Impact of Diagnosis and Early Treatment on the Course of Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a progressive inflammatory disease of the central nervous system that results in neurological dysfunction and disability. The initiation of disease-modifying therapy (DMT) early in the course of MS may improve the prognosis for patients with MS and reduce the occurrence of neurological damage. In patients with relapsing-remitting MS (RRMS), DMT reduces the rate of relapses, reduces the appearance of magnetic resonance imaging markers of disease activity, and slows the course of disability progression. DMT has been shown to be more effective when initiated early in the course of MS. In patients who have not yet developed clinically definite MS (CDMS), but have had 1 attack of neurological symptoms consistent with MS (ie, clinically isolated syndrome [CIS]), the initiation of DMT (specifically, interferon beta, glatiramer acetate, and teriflunomide) following this attack has been shown to delay the conversion to CDMS. Current guidelines have recognized the benefits of early treatment of MS with DMTs. However, there are a number of barriers to implementing early MS treatment. Early diagnosis and treatment of MS can be hindered because patients may delay consulting a physician about their neurological symptoms or may be reluctant to start DMT. Further, even after initiating DMT, continued adherence to treatment is often poor. These delays in treatment and a lack of adherence to treatment are associated with poor patient outcomes. The objectives of this review are to highlight the importance of early diagnosis and treatment of CIS or RRMS and discuss the favorable outcomes associated with early initiation of DMT.

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For author information and disclosures, see end of text.

Multiple sclerosis (MS), a progressive inflammatory disease of the central nervous system (CNS),[1,2] is characterized by demyelination of axons in the brain and spinal cord, with axonal damage or destruction.[3,4] Demyelination and axonal damage and loss are thought to occur early in the course of MS.[5-8] Demyelination results in altered conduction of action potentials and neuronal dysfunction, which is at least partially reversible.[1,8] However, the damage to and destruction of the axons that may follow or accompany demyelination is associated with irreversible neurological disability.[1,8] Demyelination and axonal damage and destruction are responsible for the various neurological symptoms and signs of MS, including impaired vision, weakness, numbness, cognitive dysfunction, dizziness, spasticity, and balance or coordination impairment.[3,4]

There is uncertainty about the underlying pathophysiology of MS, and while research indicates that MS has an immune-mediated pathogenesis, the immunologic response targets are not defined.[9] One recent study identified the potassium ion channel subunit KIR4.1 as a target of the autoantibody response in a subpopulation of patients with MS,[9] but further research is needed to shed more light on immunologic targets involved in MS.

Disease-modifying therapies (DMTs) for MS, which include immunomodulatory, anti-inflammatory, and immunosuppressive drugs,[10] slow MS-related neurological damage and progression of disability.[10-12] Early DMT may improve the long-term course of MS and reduce permanent neurological damage.[5-8] Recent studies have shown the efficacy of DMTs for reducing the rate of relapses in patients with relapsing-remitting MS (RRMS) and for slowing the course of MS progression, particularly when treatment is initiated early (**Table 1**).[13-34] In patients with clinically isolated syndrome (CIS), a single attack consisting of 1 or more neurological symptoms secondary to a demyelinating inflammatory event, DMTs have been shown to delay the conversion to clinically definite MS (CDMS).[13,17,33,34] This review discusses current guidelines for the early treatment of MS, describes the risks of delaying treatment, and summarizes current literature regarding the benefits of early initiation of DMT.

Table 1. Summary of the Benefits of DMT in Patients With CIS or RRMS[13-32]

DMT	Key Outcomes
CIS	
SC IFN beta-1b	• Significantly lower risk of conversion to CDMS with IFN beta-1b vs placebo ($P \leq .0001$)[13] • Significant reductions in MRI markers of disease activity with IFN beta-1b vs placebo ($P < .0001$)[13] • 40% reduction in the risk of disability progression at 3 years for patients who were initially treated with IFN beta-1b vs those initially treated with placebo (late treatment group)[13]
IM IFN beta-1a	• Significant reduction in the risk of conversion to CDMS with IM IFN beta-1a vs placebo ($P = .0002$)[14] • Significant improvement in MRI markers of disease activity with IM IFN beta-1a vs placebo ($P < .001$)[14]
SC IFN beta-1a	• Significantly lower rate of conversion to CDMS with SC IFN beta-1a vs placebo ($P \leq .047$)[15,16] • Significantly smaller decrease in brain volume with SC IFN beta-1a vs placebo ($P = .0031$)[16] and significant improvement in MRI markers of disease activity with SC IFN beta-1a vs placebo ($P < .0001$)[15]
Glatiramer acetate	• Approximate 45% lower risk of conversion to CDMS and an approximate 386-day delay in the conversion to CDMS compared with placebo ($P \leq .0041$)[17] • Significant improvements in MRI measures of MS disease progression with glatiramer acetate vs placebo ($P < .0001$)[17] • Significantly lower rate of second relapse with glatiramer acetate vs placebo ($P < .0001$)[17]
Teriflunomide	• Up to 43% reduction in the risk of conversion to CDMS for teriflunomide vs placebo ($P < .05$)[18]
RRMS	
IFN beta	• Approximate 30% reduction in the relapse rate with all formulations of IFN beta vs placebo[19-21] • Significant reduction in MRI markers of disease activity with all formulations of IFN beta vs placebo ($P < .05$)[19-21] • Significant delays in the time to sustained disability progression with IFN beta-1a vs placebo ($P < .05$)[19,20]
Glatiramer acetate	• Approximate 29% reduction in the 2-year relapse rate with glatiramer acetate vs placebo[22] • Significant improvement in MRI markers of disease activity with glatiramer acetate vs placebo ($P \leq .003$)[23]
Natalizumab	• 68% reduction in the annualized relapse rate with natalizumab vs placebo ($P < .001$)[24] • 42% reduction in the risk of sustained disability with natalizumab vs placebo ($P < .001$)[24] • Significant improvements in MRI markers of disease activity with natalizumab vs placebo ($P < .001$)[25]
Fingolimod	• 53%-55% decrease in the annualized relapse rate with fingolimod vs placebo[26] • Significant reduction in MRI markers of disease progression with fingolimod vs placebo ($P < .001$)[26] • Significant reduction in the risk of disability progression over 2 years vs placebo ($P = .02$)[27]
Teriflunomide	• 31% reduction in the annualized relapse rate with teriflunomide vs placebo ($P < .001$)[28] • Significant improvements in MRI markers of disease activity with teriflunomide vs placebo ($P \leq .05$)[28-30] • Significant reduction in the risk of disability progression with teriflunomide vs placebo ($P \leq .05$)[28,29]
Dimethyl fumarate	• Up to 53% reduction in the annualized relapse rate with dimethyl fumarate vs placebo ($P < .001$)[31] • Significant improvements in MRI markers of disease progression with dimethyl fumarate vs placebo ($P \leq .02$)[32] • Significant reduction in the risk of disability progression with dimethyl fumarate vs placebo ($P \leq .01$)[31]

CDMS indicates clinically definite multiple sclerosis; CIS, clinically isolated syndrome; DMT, disease-modifying therapy; IFN, interferon; IM, intramuscular; MRI, magnetic resonance imaging; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous.

Guidelines for the Diagnosis and Early Treatment of MS

A diagnosis of MS is based on both clinical signs and symptoms, which are consistent with an inflammatory demyelinating process that affects the CNS and demonstrates evidence of dispersion in time and space of the underlying pathological process.[35] The McDonald criteria, developed by the International Panel on the Diagnosis of MS and most recently revised in 2010, provide guidelines for the diagnosis of MS and include clinical, laboratory, and magnetic resonance imaging (MRI) criteria.[35] The McDonald criteria are both sensitive and specific for the definitive diagnosis of MS, and the use of these criteria has led to an earlier diagnosis.[35] In addition to identifying the clinical, laboratory, and MRI indicators of MS, differential diagnosis remains a critical consideration in the process of diagnosing MS.[35] According to the McDonald criteria, a diagnosis of MS can be made based on clinical criteria alone or a predefined combination of MRI evidence and clinical criteria.[35] The fundamental clinical evidence for MS is the occurrence of an attack of symptoms that are consistent with an acute inflammatory demyelinating CNS event.[35] For a definitive diagnosis of MS, the clinical evidence of this attack should be confirmed by neurological examination findings, visual evoked potential response (for

patients with prior visual disturbance), or MRI evidence of demyelination in the CNS area that is suggested by the symptoms.[35] The MRI evidence of demyelination is the presence of sclerotic plaques, or lesions, in the CNS which appear as areas of high signal on T2-weighted images.[1,2] These plaques can be further evaluated using gadolinium (Gd)-enhanced T1-weighted MRI, which allows for differentiation between active and inactive lesions; a Gd-enhanced lesion, which appears as a brighter spot on the MRI, is indicative of an active lesion.[36,37] The dissemination of these lesions in space and/or time can track the progression of MS.[3,35] According to the McDonald criteria, patients with a single attack of neurological symptoms suggestive of a demyelinating event and objective clinical evidence of a lesion are considered to have CIS.[35] For a diagnosis of CDMS to be made in patients with CIS, there must be a second clinical attack, or evidence of dissemination of MRI lesions in time (ie, simultaneous presence of asymptomatic Gd-enhancing and nonenhancing lesions, or new T2 or Gd-enhancing lesions on follow-up MRI) and space (ie, 1 or more T2 lesions in 2 or more MS-typical regions of the CNS).[35] The most recent 2010 McDonald criteria advocate the ability to make a diagnosis of MS even at the time of first event with first MRI if the specific locations of lesions fulfill the requirement for dispersion in space and if an additional Gd active lesion(s) is seen in a location different from that of the lesion responsible for the presenting clinical symptom.[35]

The recommendations for initiating DMT from various guidelines are summarized in **Table 2**.[38-41] In a set of guidelines that were developed in 2002 by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines, the use of interferon (IFN) beta, which is considered to be a first-line DMT for MS, was recommended for patients who were considered to be high risk for the development of CDMS and those with relapsing MS (RMS) (including RRMS and secondary-progressive MS with relapses).[38] In a separate 2008 consensus statement regarding MS disease management from the National Multiple Sclerosis Society, early treatment with glatiramer acetate (GA) or IFN beta was recommended to slow the development of permanent neurological damage.[40] Recently, a series of consensus statements regarding the management of treatments for MS was published that were based on feedback from a panel of pharmacy and medical directors.[41] The panel agreed that the patient's healthcare provider should be permitted to make the decision of whether to initiate DMT in patients with CIS, and that the majority of patients with CDMS should be started on DMT.[41] Further, the panel concluded that health plans should not restrict access to DMTs for patients with CIS or CDMS and should provide access to GA and at least 1 IFN beta formulation.[41] (GA has been shown to have an effect similar to that of IFN beta in preventing conversion to CDMS.[17]) The panel recommended more stringent limitations for access to the other DMTs (eg, natalizumab and fingolimod), largely due to safety issues associated with natalizumab and a lack of long-term clinical efficacy and safety data for fingolimod.[41] Newer options for the management of MS, including the recently approved oral agents teriflunomide and dimethyl fumarate, have not yet been integrated into these guidelines.

Risks of Delayed MS Diagnosis and Treatment

Brain atrophy, which accompanies axonal damage and loss, can be observed early in the MS disease course, even in patients with CIS.[2,42,43] Brain atrophy continues to progress in patients with CIS; however, treatment with IFN beta-1a has been shown to reduce the rate of atrophy in patients with CIS.[43] Delays in the diagnosis of MS and DMT allow for the accumulation of axonal damage, progression of brain atrophy, and the development of severe and irreversible neurological disability.[2,8,42] In the open-label, 5-year study of CIS with GA, patients who were treated with GA from the beginning showed significantly less brain atrophy compared with those who initiated therapy later (mean % change in brain atrophy: –1.28% vs –0.99%; $P = .0209$).[44]

Persisting clinical signs of MS are evident early, even in patients with CIS or early MS.[6,7] A study in patients with CIS who were at high risk for the development of CDMS (more than 2 MRI lesions in addition to the lesion responsible for clinical presentation) showed that cognitive impairment was present in 29% of those at baseline and 54% of those at 5 years after initial screening; approximately 96% of the patients in this study developed CDMS after 5 years.[7] A separate study in patients with CIS or early MS (≤6 years since their first symptom) showed that these patients experienced significant deterioration in measures of cognitive functioning, including measures of working memory and speed of information processing and immediate and delayed visual spatial memory.[6] The presence of cognitive impairment in patients with CIS may be particularly telling because many patients presenting with CIS have experienced prior demyelination events that went unnoticed and unreported and they may have already accumulated associated neurological damage.[45]

Delaying the treatment of MS even after patients have developed CDMS is associated with a negative impact on MS prognosis.[46-49] Each subsequent relapse that patients with RRMS experience is associated with a period of acute neuro-

Table 2. Recommendations for the Initiation of DMT in Early MS[38-41]

Group	Recommendations
Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and MS Council for Clinical Practice Guidelines[38]	• IFN beta treatment is recommended for patients with CIS who are at high risk for the development of CDMS • IFN beta and GA are both recommended for the treatment of patients with RRMS
National Institute for Clinical Excellence[39]	• IFN beta and GA are both recommended for the treatment of patients with RRMS
National Multiple Sclerosis Society[40]	• Early treatment with IFN beta or GA is recommended to slow the development of permanent neurological damage
Consensus statements from a panel of US managed care pharmacists and physicians[41]	• The majority of patients with CDMS should be started on DMT • The patient's healthcare provider should be permitted to make the decision of whether to initiate DMT in patients with CIS • Health plans should not restrict access to DMTs for patients with CIS or CDMS and should provide access to GA and at least 1 IFN beta formulation; however, more stringent limitations should be in place for access to natalizumab and fingolimod, largely due to safety issues associated with natalizumab and a lack of long-term clinical efficacy and safety data for fingolimod

CDMS indicates clinically definite multiple sclerosis; CIS, clinically isolated syndrome; DMT, disease-modifying therapy; GA, glatiramer acetate; IFN, interferon; MS, multiple sclerosis; RRMS, relapsing-remitting MS.

logical dysfunction, from which patients may partially or fully recover, or may be associated with accumulation of irreversible neurological damage and disability.[5,48] In a study of patients with RRMS, a higher rate of relapses during the first 2 years was associated with a significantly higher risk of conversion to secondary-progressive MS ($P = .003$) and a significantly increased risk of accumulating disability ($P \leq .002$).[48]

Delayed diagnosis and treatment of MS may largely result from delays in seeking medical advice for a demyelinating event.[45,50-52] In a study of Spanish patients diagnosed at specialized MS units, the median time from the initial onset of symptoms to the first visit to a physician was 19.2 months; this was the longest delay in the time between onset of symptoms and diagnosis.[50] Diagnosis of MS can also be delayed by the presence of certain comorbidities; in a study of patients from the North American Research Committee on Multiple Sclerosis registry, the time to diagnosis of MS was significantly longer for adult patients under 40 years of age with vascular, autoimmune, musculoskeletal, gastrointestinal, visual, or mental comorbidities than for age-matched patients without these comorbidities ($P < .0001$).[53]

In addition, patients may be reluctant to initiate DMT, which requires a commitment to long-term and continuous therapy, early in the course of MS before the presentation of more severe MS symptoms.[54] Even following initiation of therapy, continued patient adherence to DMT remains problematic.[55,56] Poor patient adherence to therapy may be, in part, related to the mode of administration of DMT[57]; IFN beta and GA are administered via subcutaneous (SC) or intramuscular (IM) injection.[57] The increasing costs of MS treatment[58] may also reduce patient adherence to DMT[59,60]; patients with higher out-of-pocket costs have lower adherence to therapy.[59,60] Insurance coverage of DMT may be hindered by the absence of comprehensive, up-to-date US-based treatment guidelines. Patient education regarding the importance of early and continued therapy with DMT and strategies to reduce the impact of side effects of these medications may help improve adherence to treatment.[54,61] The development of improved DMT options that are administered orally may also have a positive benefit on long-term adherence to DMT.[62-66]

Identifying those patients that may benefit most from early DMT may assist in appropriate decision making regarding the management of patients with MS. In patients with CIS, there are certain risk factors that are associated with a higher likelihood of developing CDMS, while in patients with early MS, there are certain risk factors associated with progression of cognitive dysfunction and disability; assessing these risk factors may help to identify patients who would benefit most from early DMT.[67-73] In a study of patients with CIS, the rate of CDMS (based on the McDonald criteria) was higher for patients with an abnormal brain MRI (more than 2 lesions in addition to the lesion responsible for clinical presentation) at baseline (72%) than for those with a normal brain MRI (presence of only the lesion responsible for clinical presentation) at baseline (9%).[72] Other factors that may be indicative of a higher likelihood of a positive response to specific types of DMT are under investigation. Although not

currently validated for clinical use, biomarkers have been identified that may indicate the responsiveness of patients to treatment with IFN beta, GA, and natalizumab[74-82]; the identification of reliable biomarkers for predicting disease severity and response to therapy would be extremely useful for the selection of patients who are the best candidates for DMT. For example, patients with neutralizing antibodies to IFN beta have a poorer response to IFN beta therapy than those who are negative for neutralizing antibodies; the presence of these antibodies might serve as an indicator that an alternative DMT should be considered for these patients.[83]

Summary of Early Treatment Data for DMTs

Delaying the Conversion From CIS to CDMS

The efficacy of early treatment with IFN beta and GA for delaying the conversion of CIS to CDMS has been evaluated in several recent studies.[13,15,17,73,84-88] In the BENEFIT (BEtaferon in Newly Emerging MS for Initial Treatment) study, a 2-year, randomized, double-blind, placebo-controlled study of IFN beta-1b for CIS, IFN beta-1b was associated with significant delays in the time to progression to CDMS and the time to MS diagnosis according to the McDonald criteria[35] compared with placebo (P <.0001 for both comparisons).[13] Patients who received IFN beta-1b had an approximately 50% lower risk of conversion to CDMS and McDonald diagnosis of MS than those in the placebo group.[13] Results of an open-label extension of the BENEFIT study (in which all patients, regardless of initial randomization, received IFN beta-1b) have shown continued benefits with IFN beta-1b treatment for as long as almost 9 years after initial randomization.[84,89,90] At 3 years after initial randomization, reductions of approximately 40% were observed in the risk for developing CDMS and the risk for disability progression in patients who were initially randomized to treatment with IFN beta-1b during the 2-year parent study (early treatment group) compared with those who received placebo during the parent study (late treatment group).[89] At 5 years and approximately 9 years after randomization in the BENEFIT study, reductions of approximately 37% and 32%, respectively, were observed in the risk of conversion to CDMS for patients in the early treatment group compared with those in the late treatment group.[84,90]

IFN beta-1a treatment has also been shown to delay the conversion to CDMS.[15,43,73,85,88,91,92] In CHAMPS (Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study), a 3-year, randomized, double-blind, placebo-controlled study of IFN beta-1a for CIS, the cumulative 3-year probability of developing CDMS was significantly lower in the IFN beta-1a group than in the placebo group (P = .0002).[14] A post hoc analysis of data from CHAMPS showed an approximately 66% reduction in the rate of conversion from CIS to CDMS with IFN beta-1a compared with placebo over 3 years.[91] Continued benefits of early treatment with IFN beta-1a were shown in a 10-year follow-up to CHAMPS (in which all patients received IFN beta-1a); patients who were initially randomized to IFN beta-1a in the parent study (immediate treatment group) had a significantly lower 10-year rate of CDMS (P = .004) and annualized relapse rate during the last 5 years of follow-up (P = .03) compared with patients who were initially randomized to placebo.[73] Other improvements in patient outcomes have been observed with IFN beta treatment in patients with CIS; treatment with IFN beta-1a or IFN beta-1b has been shown to improve MRI measures of MS disease activity.[13,14,43] A previous study suggested that early treatment of MS with IFN beta-1a may slow the development of confirmed disability[89]; however, recent data by Shirani et al showed that administration of IFN beta-1a or IFN beta-1b was not associated with a reduction in disability progression in patients with MS.[93] Therefore, the relationship between IFN beta and disability progression remains uncertain and warrants further investigation.

Treatment with GA has also been shown to delay the conversion to CDMS in patients with CIS.[17] In a recent randomized, double-blind, placebo-controlled study, PreCISe (Early Glatiramer Acetate Treatment in Delaying Conversion to CDMS in Subjects Presenting With a Clinically Isolated Syndrome), treatment with GA was associated with an approximately 45% lower risk of conversion to CDMS and a delay of approximately 386 days in the conversion to CDMS compared with placebo ($P \leq .0041$).[17] As with IFN beta, this study showed that GA provided significant improvements in MRI measures of MS disease progression.[17] In addition, the rate of second relapse was significantly lower for patients taking GA compared with placebo (P <.0001).[17] The major outcomes from studies of IFN beta and GA in patients with CIS are summarized in Table 1.[13-32]

Results of a recent randomized, double-blind, placebo-controlled study (TOPIC [Teriflunomide Versus Placebo in Patients With First Clinical Symptom of Multiple Sclerosis] study) showed that teriflunomide treatment was associated with a reduction in the risk of conversion to CDMS in patients with CIS.[18] Daily doses of teriflunomide 7 mg and 14 mg over 2 years of treatment were associated with respective 37% and 43% reductions in the risk of conversion to CDMS compared with placebo (P <.05).[18]

Reducing the Relapse Rate in RRMS

IFN beta is available in 3 formulations (IFN beta-1b

SC, IFN beta-1a SC, and IFN beta-1a IM),[94] all of which have been shown to reduce the annualized relapse rate by approximately 30% and to significantly reduce MRI markers of disease activity compared with placebo (P <.05) in patients with RRMS.[19-21,40] IFN beta-1a treatment has also been associated with significant delays in the time to sustained disability progression compared with placebo (P <.05).[19,20] Slight differences have been observed in the efficacy of these formulations for reducing the occurrence of relapses; the risk of relapse was shown to be significantly lower for patients taking IFN beta-1a SC or IFN beta-1b SC than for those taking IFN beta-1a IM.[95-98] It is important to consider that these were head-to-head studies which are more useful for clinical decisions than earlier DMT versus placebo trials.

GA treatment has been associated with a 29% reduction in the 2-year relapse rate in patients with RRMS.[22] In addition, GA treatment has been shown to significantly improve MRI markers of disease activity compared with placebo in patients with RRMS (P ≤.003).[23] Direct comparisons of GA with IFN beta in patients with RRMS have shown little difference in relapse rates or disease progression.[99-101]

Natalizumab treatment has been shown to reduce the risk of relapse by approximately 68% and to reduce the risk of sustained disability progression by approximately 42% compared with placebo.[24] As with IFN beta and GA, natalizumab treatment has been associated with significant improvements in MRI markers of disease activity.[25] Natalizumab treatment has also been associated with improvements in measures of attention, memory, mood, and well-being,[102] as well as reductions in vision loss in patients with RRMS.[103] Natalizumab has been shown to reduce the risk of confirmed progression of cognitive deficits by 43% compared with placebo, to reduce the annualized rate of MS-related hospitalizations by 64%, and to significantly reduce the percentage of patients with disability progression (P ≤.002).[104] Treatment with natalizumab may result in additional costs and burden associated with safety tests, and requires careful articulation of patient risks versus benefits.

Fingolimod, which was the first oral DMT approved by the US Food and Drug Administration (FDA) for the treatment of MS, has been associated with a 53% to 55% decrease in the annualized relapse rate compared with placebo.[26] Fingolimod has also been shown to significantly reduce MRI markers of disease progression relative to placebo in patients with RRMS (P <.001).[26] Compared with IM IFN beta-1a, fingolimod has been associated with a significantly lower annualized relapse rate in patients with RRMS (P <.001).[105] Results of a randomized, placebo-controlled study also showed that fingolimod was associated with significant reduction in the risk of disability progression over 2 years compared with placebo (P = .02).[27] The major outcomes from studies of DMTs in patients with RRMS are summarized in Table 1.[13-32]

Teriflunomide, which received FDA approval for the treatment of RMS in September 2012,[106] has been shown to reduce the annualized relapse rate in patients with RMS by approximately 31% compared with placebo (P <.001).[28] In patients with RMS, teriflunomide has also been associated with significant improvements in MRI markers of disease activity compared with placebo (P ≤.05)[28-30] and with a significant reduction in the risk of disability progression (P ≤.05).[28,29] As an add-on to GA or IFN beta therapy for RMS, teriflunomide has been shown to significantly reduce MRI markers of disease activity compared with GA or IFN beta alone (P ≤.05).[107,108]

Dimethyl fumarate, an oral DMT, has also recently received FDA approval for the treatment of RRMS.[109] In patients with RRMS, dimethyl fumarate has been associated with reductions in the annualized relapse rate of up to 53% compared with placebo (P <.001).[31] Treatment with dimethyl fumarate has also been shown to result in significant improvements in MRI markers of disease progression compared with placebo (P ≤.02).[32] Compared with placebo, dimethyl fumarate has also been shown to significantly reduce the risk of disability progression (P ≤.01) in 1 of 2 phase 3 trials.[31]

The results of the previously described studies[13,15,17,19-22,26,40,73,84-88,105] generally indicate that early treatment with DMTs can delay the development of CDMS in patients with CIS and can slow disease progression and reduce the relapse rate in patients with RRMS; however, the lifelong effects of DMTs on disability or disease progression may not be accurately represented by these results given the limited time frames of these studies. In addition, patients who choose to start DMTs earlier may differ from those who delay or never take DMTs, so the patients who were initiated on DMT in these studies may not accurately represent the general patient population seen in clinical practice.

Overall, early initiation of DMT therapy appears to have beneficial effects in patients with MS.[42,52,89,110,111] Of note, a cost-analysis study recently demonstrated that for patients with MS, starting DMT earlier may be more cost-effective than starting DMT at later stages of the disease, in part because starting DMT earlier may reduce the substantial costs associated with late-stage MS and disability.[112] A shared decision-making process that emphasizes a patient-based approach may help patients and their caregivers make mutu-

ally informed decisions about healthcare and treatment. Further, comparative effectiveness studies will also provide pertinent information on the use of DMTs.

Safety and Tolerability of Current DMTs

GA and IFN beta are generally safe and well tolerated.[113,114] The most common side effects associated with IFN beta therapy are flu-like symptoms, such as fever, chills, myalgias, and headache, while the most common side effects associated with GA therapy are injection site reactions.[113,114]

Natalizumab is also generally well tolerated but has been associated with the occurrence of a rare and often fatal infection of the CNS (progressive multifocal leukoencephalopathy [PML]).[114,115] The identification of PML in patients receiving natalizumab led to the voluntary suspension of commercial and clinical trial dosing of natalizumab in 2005. A year later, natalizumab received FDA reapproval for use in patients with highly active relapsing MS and those who are unable to tolerate or do not respond to IFN beta or GA.[116] A risk stratification algorithm was developed based on JC virus antibody status, previous exposure to other chemotherapies, and length of therapy over 2 years.[117,118]

Fingolimod is relatively safe and well tolerated, although due to its relatively recent approval status, there is a lack of long-term clinical data regarding its efficacy and safety.[114,119] Fingolimod treatment has most commonly been associated with the adverse events of headache, influenza, nasopharyngitis, dyspnea, diarrhea, and nausea.[26] Fingolimod treatment has also been associated with dose-dependent decreases in heart rate within an hour after dosing.[26,105] Only a 0.5-mg dose of fingolimod was approved for use in patients with RRMS; as a safety measure, it is recommended that patients be monitored for 6 hours after their first dose of fingolimod to detect any potential bradycardia symptoms.[120] New recommendations require an electrocardiogram prior to dosing and 6 hours after the initial assessment, and 24 hours of monitoring for patients at higher risk for cardiac dysfunction or prolonged bradycardia.[120] Fingolimod treatment has also been associated with macular edema.[27,105]

Although teriflunomide is generally safe and well tolerated,[28] as with fingolimod, there is a lack of long-term safety and tolerability evidence due to its recent approval. Nevertheless, teriflunomide is the active metabolite of leflunomide, which has been on the market for the treatment of rheumatoid arthritis since 1998.[121] Results from a randomized, placebo-controlled, phase 3 study in patients with RRMS showed that teriflunomide treatment was associated with a higher incidence of the following treatment-emergent adverse events (TEAEs) relative to placebo: diarrhea, nausea, hair thinning or decreased hair density, and elevated alanine aminotransferase (ALT) levels.[28] However, the incidence of TEAEs leading to discontinuation of study drug was similar for placebo and teriflunomide.[28] Teriflunomide may also be associated with hepatotoxicity, particularly in patients with preexisting liver disease or with elevated ALT levels prior to treatment, and it is contraindicated in pregnant women based on evidence of teratogenicity from animal studies.[106] In a recent analysis of pregnancy outcomes in female patients and partners of males exposed to teriflunomide across 9 phase 2/3 clinical studies, all 20 live births in women exposed to teriflunomide resulted in no structural or functional abnormalities in these children at birth.[122]

As with the other 2 recently approved oral DMTs, long-term data on the safety and tolerability of dimethyl fumarate are lacking. Nevertheless, results of phase 3 studies indicate that dimethyl fumarate is relatively safe and well tolerated in patients with RRMS, with the most commonly reported adverse events including flushing, gastrointestinal adverse events (eg, diarrhea, nausea, and vomiting), pruritus, and proteinuria.[31,123] Dimethyl fumarate has been associated with a decrease in lymphocyte counts; however, treatment with dimethyl fumarate has not been shown to result in an increase in the rate of infections or serious infections.[109]

Comprehensive Care in MS

Starting early in the course of the disease, MS affects many areas of patient well-being, causing physical disability, cognitive impairment (in about half of patients with MS), and mental health problems (eg, anxiety, depression, and panic attacks in nearly half of all patients with MS over their lifetime).[124] Despite the diverse array of symptoms and multiple comorbidities, many patients with CIS or MS are managed by a single specialist and do not receive MS comprehensive care (MSCC).[125,126] MSCC involves the coordinated efforts of a multidisciplinary team of specialists, including neurologists, rehabilitation specialists, psychologists, ophthalmologists, urologists, speech pathologists, wound specialists, and social workers.[126] This type of coordinated management approach has implications for the timing and type of treatment in patients with MS. Early implementation of an MSCC approach may increase the likelihood that patients with CIS or early MS will be monitored appropriately for markers of disease progression, an important step in the management of early MS,[2,51,71,127] and will allow for earlier initiation of treatment. For example, screening for cognitive problems, which is considered a key component of an MSCC approach,[126,128] may be particularly important for patients with CIS or early MS because these problems often occur early in the course

of MS and potentially in the absence of other physical symptoms.[2,7,129] Use of MSCC, which involves coordination among numerous healthcare settings, as well as between medical and social services, can help ensure delivery of seamless care from initial diagnosis throughout the course of MS, improve patient satisfaction, and delay patient functional disability with the potential for reducing the economic burden of illness.[126]

Conclusion

Delays in the treatment of MS may have serious deleterious consequences for patients with MS and may result in poorer response to DMT and more severe neurological disability.[45,50-52] Early treatment of CIS with disease-modifying therapeutics is associated with delays in the development of CDMS and reductions in the rate of relapses.[13,15,17,54,73,84-87] For these reasons, early DMT in patients with CDMS or CIS has been advocated in a number of guidelines.[38,40,41,57,114]

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