With ongoing treatment, the estimated risk of macular edema with fingolimod 0.5 mg is 0.4%.[85] Patients should also be monitored for symptoms of infections. There have been isolated case reports of cryptococcal meningitis.[86] Patients should be assessed for prior exposure to varicella zoster virus (VZV) before initiating fingolimod due to the risk of infection; vaccination is recommended in patients who are VZV antibody-negative. Two patients treated with fingolimod without prior natalizumab exposure developed progressive multifocal leukoencephalopathy (PML). Fingolimod should be used with caution in patients with severe respiratory disease. Pulmonary function testing should be performed during treatment if clinically indicated. Liver enzymes should be evaluated every 3 months for the first year and periodically thereafter.

The principal concern with natalizumab is the risk of PML, which is estimated to be 1.3% in anti–John Cunningham (JC) virus antibody-positive patients with prior exposure to immunosuppressants receiving >24 natalizumab infusions.[87] If PML is diagnosed, rapid natalizumab withdrawal can result in a potentially fatal immune reconstitution inflammatory syndrome.[88] One case of JC virus granule cell neuronopathy has been reported.[89] Other serious adverse effects may include hepatic injury, infections, anaphylaxis, suicidal ideation, and cholelithiasis.[90] Fatal opportunistic infections have occurred, and there are rare reports of encephalitis and meningitis deaths associated with herpesvirus infection.[90] There is one case of cryptococcal meningitis reported with natalizumab.[91]

With alemtuzumab, most patients will experience infusion-related reactions and precautionary treatment with corticosteroids is advised; antihistamines and antipyretics may also be used. Patients without a history of prior VZV exposure should undergo VZV antibody testing and immunization should be considered for VZV antibody-negative patients. A 1-month course of antiviral prophylaxis is recommended after each treatment course because of the risk of VZV infection or reactivation. Other potential safety issues include secondary autoimmunity, including thyroid disorders (cumulative incidence, 34.7% at 4 years), immune thrombocytopenic purpura (2.5% at 4 years), and antiglomerular basement membrane disease (<1%).[92,93] Thyroid function testing should be performed before treatment initiation and every 3 months thereafter. Patients should be evaluated for active or latent tuberculosis before treatment initiation. Cervical human papillomavirus infection, including cervical dysplasia, has been reported (2%),[92] and annual screening for human papillomavirus is recommended for female patients. Serum creatinine levels and urinalysis should be obtained before treatment initiation and monthly thereafter until 48 months after the last infusion.

TREATMENT INITIATION AND ESCALATION

In accordance with recent recommendations, treatment should be considered for all patients with CIS at high risk of developing clinically definite MS, such as those with extensive MRI burden of disease or positive oligoclonal banding.[94] At present, only first-generation injectables and teriflunomide have demonstrated efficacy in this patient population.[95-99] The benefits of early treatment with interferon-β or GA on longer term disability are uncertain.[100,101] CIS patients who subsequently meet diagnostic criteria for MS may be viewed as having experienced breakthrough disease on treatment, and consideration should be given to employing a more potent therapy to achieve more optimal disease control.

Ideally, all RRMS patients should be started on a DMT, with the initial choice of therapy determined by the clinical presentation. Recent experience indicates that oral therapies are preferred because their efficacy appears to be either comparable, or superior, in cases where head-to-head studies have been conducted, to that of the injectables.[102-104] The oral route of administration may also be preferred by patients and may promote better adherence, as a number of authors have recently suggested.[105,106] Safety considerations with oral teriflunomide include a risk of elevated liver enzymes (14%) and peripheral neuropathy (2%);[107] active elimination is required before pregnancy because of the teratogenic potential.[108] With oral dimethyl fumarate (DMF), a limitation is poor tolerability because of the high incidence of flushing (38%), diarrhea (15%), and nausea (13%).[109] So far, two cases of PML associated with the branded formulation of DMF have been reported in MS patients with lymphopenia,[110] and one case in a patient with psoriasis and suspected MS treated with a compounded formulation of DMF.[111] Although periodic monitoring for severe lymphopenia may mitigate the risk,[112] a case of PML has recently been reported in a patient with psoriasis without severe lymphopenia treated with compounded DMF.[113]

A baseline cognitive assessment is recommended in all patients, with routine follow-up evaluations obtained annually. More frequent assessments are advised if cognitive dysfunction is suspected by the patient, family member, clinician, or MS nurse. The Symbol Digit Modalities Test (SDMT) is recommended to evaluate information processing speed and working memory.[114] Additional testing may be required for other cognitive domains. Relapses have been shown to be associated with worsening cognitive function as evaluated by SDMT.[115] A recent meta-analysis also found a moderate-to-strong correlation between T2 lesion volume and information processing speed as evaluated by SDMT.[116] Therefore, a frank decline in cognitive function during

therapy may indicate treatment failure and consideration should be given to employing a more potent agent.

As treatment effects may be delayed for several months after initiation, a brain MRI is advised 6 months after starting therapy. This scan will serve as a new baseline for comparison with subsequent MRIs. The therapeutic response should be evaluated 6 to 12 months after the on-treatment reference scan, in accordance with Canadian treatment optimization recommendations.[94] Clear evidence of ongoing clinical or radiological disease activity in the first year of treatment should prompt a reexamination of the initial treatment choice and consideration should be given to employing a more potent agent.

Close monitoring is required throughout the disease course to evaluate ongoing treatment response and adverse effects, and semiannual clinic visits and annual brain MRI assessments are recommended.

The most obvious concern with a more aggressive treatment approach is the risk of serious adverse effects. These concerns should not be minimized, and require a full discussion of the side effect profile with the patient. It is important to add that any benefit-risk assessment must be made within the context of the known risks of MS itself. For patients to make an informed choice, they must be aware of the need to adequately control the disease process to minimize the long-term physical and cognitive impairments associated with MS.

IS ESCALATION EFFECTIVE?

The core principles of treatment optimization are the prompt recognition of an inadequate response and the selection of a new agent based on its likelihood of achieving better disease control and improved long-term outcomes.[94] One strategy for suboptimal responders is to switch to an injectable DMT, teriflunomide, or DMF. An alternative approach would be to switch to an agent with a different mechanism of action and greater potency, such as fingolimod, natalizumab, alemtuzumab, or additional novel therapies as they become available.

Data from randomized controlled phase III studies have suggested that switching treatment can achieve improved disease control (Table 2). In the Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis (CONFIRM) extension, the annualized relapse rate (ARR) was initially unchanged in the GA group in the first year after switching to DMF, but declined 24.7% and 35.2% at 2 and 3 years, respectively, after switching to DMF.[117] Because there is a limited time window in which to optimize therapy, escalation to a more potent agent may be more likely to influence the disease course. In the Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis (TRANSFORMS) extension, there was a 29% reduction in ARR in the interferon-β-1a group in the first 12 months after switching to fingolimod.[119] For the Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS) extension studies, there was a 69% to 71% reduction in ARR in the interferon-β-1a groups in the 24 months after switching to alemtuzumab.[120,121] No phase III studies have examined the benefit of a switch to natalizumab.

An earlier switch may also slow the rate of brain volume loss. In the TRANSFORMS trial, brain volume loss was 31% lower with fingolimod versus interferon-β-1a in the first year of treatment.[119] In the year after switching to fingolimod, patients in the interferon-β-1a group demonstrated a 51% reduction in the amount of brain volume loss. In the AFFIRM trial, brain volume loss was greater in the first year of natalizumab because of pseudoatrophy, but there was a reduction in the atrophy rate in the second year of treatment.[122] Similar results were obtained in the CARE-MS studies. The mean change from baseline in brain parenchymal fraction was similar with alemtuzumab and interferon-β-1a in year 1. However, in year 2, mean brain parenchymal fraction change was 32% lower with alemtuzumab in previously untreated patients with highly active disease[123] and 37% lower in previously treated patients receiving alemtuzumab versus interferon-β-1a.[124]

An implication of these findings is that agents with more direct CNS effects, such as fingolimod, DMF, or teriflunomide may serve as better platform therapies in the future. Fingolimod crosses the blood-brain barrier and has been shown in laboratory studies and animal models to interact with astrocytes and oligodendrocytes, which may promote remyelination.[125-127] Preclinical data have shown that DMF may have protective effects on axonal and neuronal integrity through its interaction with the nuclear

Table 2: Phase III extension data on the impact of switching from an injectable disease-modifying therapy to an oral or infusion disease-modifying therapy

Trial	Prior/current therapy	Duration of follow-up*	ARR	Number of new/enlarged T2	Number of Gd + T1	EDSS change
CONFIRM[117]	GA → DMF BID	1 year 2 years 3 years	No change ↓ 25% ↓ 35%	NR	NR	NR
TENERE[118]	IFN-β → Teriflunomide	2.8 years	No change	NR	NR	NR
TRANSFORMS[119]	IFN-β IM → Fingolimod	1 year	↓ 29%	↓ 67%	↓ 80%	NS
CARE-MS I[120]	IFN-β SC → Alemtuzumab	1 year 2 year	NR ↓ 69%	NR	NR	No change +0.11
CARE-MS II[121]	IFN-β SC → Alemtuzumab	1 year 2 years	NR ↓ 71%	NR	NR	+0.03 +0.10

*after switch

CARE-MS, Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis; CONFIRM, Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis; IFN-β, interferon-β-1a; IM, intramuscular; SC, subcutaneous; NR, not reported; NS, not significant; TENERE, Teriflunomide and Rebif®; TRANSFORMS, Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis.

factor (erythroid-derived 2)-like 2 antioxidant pathway,[128] and that teriflunomide may promote oligodendrocyte survival.[129]

At present, there are limited data on the impact of more potent therapies on cognitive outcomes. The Natalizumab for the Relief of MS Associated Fatigue (ENER-G) study reported that cognitive function was stable or improved with natalizumab.[130] Although this may be attributed in part to a reduction in fatigue, a 1-year observational study did find improvements in memory and executive function with natalizumab.[131] An analysis of TRANSFORMS data reported significantly less deterioration in cognition at 1 year, as assessed by the three-second Paced Auditory Serial Addition Test, with fingolimod compared with intramuscular interferon-β.[132] A separate 1-year study reported that global cognition scores were stable with fingolimod.[133] Additional research is needed to confirm these findings.

For patients with rapidly evolving RRMS, the most aggressive approach would be induction with an immunosuppressant followed by maintenance with a DMT. Vollmer and colleagues reported an 70% greater reduction in gadolinium-enhancing lesions at 1 year with mitoxantrone followed by GA compared with GA alone.[134] A separate study reported a 65% reduction in disability worsening with mitoxantrone induction before interferon-β-1b.[135] Cyclophosphamide induction with pulse maintenance therapy has also been shown to produce benefits in PPMS (with adrenocorticotropic hormone) and in aggressive pediatric MS.[136,137] Although long-term maintenance with immunosuppressants is limited by toxicities, a form of induction may be achieved with alemtuzumab, with a maintenance regimen of annual courses of alemtuzumab, or ongoing treatment with another DMT. This approach has not yet been examined with alemtuzumab, and more data on the long-term efficacy and safety of induction strategies are required.

CONCLUSIONS

The past 2 decades have seen significant advances in our understanding of the MS disease process and how therapeutic interventions need to be evaluated. Some newer, high-efficacy DMTs have been shown to be more effective than first-generation agents in reducing inflammation and tissue damage, as assessed by clinical and radiological endpoints, with about one-third of patients achieving NEDA. The caveat is that these potential benefits must be weighed against the risk of possible adverse effects. Natalizumab, fingolimod, and alemtuzumab produce rapid and profound reductions in inflammatory disease activity, and fingolimod has been shown to have an early, consistent effect on the rate of brain volume loss. Thus, some of the newer-generation DMTs may be the first agents to modify the MS disease process. A more complete understanding of the risks associated with these agents will become evident over time.

Even with the most potent agents available, there is a limited time window for effective intervention. Time is brain, and the tissue loss that occurs during the years of switching from one first-line agent to another cannot be regained. There is sufficient evidence to show that NEDA-3 can be achieved in a substantial proportion of RRMS patients, and NEDA-4 data demonstrate that effective therapy can slow the development of early brain atrophy. In the near future, it can be expected that more aggressive treatment strategies will be routinely employed in patients with evidence of an accelerated rate of brain volume loss.

NEDA-3 and NEDA-4 are redefining the standard for treatment efficacy. They provide the rationale for an early, more aggressive treatment strategy in RRMS patients, with the goal of more effectively reducing the extensive tissue damage and minimizing the physical and cognitive impairments that occur during the clinical course of MS.

REFERENCES

1. Charcot JM. Histologie de la sclérose en plaques. Gaz Hopital (Paris). 1868;41:554-66.
2. Simon B, Schmidt S, Lukas C, et al. Improved in vivo detection of cortical lesions in multiple sclerosis using double inversion recovery MR imaging at 3 Tesla. Eur Radiol. 2010;20:1675-83.
3. Gilmore CP, Donaldson I, Bö L, Owens T, Lowe J, Evangelou N. Regional variations in the extent and pattern of grey matter demyelination in multiple sclerosis: a comparison between the cerebral cortex, cerebellar cortex, deep grey matter nuclei and the spinal cord. J Neurol Neurosurg Psychiatry. 2009;80:182-7.
4. Kutzelnigg A, Faber-Rod JC, Bauer J, et al. Widespread demyelination in the cerebellar cortex in multiple sclerosis. Brain Pathol. 2007;17:38-44.

5. Mayo L, Trauger SA, Blain M, et al. Regulation of astrocyte activation by glycolipids drives chronic CNS inflammation. Nat Med. 2014;20:1147-56.

6. van Horssen J, Singh S, van der Pol S, et al. Clusters of activated microglia in normal-appearing white matter show signs of innate immune activation. J Neuroinflammation. 2012;9:156.

7. Rissanen E, Tuisku J, Rokka J, et al. In vivo detection of diffuse inflammation in secondary progressive multiple sclerosis using PET imaging and the radioligand 11C-PK11195. J Nucl Med. 2014;55:939-44.

8. Stadelmann C, Brück W. Interplay between mechanisms of damage and repair in multiple sclerosis. J Neurol. 2008;255(Suppl 1):12-8.

9. Leray E, Yaouanq J, Le Page E, et al. Evidence for a two-stage disability progression in multiple sclerosis. Brain. 2010;133 (Pt 7):1900-13.

10. Kutzelnigg A, Lucchinetti CF, Stadelmann C, et al. Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain. 2005;128:2705-12.

11. Kutzelnigg A, Lassmann H. Pathology of multiple sclerosis and related inflammatory demyelinating diseases. In: Goodin ES editor. Handbook of clinical neurology Vol. 122 (3rd series). Amsterdam: Elsevier BV; 2014.

12. Henry RG, Shieh M, Okuda DT, Evangelista A, Gorno-Tempini ML, Pelletier D. Regional grey matter atrophy in clinically isolated syndromes at presentation. J Neurol Neurosurg Psychiatry. 2008;79:1236-44.

13. Chard DT, Griffin CM, Parker GJ, Kapoor R, Thompson AJ, Miller DH. Brain atrophy in clinically early relapsing-remitting multiple sclerosis. Brain. 2002;125(Pt 2):327-37.

14. Audoin B, Davies G, Rashid W, Fisniku L, Thompson AJ, Miller DH. Voxel-based analysis of grey matter magnetization transfer ratio maps in early relapsing remitting multiple sclerosis. Mult Scler. 2007;13:483-9.

15. Fisher E, Lee JC, Nakamura K, Rudick RA. Gray matter atrophy in multiple sclerosis: a longitudinal study. Ann Neurol. 2008;64:255-65.

16. Lebrun C, Blanc F, Brassat D, Zephir H, de Seze J, CFSEP. Cognitive function in radiologically isolated syndrome. Mult Scler. 2010;16:919-25.

17. Amato MP, Hakiki B, Goretti B, et al. Association of MRI metrics and cognitive impairment in radiologically isolated syndromes. Neurology. 2012;78:309-14.

18. Zipoli V, Goretti B, Hakiki B, et al. Cognitive impairment predicts conversion to multiple sclerosis in clinically isolated syndromes. Mult Scler. 2010;16:62-7.

19. Okuda DT, Mowry EM, Beheshtian A, et al. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. Neurology. 2009;72:800-5.

20. Fischer M, Kunkel A, Bublak P, et al. How reliable is the classification of cognitive impairment across different criteria in early and late stages of multiple sclerosis? J Neurol Sci. 2014;343:91-9.

21. Van Schependom J, D'hooghe MB, Cleynhens K, et al. Reduced information processing speed as primum movens for cognitive decline in MS. Mult Scler. 2015;21:83-91.

22. Chruzander C, Ytterberg C, Gottberg K, Einarsson U, Widén Holmqvist L, Johansson S. A 10-year follow-up of a population-based study of people with multiple sclerosis in Stockholm, Sweden: changes in health-related quality of life and the value of different factors in predicting health-related quality of life. J Neurol Sci. 2014;339:57-63.

23. Ben Ari Shevil E, Johansson S, Ytterberg C, Bergström J, von Koch L. How are cognitive impairment, fatigue and signs of depression related to participation in daily life among persons with multiple sclerosis? Disabil Rehabil. 2014;36:2012-8.

24. Krause I, Kern S, Horntrich A, Ziemssen T. Employment status in multiple sclerosis: impact of disease-specific and non-disease-specific factors. Mult Scler. 2013;19:1792-9.

25. Benedict RH, Weinstock-Guttman B, Fishman I, Sharma J, Tjoa CW, Bakshi R. Prediction of neuropsychological impairment in multiple sclerosis: comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. Arch Neurol. 2004;61:226-30.

26. Randolph JJ, Wishart HA, Saykin AJ, et al. FLAIR lesion volume in multiple sclerosis: relation to processing speed and verbal memory. J Int Neuropsychol Soc. 2005;11:205-9.

27. Calabrese M, Poretto V, Favaretto A, et al. Cortical lesion load associates with progression of disability in multiple sclerosis. Brain. 2012;135(Pt 10):2952-61.

28. Filippi M, Preziosa P, Copetti M, et al. Gray matter damage predicts the accumulation of disability 13 years later in MS. Neurology. 2013;81:1759-67.

29. Faiss JH, Dähne D, Baum K, et al. Reduced magnetisation transfer ratio in cognitively impaired patients at the very early stage of multiple sclerosis: a prospective, multicenter, cross-sectional study. BMJ Open. 2014;4:e004409.

30. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69:292-302.

31. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology. 2014;83:278-86.

32. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33:1444-52.

33. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain. 2003;126(Pt 4):770-82.

34. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. Brain. 2010;133(Pt 7):1914-29.

35. Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. N Engl J Med. 2007;356:2603-13.

36. Koch M, Kingwell E, Rieckmann P, Tremlett H, UBC MS Clinic Neurologists. The natural history of secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry. 2010;81:1039-43.

37. Harding KE, Wardle M, Moore P, et al. Modelling the natural history of primary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry. 2015;86:13-9.

38. Kremenchutzky M, Rice GP, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of multiple sclerosis: a geographically based study 9: observations on the progressive phase of the disease. Brain. 2006;129(Pt 3):584-94.

39. Jick SS, Li L, Falcone GJ, Vassilev ZP, Wallander MA. Mortality of patients with multiple sclerosis: a cohort study in UK primary care. J Neurol. 2014;261:1508-17.

40. Kingwell E, van der Kop M, Zhao Y, Shirani A, Zhu F, Oger J, Tremlett H. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. J Neurol Neurosurg Psychiatry. 2012;83:61-6.

41. Lalmohamed A, Bazelier MT, Van Staa TP, et al. Causes of death in patients with multiple sclerosis and matched referent subjects: a population-based cohort study. Eur J Neurol. 2012;19:1007-14.

42. Goodin DS, Corwin M, Kaufman D, et al. Causes of death among commercially insured multiple sclerosis patients in the United States. PLoS One. 2014;9:e105207.

43. Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. Neurology. 2003;61:1528-32.

44. Hirst C, Ingram G, Pearson O, Pickersgill T, Scolding N, Robertson N. Contribution of relapses to disability in multiple sclerosis. J Neurol. 2008;255:280-7.

45. Langer-Gould A, Popat RA, Huang SM, et al. Clinical and demographic predictors of long-term disability in patients with relapsing-remitting multiple sclerosis: a systematic review. Arch Neurol. 2006;63:1686-91.

46. Binquet C, Quantin C, Le Teuff G, Pagliano JF, Abrahamowicz M, Moreau T. The prognostic value of initial relapses on the evolution of disability in patients with relapsing-remitting multiple sclerosis. Neuroepidemiology. 2006;27:45-54.

47. Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y, UBC Neurologists. Impact of multiple sclerosis relapses on progression diminishes with time. Neurology. 2009;73:1616-23.

48. Degenhardt A, Ramagopalan SV, Scalfari A, Ebers GC. Clinical prognostic factors in multiple sclerosis: a natural history review. Nat Rev Neurol. 2009;5:672-82.

49. Rudick RA, Lee JC, Simon J, Ransohoff RM, Fisher E. Defining interferon beta response status in multiple sclerosis patients. Ann Neurol. 2004;56:548-55.

50. Prosperini L, Gallo V, Petsas N, Borriello G, Pozzilli C. One-year MRI scan predicts clinical response to interferon beta in multiple sclerosis. Eur J Neurol. 2009;16:1202-9.

51. Sormani MP, Rio J, Tintorè M, et al. Scoring treatment response in patients with relapsing multiple sclerosis. Mult Scler. 2013;19:605-12.

52. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet. 1998;352:1498-504.

53. Fahrbach K, Huelin R, Martin AL, Kim E, Dastani HB, Rao S, Malhotra M. Relating relapse and T2 lesion changes to disability progression in multiple sclerosis: a systematic literature review and regression analysis. BMC Neurol. 2013;13:180.

54. Achiron A, Chapman J, Magalashvili D, et al. Modeling of cognitive impairment by disease duration in multiple sclerosis: a cross-sectional study. PLoS One. 2013;8:e71058.

55. Michel L, Larochelle C, Prat A. Update on treatments in multiple sclerosis. Presse Med. 2015;44(4 Pt 2):e137-51.

56. Ford C, Goodman AD, Johnson K, et al. Continuous long-term immunomodulatory therapy in relapsing multiple sclerosis: results from the 15-year analysis of the US prospective open-label study of glatiramer acetate. Mult Scler. 2010;16:342-50.

57 La Mantia L, Munari LM, Lovati R. Glatiramer acetate for multiple sclerosis. Cochrane Database Syst Rev. 2010 May12(5): CD004678.

58. Copaxone (glatiramer acetate) product monograph. TEVA Pharmaceuticals USA, Inc., North Wales, PA. NDA 020622/S-089 FDA Approved Labeling Text; January 28, 2014.

59. Kappos L, Traboulsee A, Constantinescu C, et al. Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. Neurology. 2006;67:944-53.

60. Bermel RA, Weinstock-Guttman B, Bourdette D, Foulds P, You X, Rudick RA. Intramuscular interferon beta-1a therapy in patients with relapsing-remitting multiple sclerosis: a 15-year follow-up study. Mult Scler. 2010;16:588-96.

61. Ebers GC, Traboulsee A, Li D, Langdon D, et al. Analysis of clinical outcomes according to original treatment groups 16 years after the pivotal IFNB-1b trial. J Neurol Neurosurg Psychiatry. 2010;81: 907-912.

62. Goodin DS, Traboulsee A, Knappertz V, et al. Relationship between early clinical characteristics and long term disability outcomes: 16 year cohort study (follow-up) of the pivotal interferon β-1b trial in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2012;83:282-7.

63. Goodin DS, Reder AT, Ebers GC, et al. Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial. Neurology. 2012;78:1315-22.

64. Shirani A, Zhao Y, Karim ME, et al. Association between use of interferon beta and progression of disability in patients with relapsing-remitting multiple sclerosis. JAMA. 2012;308:247-56.

65. Curro' D, Vuolo L, Gualandi F, Bacigalupo A, Roccatagliata L, Capello E, et al. Low intensity lympho-ablative regimen followed by autologous hematopoietic stem cell transplantation in severe forms of multiple sclerosis: A MRI-based clinical study. Mult Scler. 2015, epublished January 12, 2015.

66. Bonab MM, Sahraian MA, Aghsaie A, Karvigh SA, Hosseinian SM, Nikbin B, et al. Autologous mesenchymal stem cell therapy in progressive multiple sclerosis: an open label study. Curr Stem Cell Res Ther. 2012;7:407-14.

67. Burt RK, Loh Y, Cohen B, Stefoski D, Balabanov R, Katsamakis G, et al. Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase I/II study. Lancet Neurol. 2009;8:244-53.

68. Connick P, Kolappan M, Crawley C, Webber DJ, Patani R, Michell AW, et al. Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study. Lancet Neurol. 2012;11:150-6.

69. Mancardi GL, Sormani MP, Di Gioia M, Vuolo L, Gualandi F, Amato MP, et al. Autologous haematopoietic stem cell transplantation with an intermediate intensity conditioning regimen in multiple sclerosis: the Italian multi-centre experience. Mult Scler. 2012;18:835-42.

70. Fassas A, Kimiskidis VK, Sakellari I, Kapinas K, Anagnostopoulos A, Tsimourtou V, et al. Long-term results of stem cell transplantation for MS: a single-center experience. Neurology. 2011;76: 1066-70.

71. Havrdova E, Galetta S, Hutchinson M, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. Lancet Neurol. 2009;8:254-60.

72. Kappos L, Radue E-W, O'Connor P, et al. Fingolimod treatment increases the proportion of patients who are free from disease activity in multiple sclerosis: results from a phase 3, placebo-controlled study (FREEDOMS). Presented at the 63rd annual meeting of the American Academy of Neurology, Honolulu, HI; April 9-16, 2011: abstract PD6.002.

73. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380:1819-28.

74. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380: 1829-39.

75. Giovannoni G, Gold R, Kappos L, et al. Analysis of clinical and radiological disease activity-free status in patients with relapsing-remitting multiple sclerosis treated with BG-12 from the DEFINE study. Presented at the 64th annual meeting of the American Academy of Neurology, New Orleans, LA; April 22-27, 2012: abstract P459.

76. Havrdova E, Gold R, Fox R, et al. BG-12 (dimethyl fumarate) treatment for relapsing–remitting multiple sclerosis (RRMS) increases the proportion of patients free of measured clinical and neuroradiologic disease activity in the phase 3 studies. Presented at the 65th annual meeting of the American Academy of Neurology, San Diego, CA; March 16-23, 2013: abstract P07.106.

77. Freedman M, O'Connor P, Wolinsky J, et al. Teriflunomide increases the proportion of patients free from disease activity in the TEMSO phase III study. Presented at the 64th annual meeting of the American Academy of Neurology, New, LA; April 22-27, 2012: abstract PD5.007.

78. Chitnis T, Karlsson G, Häring DA, Ghezzi A, Pohl D, Putzki N. Fingolimod effect on clinical and MRI disease activity in young adult patients with relapsing multiple sclerosis. Presented at the Joint Americas Committee for Treatment and Research in Multiple Sclerosis-European Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS-ECTRIMS), Boston, MA; September 10-13, 2014: abstract P317.

79. Bevan CJ, Cree BAC. Disease activity free status: a new end point for a new era in multiple sclerosis clinical research? JAMA Neurol. 2014;71:269-70.

80. Zivadinov R, Sepcic J, Nasuelli D, et al. A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. J Neurol Neurosurg Psychiatry. 2001 Jun; 70:773-80.

81. De Stefano N, Sprenger T, Freedman MS, et al. Including threshold rates of brain volume loss in the definition of disease activity-free in multiple sclerosis using fingolimod phase 3 data. Presented at the Joint Americas Committee for Treatment and Research in Multiple Sclerosis-European Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS-ECTRIMS), Boston, MA; September 10-13, 2014: abstract P290.

82. Kappos L, Radue E-W, Freedman MS, et al. Inclusion of brain volume loss in a revised measure of multiple sclerosis disease-activity freedom: the effect of fingolimod. Presented at the Joint Americas Committee for Treatment and Research in Multiple Sclerosis-European Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS-ECTRIMS), Boston, MA; September 10-13, 2014: abstract FC1.5.

83. Balk LJ, Steenwijk MD, Tewarie P, Daams M, Killestein J, Wattjes MP, et al. Bidirectional trans-synaptic axonal degeneration in the visual pathway in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2015;86:419-24.

84. Gold R, Comi G, Palace J, Siever A, Gottschalk R, Bijarnia M, et al. Assessment of cardiac safety during fingolimod treatment initiation in a real-world relapsing multiple sclerosis population: a phase 3b, open-label study. J Neurol. 2014;261:267-76.

85. Zarbin MA, Jampol LM, Jager RD, Reder AT, Francis G, Collins W, et al. Ophthalmic evaluations in clinical studies of fingolimod (FTY720) in multiple sclerosis. Ophthalmology. 2013;120:1432-9.

86. Gilenya (fingolimod) product monograph. Novartis Pharmaceuticals Canada Inc., May 6, 2015.

87. Barts-MS PML risk guide, May 2014. http://multiple-sclerosis-research.blogspot.com/2015/01/clinicspeak-natalizumab-pml-update-q4.html.

88. Kleinschmidt-DeMasters BK, Miravalle A, Schowinsky J, Corboy J, Vollmer T. Update on PML and PML-IRIS occurring in multiple sclerosis patients treated with natalizumab. J Neuropathol Exp Neurol. 2012;71:604-17.

89. Schippling S, Kempf C, Büchele F, Jelcic I, Bozinov O, Bont A, et al. JC virus granule cell neuronopathy and GCN-IRIS under natalizumab treatment. Ann Neurol. 2013;74:622-6.

90. Tysabi (natalizumab) product monograph. Biogen Idec Canada Inc., April 7, 2015.

91. Valenzuela RM, Pula JH, Garwacki D, Cotter J, Kattah JC. Cryptococcal meningitis in a multiple sclerosis patient taking natalizumab. J Neurol Sci. 2014;340:109-11.

92. Lemtrada (alemtuzumab) product monograph. Genzyme Canada, December 12, 2013.

93. Havrdova E, Giovannoni G, Arnold DL, Coles AJ, Fox EJ, Hartung H-P, et al. Durable effect of alemtuzumab on clinical outcomes in patients with relapsing-remitting multiple sclerosis who relapsed on prior therapy: 4-year follow-up of CARE-MS II. Presented at the 67thAnnual Meeting of the American Academy of Neurology (AAN); April 18-25, 2015, Washington, DC: abstract 7.276.

94. Freedman MS, Selchen D, Arnold DL, et al. Treatment optimization in MS: Canadian MS Working Group updated recommendations. Can J Neurol Sci. 2013;40:307-23.

95. Jacobs LD, Beck RW, Simon JHS, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. N Engl J Med. 2000;343:898-904.

96. Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology. 2006;67:1242-9.

97. Comi G, Martinelli v, Rodegher M, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. Lancet. 2009;374:1503-11.

98. Comi G, De Stefano N, Freedman MS, et al. Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): a phase 3 randomised controlled trial. Lancet Neurol. 2012;11:33-41.

99. Miller AE, Wolinsky JS, Kappos L, et al. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13:977-86.

100. Kinkel RP, Dontchew M, Kollman C, et al. Association between immediate initiation of intramuscular interferon beta-1a at the time of a clinically isolated syndrome and long-term outcomes: a 10-year follow-up of the Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance. Arch Neurol. 2012;69:183-90.

101. Kappos L, Freedman MS, Polman CH, et al. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. Lancet Neurol. 2009;8:987-97.

102. Vermersch P, Czlonkowska A, Grimaldi LM, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler. 2014;20:705-16.

103. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367:1087-97.

104. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362:402-15.

105. Fox RJ. In the coming year we should abandon interferons and glatiramer acetate as first-line therapy for MS: Yes. Mult Scler. 2013;19:24-5.

106. Kim W, Zandoná ME, Kim SH, Kim HJ. Oral disease-modifying therapies for multiple sclerosis. J Clin Neurol. 2015;11:9-19.

107. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011;365:1293-303.

108. Aubagio (teriflunomide) product monograph. Genzyme Canada, November 12, 2013.

109. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012;367:1098-107.

110. Rosenkranz T, Novas M, Terborg C. PML in a patient with lymphocytopenia treated with dimethyl fumarate. N Engl J Med. 2015;372:1476-8.

111. van Oosten BW, Killestein J, Barkhof F, Polman CH, Wattjes MP. PML in a patient treated with dimethyl fumarate from a compounding pharmacy. N Engl J Med. 2013;368:1658-9.

112. Sweetser MT, Dawson KT, Bozic C. Manufacturer's response to case reports of PML. N Engl J Med. 2013;368:1659-61.

113. Nieuwkamp DJ, Murk JL, van Oosten BW, Cremers CH, Killestein J, Viveen MC, et al. PML in a patient without severe lymphocytopenia receiving dimethyl fumarate. N Engl J Med. 2015;372:1474-6.

114. Smith A. Symbol Digit Modalities Test: manual. Western Psychological Services, Los Angeles, CA, 1982.

115. Benedict RH, Morrow S, Rodgers J, et al. Characterizing cognitive function during relapse in multiple sclerosis. Mult Scler. 2014;20:1745-52.

116. Rao SM, Martin AL, Huelin R, et al. Correlations between MRI and information processing speed in MS: a meta-analysis. Mult Scler Int. 2014;2014:975803.

117. Gold R, Phillips JT, Bar-Or A, et al. Five-year follow-up of delayed-release dimethyl fumarate in RRMS: integrated clinical efficacy data from the DEFINE, CONFIRM, and ENDORSE studies. Presented at the Joint Americas Committee for Treatment and Research in Multiple Sclerosis-European Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS-ECTRIMS), Boston, MA; September 10-13, 2014: abstract P110.

118. de Seze J, Olsson TP, Czlonkowska A, Benamor M, Truffinet P, Dukovic D, et al. Safety and efficacy of teriflunomide in patients switching from subcutaneous interferon beta-1a. Presented at the 67th Annual Meeting of the American Academy of Neurology (AAN), Washington, DC; April 18-25, 2015: abstract P7.275.

119. Khatri B, Barkhof F, Comi G, et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. Lancet Neurol. 2011;10:520-9.

120. Coles AJ, Arnold DL, Cohen JA, et al. Efficacy and safety of alemtuzumab in treatment-naive patients with relapsing-remitting MS: four-year follow-up of the CARE-MS I Study. Presented at the Joint Americas Committee for Treatment and Research in Multiple Sclerosis-European Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS-ECTRIMS), Boston, MA; September 10-13, 2014: abstract P090.

121. Hartung H-P, Arnold DL, Cohen JA, Coles AJ, Fox EJ, Giovannoni G, et al. Efficacy and safety of alemtuzumab in patients with relapsing-remitting MS who relapsed on prior therapy: four-year follow-up of the CARE-MS II study. Presented at the Joint Americas Committee for Treatment and Research in Multiple Sclerosis-European Committee for Treatment and Research in

Multiple Sclerosis (ACTRIMS-ECTRIMS), Boston, MA; September 10-13, 2014: abstract P043.

122. Miller DH, Soon D, Fernando KT, MacManus DG, Barker GJ, Yousry TA, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. Neurology. 2007;68:1390-401.

123. Krieger S, Lubetzki C, Arnold DL, et al. Alemtuzumab reduces disease activity in treatment-naive patients with highly active relapsing-remitting multiple sclerosis. Presented at the Joint Americas Committee for Treatment and Research in Multiple Sclerosis-European Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS-ECTRIMS), Boston, MA; September 10-13, 2014: abstract P088.

124. Fisher E, Barkhof F, Cohen JA, et al. Alemtuzumab improves MRI outcomes in relapsing-remitting multiple sclerosis patients who relapsed on prior therapy: three-year follow-up of CARE-MS II. Presented at the Joint Americas Committee for Treatment and Research in Multiple Sclerosis-European Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS-ECTRIMS), Boston, MA; September 10-13, 2014: abstract P103.

125. Wu C, Leong SY, Moore CS, et al. Dual effects of daily FTY720 on human astrocytes in vitro: relevance for neuroinflammation. J Neuroinflammation. 2013;10:41.

126. Miron VE, Jung CG, Kim HJ, Kennedy TE, Soliven B, Antel JP. FTY720 modulates human oligodendrocyte progenitor process extension and survival. Ann Neurol. 2008;63:61-71.

127. Slowik A, Schmidt T, Beyer C, Amor S, Clarner T, Kipp M. FTY720 is neuroprotective after cuprizone-induced central nervous system demyelination. Br J Pharmacol. 2015;172:80-92.

128. Fox RJ, Kita M, Cohan SL, et al. BG-12 (dimethyl fumarate): a review of mechanism of action, efficacy, and safety. Curr Med Res Opin. 2014;30:251-62.

129. Petty M, Lee L, Ying X. Teriflunomide treatment reduces infiltration of macrophages, T cells and B cells, and increases survival of oligodendrocytes in the spinal cord of the Dark Agouti rat model of experimental allergic encephalomyelitis. Presented at the 62nd Annual Meeting of the American Academy of Neurology (AAN), Toronto, ON; April 10-17, 2010: abstract P05.033.

130. Wilken J, Kane RL, Sullivan CL, et al. Changes in fatigue and cognition in patients with relapsing forms of multiple sclerosis treated with natalizumab: the ENER-G study. Int J MS Care. 2013;15:120-8.

131. Mattioli F, Stampatori C, Capra R. The effect of natalizumab on cognitive function in patients with relapsing-remitting multiple sclerosis: preliminary results of a 1-year follow-up study. Neurol Sci. 2011;32:83-8.

132. Pelletier J, Karlsson G, Li B, et al. Effect of fingolimod on Multiple Sclerosis Functional Composite (MSFC) defined disability progression in patients with relapsing remitting MS (RRMS): results from two phase III studies. Presented at the 63rd Annual Meeting of the American Academy of Neurology (AAN), Honolulu, HI; April 9-16, 2011: abstract P07.191.

133. Barak Y, Magalashvili D, Paz T, Achiron A. Fingolimod (Gilenya) confers cognitive stability in active relapsing-remitting multiple sclerosis patients. Presented at the Joint Americas Committee for Treatment and Research in Multiple Sclerosis-European Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS-ECTRIMS), Boston, MA; September 10-13, 2014: abstract P322.

134. Vollmer T, Panitch H, Bar-Or A, Dunn J, Freedman MS, Gazda SK, et al. Glatiramer acetate after induction therapy with mitoxantrone in relapsing multiple sclerosis. Mult Scler. 2008;14:663-70.

135. Edan G, Comi G, Le Page E, Leray E, Rocca MA, Filippi M, French–Italian Mitoxantrone Interferon-beta-1b Trial Group. Mitoxantrone prior to interferon beta-1b in aggressive relapsing multiple sclerosis: a 3-year randomised trial. J Neurol Neurosurg Psychiatry. 2011;82:1344-50.

136. Weiner HL, Mackin GA, Orav EJ, Hafler DA, Dawson DM, LaPierre Y, et al. Intermittent cyclophosphamide pulse therapy in progressive multiple sclerosis: final report of the Northeast Cooperative Multiple Sclerosis Treatment Group. Neurology. 1993;43:910-8.

137. Makhani N, Gorman MP, Branson HM, Stazzone L, Banwell BL, Chitnis T. Cyclophosphamide therapy in pediatric multiple sclerosis. Neurology. 2009;72:2076-82.