Clinician’s Primer on Multiple Sclerosis
Clinically Isolated Syndrome

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Posttest

Evaluation Form
TARGET AUDIENCE
This activity has been designed to meet the educational needs of neurologists, neurology residents, and nurses involved in the care of patients with multiple sclerosis (MS) or a clinically isolated syndrome (CIS).

ACTIVITY DESCRIPTION
MS is a progressive disease of the central nervous system (CNS) affecting approximately 400,000 people in the United States. The first presentation of MS in patients is a clinically isolated syndrome (CIS), a clinical and neurological event suggestive of MS lasting ≥ 24 hours and is caused by inflammation/demyelination in one or more sites in the CNS. Common presentations are optic neuritis, spinal cord syndromes, or brainstem-cerebellar syndromes.

The Clinician’s Primer on Multiple Sclerosis: Clinically Isolated Syndrome is an all-inclusive reference source on the aspects of a CIS. It provides the most current information on clinical features, diagnostic testing, diagnostic criteria, differential diagnosis, the natural history and prognosis of CIS patients, and currently recommended approaches to treat CIS patients. This information will educate clinicians who treat CIS patients in order to reduce the likelihood of disease progression and enhance clinical outcomes.

EDUCATIONAL OBJECTIVES
Upon completion of this activity, participants should be able to:
• Describe the clinical challenges of accurately diagnosing patients presenting with a CIS
• Discuss the role of MRI in the diagnosis of a CIS and in the risk stratification of patients who develop MS
• Identify common presenting features in CIS patients
• Discuss the rationale for early initiation of therapy in CIS patients
• Review disease-modifying therapies shown to improve clinical outcomes in CIS patients

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**Clinician’s Primer on Multiple Sclerosis**

**Clinically Isolated Syndrome**

1

**INTRODUCTION**

Multiple sclerosis (MS) is a chronic, immune-mediated, inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS) that affects approximately 400,000 individuals in the United States.\(^1\)\(^4\) Typically progressive and debilitating, MS is the leading cause of non-traumatic neurological impairment in young adults, usually affecting those in the 20-40 year age range, with a male to female ratio of 1:2 in most populations.\(^5\)\(^7\) There is an increased incidence and prevalence of MS in Caucasian populations of northern European descent and in those who live in temperate climates.\(^8\)

The exact pathogenesis of MS is unknown, but research indicates that interactions between genetic and environmental factors trigger an abnormal immune-mediated cascade, causing acute inflammation directed against neuronal myelin within the CNS. Discrete pathological lesions or plaques in the CNS are formed by immune and inflammatory processes, demyelination of neuronal axon sheaths, axonal damage and loss with subsequent postinflammatory tissue changes, gliosis, and scarring.\(^9\) Studies demonstrate that irreversible neurological tissue damage occurs long before the first clinical manifestation and is persistent, leading to progressive neurologic disability in most patients in the long term.\(^10\)\(^12\) Early and ongoing axonal degeneration is thought to be the major cause of neurologic and functional disability in MS.\(^13\)

Approximately 85% of patients develop relapsing-remitting MS (RRMS), and the first presentation in these patients is a clinically isolated syndrome (CIS) or initial demyelinating event, which is the focus of this Primer.\(^11\)\(^14\)\(^16\) A CIS is defined as a first clinical and neurological event suggestive of MS lasting ≥ 24 hours and is caused by inflammation/demyelination in 1 (monofocal) or more (multifocal) sites in the CNS.\(^7\) Common CIS presentations include optic neuritis (ON), spinal cord syndromes, or brainstem-cerebellar syndromes.\(^15\)\(^18\)

Studies demonstrate that approximately two-thirds of patients presenting with a CIS have multiple clinically silent brain lesions on baseline magnetic resonance imaging (MRI) typical of those seen in patients with MS, confirming that subclinical disease activity predates the initial clinical event.\(^19\)\(^22\) CIS patients with baseline MRI lesions have a 50%-98% risk of being diagnosed with MS in the future compared with a < 25% risk in those with no detectable baseline lesions.\(^12\)\(^21\)\(^23\)\(^33\)

However, the occurrence of a CIS does not necessarily mean the patient has or will develop MS.\(^35\)\(^34\)\(^35\) Rather, a CIS indicates a risk for subsequent development of MS months or even years later.\(^15\)\(^16\)\(^36\) A definite diagnosis of MS is established based on clinical criteria, almost always in combination with MRI findings. Additional testing in selected patients, such as analysis of the cerebrospinal fluid (CSF) or visual evoked potential (VEP) may be necessary in some patients. However, no single test result is pathognomonic of MS, and multiple alternative diagnoses need to be excluded.

Recent evidence indicates that axonal damage and loss, brain atrophy, and widespread CNS tissue damage are evident in patients presenting with a CIS.\(^10\)\(^11\)\(^37\)\(^43\) Research shows that CNS tissue damage and disease progression in MS usually are persistent and continuous and may be independent of subsequent acute clinical events, with ongoing axonal damage and loss being a major contributor to permanent future disability.\(^10\)\(^11\)

Reducing the occurrence of relapses, delaying disease progression, minimizing functional disability, and promoting quality of life are the central goals in treating patients with MS. Currently available disease-modifying therapies (DMTs) for MS include 3 interferon (IFN) beta preparations (intramuscular [IM] IFN beta-1a, subcutaneous [SC] IFN beta-1a, SC IFN beta-1b), glatiramer acetate (GA), fingolimod, natalizumab, and mitoxantrone. Studies using IM IFN beta-1a, IFN beta-1b, and GA to treat CIS patients have shown significant benefits in reducing the risk of developing MS and, as such, recently have been approved by the United States Food and Drug Administration (FDA) for treating clinically isolated syndromes.\(^44\)

In managing CIS patients, current evidence clearly indicates the importance of excluding other diseases, diagnosing MS promptly and accurately, developing a management plan, and initiating DMT as soon as possible to help prevent subclinical
CNS damage and delay the onset of MS and disease progression. However, patients who have experienced 1 neurological event with few or no residual symptoms may be unwilling to commit to long-term, costly, injectable treatments. Therefore, effective clinician-patient communication and education regarding the benefits and risks of treatment are essential when counseling CIS patients.

Clinicians managing patients presenting with a CIS must address the following challenges: Is the neurological event due to a disorder other than MS? Is it possible to predict whether this individual subsequently will develop MS, and if so, what is the likelihood and extent of future disability? How should the patient be assessed? Should treatment be initiated in an effort to hasten recovery of the CIS/relapse and/or delay the development of MS? What are the risks and benefits of treatment for each CIS patient? In order to address these challenges and optimize patient outcomes, the following key issues in managing a CIS are discussed in this Primer: clinical features, diagnostic testing, diagnostic criteria, differential diagnosis, natural history and prognosis of CIS patients, and currently recommended approaches to treatment based on a synthesis of the literature and approaches suggested by MS experts.

2 OVERVIEW OF MS

The following section provides an overview of MS specifically relevant to clinicians managing CIS patients.

OVERVIEW OF MS NEUROPATHOGENESIS
MS is an inflammatory, immune-mediated disease that targets neuronal myelin and axons in the CNS. Although the disease processes causing MS are not understood fully, both cell-mediated (T cell) and humoral/antibody-mediated (B cell) processes appear to be involved in a dysregulated immune response to myelin autoantigens, such as myelin basic protein, proteolipid protein, and myelin oligodendrocyte glycoprotein (MOG). Key cells involved in MS pathogenesis are myelin-reactive T cells, CD4+ T helper (Th) cells, CD8+ cytotoxic T cells, regulatory T cells, B cells, lymphocytes, activated macrophages, and monocytes.

The initial step in the pathogenesis of MS is peripheral activation of immune cells, likely caused by foreign microbes, self-proteins, or microbial superantigens. Peripherally activated T cells and their subsets travel to the CNS, passing the blood-brain barrier (BBB) in a multistep process involving inflammatory cytokines, chemokines, and matrix metalloproteinases. Within the CNS, activated T cells recognize target myelin autoantigens, initiating the release of proinflammatory cytokines. This process triggers an immune cascade, leading to the formation of characteristic MS lesions, typically appearing in the periventricular white matter (WM), brain stem, cerebellum, optic nerves, and spinal cord, these lesions display histological changes consistent with inflammation, demyelination, axonal transection and loss, proliferation of astrocytes, gliosis, and scarring.

Studies in patients with MS reveal that immune-regulatory and reparative processes in the CNS are ongoing in response to inflammatory activity and neurological tissue damage. Proinflammatory and anti-inflammatory cytokines, produced by a variety of T- and B-cell subsets, have been shown to play a key role in both destructive and reparative processes in MS. Of the CD4+ T-cell subsets, recent data suggest a prominent role for interleukin (IL)-17–producing Th17 cells in mediating inflammatory immune responses.

Studies show that immune responses in patients with a CIS and MS are similar, including the presence of antibodies to MOG and correlations between the presence of B cells in the CSF and brain inflammation. However, research findings indicate higher levels of IL-17 in CIS patients and higher IFN gamma levels in acute phase CIS patients compared with RRMS patients in remission, indicating active inflammatory processes in early CIS patients.

RECENT STUDIES ON CAUSES OF TISSUE DAMAGE IN EARLY MS
Histopathological studies using advanced MRI techniques have shown that axonal damage, transection, and loss occur in the earliest phases of MS, including a CIS, and may be independent of MRI-visible inflammation.

In a study to assess early axonal pathology and its correlation with MRI-visible lesion loads, Filippi et al compared
the concentration of the neuronal metabolite whole brain N-acetylaspartate (WBNAA) in CIS patients (n = 31) with healthy matched controls (n = 16). CIS patients were assessed using conventional MRI (cMRI) and unlocalized proton magnetic resonance spectroscopy (1H-MRS) within 3 months of symptom onset. Results revealed significant reductions in WBNAA in the CIS patients, suggesting early neuronal axon damage compared with controls, and axonal pathology was largely independent of cMRI-visible inflammation. These results challenge the long-held concept that neuropathological events in MS are a sequential process with initial inflammation resulting in demyelination, and axonal damage/loss occurring later in the disease course. Instead, these data support the concept that axonal pathology occurs early in patients presenting with a CIS and that DMTs should be initiated as soon as possible after diagnosis to prevent ongoing tissue damage.42

Recent studies also have revealed that early oligodendrocyte apoptosis and loss in the absence of infiltrating lymphocytes likely are the primary events in MS pathogenesis. Mechanisms other than cell-mediated immunity against a myelin or oligodendrocyte antigen may be responsible for lesion formation.69,70

In 2004, Barnett and Prineas69 published an important study describing novel pathological changes in 12 patients with RRMS who died during or soon after the onset of a relapse. In 7 of the 12 cases, autopsy findings showed extensive oligodendrocyte apoptosis and microglial activation in myelinated tissues containing few or no lymphocytes or myelin phagocytes. These findings challenge the long-standing concept that macrophages are the primary mediators of myelin destruction in MS. In this study, the earliest change observed in the lesions examined was widespread oligodendrocyte apoptosis in tissues where T cells, macrophages, activated microglia, reactive astrocytes, and neurons appeared normal. In earlier studies, no similar lesions had been described in any experimental model of MS. This study suggests that a change in the local environment to which oligodendrocytes are exposed triggers a form of apoptosis. The possibility of a novel process is raised, such as a viral infection of oligodendrocytes, hypoxic stress secondary to ischemia, or an immune-mediated process. The lesions described by Barnett and Prineas likely represent a very early stage in the formation of most lesions that cause acute exacerbations in MS.49

In 2009, Henderson et al70 published a study that investigated the inflammatory profile of different regions within rapidly expanding MS lesions. Twenty-six active lesions from patients with early MS (n = 11) were examined with serial sections and immunostaining for T and B cells, plasma cells, ramified microglia, macrophages, monocytes, and CD209-positive dendritic cells. Cell counts then were compared in pre-phagocytic, phagocytic, and immediately post-phagocytic areas. Results showed that parenchymal T and B cells were largely absent in areas of initial oligodendrocyte loss and in areas of degenerated or dead myelin infiltrated by myelin phagocytes. However, in areas of complete demyelination packed with lipid macrophages (some lesions had regenerating oligodendrocytes), large numbers of T cells, B cells, and immunoglobulin G (IgG)-positive plasma cells were seen. Yet, lesions from 2 early cases showed relatively few T and B cells and no IgG-positive plasma cells.

The authors concluded that early loss of oligodendrocytes is a prominent feature in tissue bordering rapidly expanding MS lesions; that macrophage activity is largely an innate scavenging response to the presence of degenerate and dead myelin; and that adaptive immune activity involving T and B cells is present mainly in recently demyelinated tissue, which may show signs of oligodendrocyte regeneration. These findings challenge the previously held concept that CD4+ T-cell–dependent macrophage activation directed against a myelin or oligodendrocyte antigen is the mechanism causing myelin destruction in MS and suggest that lesion formation may have a basis other than destructive cell-mediated immunity directed against a myelin or oligodendrocyte antigen.70 It is important to note that MS biopsy and some autopsy studies are susceptible to inherent selection bias, and the findings may not be representative of typical MS.

OVERVIEW OF HETEROGENEITY

In 2000, Lucchinetti et al71 described 4 distinct patterns of tissue pathology in an immunohistopathological study of actively demyelinating MS lesions in 83 cases (51 biopsies and 32 autopsies). All lesion patterns contained an inflammatory infiltrate consisting of T cells and macrophages with
neurological and functional deterioration from onset with subsequent, occasional, intermittent relapses.\textsuperscript{84}

The high degree of variability and heterogeneity of MS is illustrated further by the wide phenotypic expressions of the disease. Occasionally, a benign course of MS is observed in patients experiencing full neurologic function 15 years after diagnosis or retaining a Kurtzke Expanded Disability Status Scale (EDSS) score of 2.0 or less (minimal disability in 1 functional system [FS]) 10 years after diagnosis. Other patients may experience a severe or malignant course that rapidly progresses, leading to disability or death in a relatively short period of time.\textsuperscript{73,85}

The pervasive pathological and clinical heterogeneity of MS is seen both between and within the disease subtypes. Variations in clinical manifestations, neuropathologic changes and mechanisms, MRI findings, and clinical course have limited clinicians’ ability to accurately predict outcomes of patients with MS.\textsuperscript{1,86,87}

Overview of grey-Matter (GM) and WM involvement in MS

Recent pathologic and advanced MRI studies in MS patients found that WM lesions represent only a fraction of visible pathology, emphasized GM involvement, and demonstrated that extensive damage to GM and normal-appearing WM (NAWM) occurs in MS.\textsuperscript{39,40,88,89} Damage to GM is seen in the earliest clinical stages of MS and may be a determinant of long-term disability.\textsuperscript{40}

If left untreated, approximately 90\% of patients with RRMS will enter the secondary progressive phase of MS within 25 years.\textsuperscript{19,77-79} SPMS is characterized by gradually progressive and irreversible neurologic deterioration, with or without superimposed relapses.\textsuperscript{80,81} Transition to SPMS from RRMS can occur despite years of apparent clinical stability.

In SPMS, physical, cognitive, emotional, social, economic, and health-related quality of life (HRQOL) decline are more evident than in RRMS, and SPMS is more refractory to treatment than is RRMS.\textsuperscript{10,46,68,73,78,81,82} Therefore, preventing or delaying long-term disability and the transition to SPMS are central goals of current disease management in patients with a CIS and RRMS.\textsuperscript{68,81}

Approximately 10\% of patients have PPMS, characterized by continuous and usually gradual deterioration of neurologic function without discrete relapses.\textsuperscript{73,83} Only 5\% of patients have PRMS, a rare subtype of MS associated with a steady neurological and functional deterioration from onset with subsequent, occasional, intermittent relapses.\textsuperscript{84}

The pervasive pathological and clinical heterogeneity of MS is seen both between and within the disease subtypes. Variations in clinical manifestations, neuropathologic changes and mechanisms, MRI findings, and clinical course have limited clinicians’ ability to accurately predict outcomes of patients with MS.\textsuperscript{1,86,87}

Overview of the Natural History of MS

The natural history of MS is characterized by disease progression and cumulative disability over time. Prior to the development of DMTs, studies revealed that 50\% of MS patients were unable to carry out employment or household
Clinical Presentation and Classifications of Clinically Isolated Syndromes

Approximately 85% of MS patients initially present with a CIS. Common presentations consist of ON, spinal cord syndromes, or brainstem-cerebellar syndromes. CIS patients occasionally present with symptoms and signs indicative of cerebral hemisphere dysfunction, such as mild cognitive dysfunction or hemiparesis. In a large database of CIS patients, Miller et al. reported that 21% presented with ON, 46% with spinal cord syndromes, 10% with brainstem-cerebellar syndromes, and 23% with multifocal abnormalities. These data indicate that approximately 23% of CIS patients have disease disseminated in space (DIS; clinical evidence of more than 1 separate lesion) at presentation. This study also suggests that the clinical features and presentation of a CIS can affect disease course and prognosis. Table 1 summarizes the demographic and clinical characteristics of CIS patients from several pivotal studies; the differing clinical and MRI inclusion criteria are described in detail in each study.

Optic Neuritis
Optic neuritis is a common clinical manifestation of a CIS and has been studied extensively. Patients with ON usually present with unilateral vision loss that evolves over hours to 7-10 days and is preceded or accompanied by ocular pain that is worse with eye movements. Findings on examination include impaired visual acuity, decreased color perception, and/or a visual field defect. An afferent pupillary defect usually is present. The optic disc may be normal or show mild swelling. Bilateral simultaneous ON, painless ON, severe visual loss with no light perception, moderate to severe disc swelling, and hemorrhages and retinal exudates are uncommon in patients who subsequently develop MS.

Progression of visual loss in ON is atypical after 2 weeks. Visual recovery is rapid in most patients. Some spontaneous recovery of vision typically is seen in the first 2-4 weeks after onset of symptoms. Ninety-eight percent of patients with visual acuity of 20/50 or worse at presentation usually improve at least 3 lines on a Snellen letter chart within 6 months after the onset of symptoms.

The initial severity of visual loss is valuable in predicting visual outcomes. However, visual recovery is still good in most patients including those with initial severe visual loss. Patients with ON who do not follow the usual course of visual recovery should be considered atypical and undergo further investigation to exclude other diagnoses.

Spinal Cord Syndromes
Patients with spinal cord syndromes usually present with a partial transverse myelitis that typically evolves over several days. Symptoms include weakness, numbness, Lhermitte’s sign (whereby neck flexion triggers what most commonly is described as an electric sensation that usually radiates from the back of the neck to the lower back and possibly into 1 or more limbs), paresthesia, erectile dysfunction, and bowel and bladder responsibilities 10 years after disease onset, 50% required at least a cane to walk 10-15 years after diagnosis, and 50% were unable to walk after 25 years.

In the Lyons natural-history cohort of 1844 MS patients (RRMS, 1562; PPMS, 282), the median time from onset of MS to an EDSS score of 4.0 (only able to walk 500 meters without aid or rest) was 8.4 years. Median times from onset of MS to an EDSS score of 6.0 (need cane or crutch to walk 100 meters with or without resting) was 20 years and to an EDSS score of 7.0 (restricted to a wheelchair) was 30 years. Evidence indicates that axonal injury and loss starts early in the course of MS, is ongoing, and correlates closely with brain atrophy and irreversible neurological and functional disability in the long term. As most patients develop MS in early adulthood and life expectancy is not substantially altered by the disease, early treatment and rehabilitation interventions to minimize functional disability and maximize HRQOL is of the utmost importance in managing patients effectively in the long term. In an effort to alter the course of MS, clinicians must be able to recognize patients presenting with a CIS and treat them promptly and effectively.
brainstem-cerebellar syndromes are common clinical manifestations of a CIS. Typically, patients present with diplopia due to a sixth nerve palsy or a bilateral internuclear ophthalmoplegia, as well as ataxia, multidirectional nystagmus, or facial numbness. Less common symptoms associated with a CIS include unilateral internuclear ophthalmoplegia, facial palsy, trigeminal neuralgia, deafness, bladder dysfunction. Asymmetric neurologic findings and predominant sensory symptoms with relative sparing of motor function is characteristic. Less common symptoms include complete acute transverse myelitis, radiculopathy, areflexia, segmental loss of pain and temperature sensation, partial Brown-Sequard syndrome (sparing posterior columns), fecal incontinence, and progressive symmetrical paraplegia.

### Brainstem-Cerebellar Syndromes

Brainstem-cerebellar syndromes are common clinical manifestations of a CIS. Typically, patients present with diplopia due to a sixth nerve palsy or a bilateral internuclear ophthalmoplegia, as well as ataxia, multidirectional nystagmus, or facial numbness. Less common symptoms associated with a CIS include unilateral internuclear ophthalmoplegia, facial palsy, trigeminal neuralgia, deafness,
and one-and-a-half syndrome. Signs and symptoms may occur alone or in combination.34

Cerebral Hemisphere Syndromes
CIS patients occasionally present with a hemiparesis, hemianopsia, or seizures.15,34,111,112 In a recent study, > 50% of CIS patients presented with cognitive dysfunction, including deficits in memory, information processing, attention, and executive functions.112 However, most CIS patients do not complain of cognitive dysfunction, and it usually is identified by detailed clinical examination and neuropsychological testing.

CIS CLASSIFICATIONS
Classifications of clinically isolated syndromes proposed by experts and MS organizations are based on a combination of clinical symptoms and MRI findings and include (1) monosymptomatic or monofocal (a single neurologic sign/symptom caused by 1 lesion) or (2) polysymptomatic or multifocal (more than 1 sign/symptom caused by lesions in more than 1 anatomical location in the CNS).17,113,114 Neurological symptoms of a CIS are monophasic (a single occurrence or event).34 Various terminologies have been used to describe the presentation of a CIS (such as monoregional, polyregional, monosymptomatic, polysymptomatic). The lack of a standardized classification scheme has led to confusion and variability in clinical assessments of disease in CIS patients.114,115 In particular, inconsistencies in clinical assessments have occurred regarding the attribution of signs/symptoms to ≥ 1 lesion on MRI.113,115

Recent efforts have been made to clarify the definition of a CIS and classify disease dissemination based on the minimum number of lesions that likely explain the clinical signs and symptoms. In 2005, Uitdehaag et al114 proposed an algorithm for classifying CIS patients.114 This method distinguishes CIS patients with monofocal and multifocal presentations based on FS scores, which in turn are based on an ordinal rating scale for individual systems, including pyramidal, cerebellar, brainstem, bowel/bladder, sensory, and visual function. Although this classification might be useful for predicting progression to MS, it is not widely used in clinical practice (although the reasons for this remain unclear).

In 2006, the International Advisory Committee on Clinical Trials in MS convened an International Task Force of 18 MS experts to define guidelines for the differential diagnosis of suspected MS and to clarify the definition and classification of a CIS.34 The Task Force proposed a list of clinical and paraclinical red flags that, in the appropriate clinical setting, might suggest diagnoses other than MS, as well as a consensus-based risk algorithm for the common clinically isolated syndromes related to MS.34 The Task Force agreed that a CIS should be defined as a monophasic presentation (a single episode at first presentation of relatively rapid onset) of neurological symptoms with suspected underlying demyelinating disease.34 Five classes of clinically isolated syndromes based on clinical and MRI criteria were proposed:

- **Type 1**: Clinically monofocal presentation with at least 1 asymptomatic MRI lesion;
- **Type 2**: Clinically multifocal presentation with at least 1 asymptomatic MRI lesion;
- **Type 3**: Clinically monofocal presentation, MRI may appear normal, no asymptomatic MRI lesions;
- **Type 4**: Clinically multifocal presentation, MRI may appear normal, no asymptomatic MRI lesions; and
- **Type 5**: No clinical symptoms or only has nonspecific symptoms (eg, headache), but MRI shows abnormalities typical for demyelination. This subtype of a CIS also has been called a radiologically isolated syndrome (RIS).

Patients with a type 5 CIS/RIS typically are identified incidentally when MRI is performed for other reasons than a concern for demyelinating disease (eg, headache or head trauma). In the absence of history and examination findings consistent with at least 1 clinical demyelinating event, a diagnosis of a CIS or MS is not possible. However, RIS patients should be followed closely as they may develop symptoms consistent with CNS demyelination and/or new MRI abnormalities characteristic of demyelination. In several studies of RIS patients, a CIS or MS has developed in about one-third of patients over 5 years.116-118

Defining and classifying the features of a CIS have been shown to have prognostic value in predicting future MS disease progression. CIS features associated with good prognosis include ON, normal MRI, isolated sensory symptoms, long interval to second relapse, and no disability after 5 years. CIS features associated with poor prognosis (increased likelihood of a second relapse and developing MS) include multifocal symptoms, abnormal
Diagnostic Testing

In patients presenting with a CIS, the diagnosis of MS is mainly a clinical judgment based on history and examination findings. However, currently the 3 main methods of testing used to help diagnose MS are: cMRI, CSF analysis, and evoked response studies.

Conventional MRI

In conjunction with clinical evaluation, cMRI now is incorporated into the diagnostic strategy for MS due to its unique sensitivity to demonstrate DIS and dissemination in time (DIT; 2 MRI lesions separated by time) of demyelinating lesions in the brain and/or spinal cord. However, cMRI findings alone cannot be used to diagnose MS, and normal cMRI findings do not necessarily exclude a diagnosis of MS.

Conventional MRI techniques include gadolinium (Gd)-enhanced T1-weighted images, T2-weighted images including fluid-attenuated inversion recovery (FLAIR), and noncontrast T1-weighted images. Because these cMRI techniques are highly sensitive in detecting typical MS lesions and may provide an assessment of inflammatory activity and lesion load, they are valuable tools in the diagnosis of MS as well as in the monitoring of disease progression and response to DMTs. However, clinical changes in MS are not consistently related to MRI changes, and this is considered a limitation of cMRI. For more detailed information, please refer to Primer 2 in this series: Clinician’s Primer on Multiple Sclerosis: Basic Course on MRI (2009).

Conventional MRI detects and characterizes the location, size, volume, and morphology of brain and spinal cord lesions in CIS and MS patients. Typical findings include enhancing lesions on Gd-enhanced T1-weighted imaging, hyperintense lesions on T2-weighted imaging, and hypointense lesions including chronic hypointense lesions (black holes) on noncontrast, T1-weighted imaging. Conventional MRI has limited specificity for pathological findings of MS (including edema, demyelination, axonal loss, and remyelination) and may be unable to detect and quantify the extent of damage in MS lesions and surrounding tissues.

Gd-Enhancing T1 Lesions

Gadolinium-enhancing lesions on T1-weighted imaging signify active perivascular inflammation, BBB disruption,
and T-cell infiltration. They typically are the first detectable cMRI finding in patients with RRMS. About 65%-80% of enhancing lesions are hypointense on pre-Gd T1-weighted sequence and almost always are associated with hyperintensity at the same location on T2-weighted imaging. Lesions are enhanced when contrast leaks through disrupted junctions of vascular endothelium and subsequently accumulates in CNS tissues. Enhancement is transitory, lessens as acute inflammation subsides, and usually resolves after 2-4 weeks (almost always by 8 weeks). Patients with persistent enhancement beyond 8 weeks should be evaluated for an alternative diagnosis.

Patterns of Gd enhancement (shape, size, rings) vary considerably between patients, reflecting the heterogeneous pathology of MS. Initial Gd-enhancing lesions usually are small, homogeneous nodules and may progress to ring-enhancing lesions, indicating more severe tissue damage. In MS, incomplete or open-ring lesions that abut GM are typical. A complete ring pattern usually is seen when lesions are confined to WM.

Gd-enhancing lesions provide a measure of CNS inflammation in currently or recently active lesions and may be used to distinguish active lesions from inactive ones. However, Gd enhancement does not provide information on tissue damage or the extent or severity of inflammatory activity and may correlate poorly with concurrent clinical disease activity, especially if Gd-enhanced scans are performed at pre-determined intervals.

**T2-Weighted Lesions**

Brain MRI typically reveals T2 hyperintense lesions in the periventricular WM, corpus callosum, centrum semiovale, juxtacortical regions, pons, floor of the fourth ventricle, cerebellar peduncles, or cerebellar hemispheres. In addition to the symptomatic lesion(s), brain MRI detects clinically silent lesions in 50%-80% of CIS patients. T2 hyperintense lesions are usually 3-15 mm in diameter, round or ovoid in shape, and clearly delineated. However, T2 hyperintense lesions are nonspecific and may represent edema, demyelination, axonal damage, matrix destruction, gliosis, and/or remyelination. Despite their lack of specificity and poor correlation with clinical relapses and disability in patients with established MS, the baseline number of T2 lesions at CIS presentation and the change in T2 lesion volume in the first 5 years following a CIS are predictive of subsequent development of MS and long-term disability, respectively.

MRI studies also show GM involvement in the cerebral cortex and basal ganglia in up to 25% of MS patients. GM involvement is present early in the disease course and correlates only partially with lesion load in WM. FLAIR is the most reliable and useful imaging techniques for identifying lesions in deep GM. It involves heavy T2-weighted imaging with nulling of the CSF signal. In general, FLAIR is a more sensitive sequence than T2 for demonstrating supratentorial lesions, but it is suboptimal for detecting infratentorial lesions. Figure 1 illustrates T2-weighted FLAIR images of lesions more specific for MS.

**FIGURE 1: FLAIR Images Specific and Not Specific for MS**

Typical T2-weighted FLAIR images from an MS patient, illustrating different types of cerebral lesions. In general, lesions are more specific for MS if they are in the corpus callosum, juxtacortical area, brainstem, or adjacent to the body of the lateral ventricles. T2 lesions in deep cerebral WM and anterior and posterior to the lateral ventricles are not specific for MS and often are seen in other conditions, including microvascular ischemic disease and aging.

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**Noncontrast T1-Weighted Lesions**

Noncontrast T1-weighted imaging in MS patients typically shows hypointense (with lower signal intensity) lesions in CNS WM. Acute hypointense T1 lesions typically represent areas of tissue edema. Up to 70% of new T1 hypointense lesions resolve and become isointense over 6-12 months, with up to 80% of all lesions developing an isointense appearance. This may be a result of resolution of edema and possibly remyelination.

Approximately 20%-45% of T1 hypointense lesions persist and are referred to as chronic black holes. Chronic
black holes represent severe tissue damage with matrix
destruction, severe demyelination, and axonal loss. They
have a much better correlation with disability than T2
lesions, especially in patients with SPMS. Of note,
chronic black holes also may be present on T1-weighted
images in CIS patients, indicating significant CNS tissue
damage at the earliest stage of MS.

Results from CHAMPS (Controlled High-Risk Subjects
Avonex MS Prevention Study) (discussed further) showed
≥ 1 black hole in approximately 50% of CIS patients who had
≥ 2 MRI lesions. In patients with early MS, approximately
50% of baseline Gd-enhancing lesions, especially in those
patients with ring-enhancing lesions, develop into black
holes. Studies exhibit that black hole lesion volume
increases with the duration of MS and correlates better with
clinical disease severity than T2-weighted lesions, especially in
patients with SPMS. Inconsistencies in patient positioning
or slice location/orientation may lead to difficulties when
interpreting tissue changes on serial imaging.

Spinal Cord Lesions
MS may involve both the brain and spinal cord, and
approximately 25% of all cases of MS involve only the
spinal cord. T2 hyperintense lesions of the spinal cord
are detected in approximately 50%-90% of patients with
MS and are asymptomatic in up to 42%. Spinal cord lesions are more common in the cervical than
the thoracic spine, appear hyperintense on T2-weighted
imaging, and have a predilection for WM in the lateral
and posterior columns. Adjacent GM commonly is
involved. Spinal short-tau inversion recovery or phase-
sensitive inversion recovery imaging offer improved tech-
niques for detecting spinal cord lesions in MS.
Hypointense lesions of the spinal cord on T1-weighted
imaging are rare. Spinal cord lesions typically extend
over < 2 spinal segments and involve < 50% of the cross-
sectional area of the spinal cord. Patients with spinal
cord lesions that do not conform to these limits (eg,
longitudinally extensive lesions) should be evaluated for
alternative diagnoses like NMO.

From 27% to 42% of CIS patients have clinically silent spinal
cord lesions. As spinal cord lesions typically do not occur in
normal aging (as T2 brain lesions often do), their detection
on MRI can be useful in diagnosing CIS patients who present
with vague symptoms and nonspecific brain MRI
abnormalities, as well as strengthening the prediction of a
patient developing subsequent MS. Studies have shown
close correlation between the number of brain lesions and
the number of spinal cord lesions in MS patients. Studies
with multisequence imaging at baseline and 3 months show
that the frequency of progression to MS was higher for
patients with both brain and spinal cord lesions at baseline
(48%) compared to those with brain lesions alone at baseline
(18%). Studies also show that cervical spinal cord atrophy
correlates with the development of disability in MS.

The Consortium of Multiple Sclerosis Centers (CMSC)
MRI guidelines specify the following indications for spinal
cord MR imaging relevant to CIS patients: if the main pre-
sentation neurological symptoms are at the level of the spinal
cord and have not resolved, both spinal cord and brain MRI
are required. Also, if the results of the brain cmRI are equiv-
ocaI and the diagnosis of MS is still being considered, spinal
cord imaging may be indicated. However, many neurolo-
gists obtain baseline spinal cord mRI in all CIS patients.

In a recent analysis of ON patients, baseline spinal cord,
infratentorial and Gd-enhancing lesions, and new T2
lesions at 3-months’ follow-up were predictive of dis-
ability after 6 years. Asymptomatic spinal cord lesions
at ON presentation significantly increased the odds of
higher disability at 6 years. This effect was independent
and stronger than brain lesion load and suggested a
possible role for spinal cord mRI in patients with ON to
predict future disability.

Brain Atrophy
Investigational assessments of whole brain atrophy can be
measured by cMRI (using serial imaging and calculating
the proportion of brain parenchymal volume divided by the
volume within the brain surface) or new computer software
for MRI. These assessments demonstrate that atrophy may
be associated with cognitive impairment and can function as
a marker for irreversible CNS tissue damage.

Clinical Value of cMRI Findings
Conventional MRI is used to assess and diagnose MS
patients as well as monitor disease progression and treat-
ment response over time. However, baseline MRI may not
help predict long-term disability in MS patients.
Studies in patients with RRMS show that inflammatory lesions in the CNS evolve continuously, with ongoing axonal damage/loss and tissue damage. This is supported by the accumulation of T2 hyperintense lesions, T1 hypointense lesions, and brain atrophy as seen on cMRI even during prolonged periods of clinical stability between relapses. Studies have revealed that at least 1 Gd-enhancing lesion is present on a single cMRI scan in approximately 50% of patients with untreated and clinically quiescent RRMS. In CIS patients without initial MRI abnormalities, progression to MS is much less likely. However, approximately 10%-20% of these patients will have a second clinical episode separated in time and space within 20 years.

Consistent accumulation of new T2 lesions over time and/or the constant presence of Gd-enhancing lesions on serial cMRI are valuable indicators in evaluating treatment response to DMTs in patients with MS or a CIS. Studies demonstrate a mismatch between clinical events and cMRI-measured disease activity, with approximately 5-10 new or enlarging Gd-enhancing or T2 brain lesions identified for every 1 clinical exacerbation. Studies suggest that MRI-measured brain atrophy correlates fairly well with disability in MS and better than cMRI metrics, and this may be of increasing importance in the future.

**MRI Protocols**

Standardized protocols for the use of cMRI in the diagnosis and follow-up of MS patients have been proposed by CMSC and the International Panel (IP) of MS Experts. The CMSC guidelines offer both a specific brain and spinal cord imaging protocol to facilitate diagnosis and follow-up of patients with a CIS or MS within and between imaging centers and practices. CMSC recommended a standardized MR imaging study for the initial evaluation of patients with a CIS or history suspicious of MS and for follow-up (Table 2, page 16). A brain MRI with Gd is recommended for the follow-up of MS patients before starting or modifying therapy to evaluate an unexpected clinical worsening, reassess the original diagnosis, or assess subclinical disease activity. A surveillance brain MRI should be considered every 1-2 years, especially early in the course of the disease. However, the exact frequency may vary depending on clinical course and other clinical features.

The IP of MS Experts recently accepted the appearance of a new lesion on cMRI as a criterion that can be used to establish evidence of DIT after a CIS in lieu of a second clinical attack. This allows for an earlier, formal diagnosis of MS, providing that criteria for DIS also are met. These criteria are based on specific lesion number and location. At the time of a CIS, these lesion counts can be performed quickly and with good reproducibility.

**MRI Findings and Risk of MS**

Between 50% and 80% of individuals presenting with a CIS will have 1 or more asymptomatic brain MRI T2 hyperintense lesions. Even a small number of lesions at baseline (eg, 1-3) has been associated with an 89% chance of developing MS over 14 years. However, an increasing lesion load over time from baseline is predictive of an earlier onset of clinically definite MS (CDMS). Wide differences in MS risk have been reported in follow-up studies based on a normal (low risk) vs abnormal (high risk) baseline MRI: 0%-19% of CIS patients with a normal brain MRI develop MS vs 55%-88% of those with an abnormal brain MRI over 14 years following a CIS. Abnormalities on initial brain MRI are the strongest predictor of subsequent development of MS. Long-term data suggest the risk of MS increases in proportion to the number of baseline T2 lesions (Table 3, page 16).

Gd-enhancing lesions at the time of CIS diagnosis also are predictive of subsequent MS. In early studies, 2 or more Gd-enhancing lesions at baseline or Gd-enhancing/T2 lesions at baseline combined with the appearance of T2 lesions on MRI at 3 months were highly predictive of subsequent MS.

**MRI Findings and Risk of Disability**

In general, a larger number of baseline brain MRI lesions at the time of a CIS indicates a greater risk of long-term disability. There also is a modest correlation between long-term disability and a change in MRI T2 lesion volume in the first 5 years. In a natural-history study, 45% of patients with at least 10 lesions on initial brain MRI had an EDSS of 6 after 20 years, and 35% had only...
### Table 2: CMSC Standardized MRI Protocol for MS

#### Brain MRI Protocol

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Diagnostic Scan for CIS</th>
<th>MS Baseline or Follow-up Scan</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 plane (or other) scout</td>
<td>Recommended</td>
<td>Set up axial sections through subcallosal line*</td>
</tr>
<tr>
<td>2</td>
<td>Sagittal fast FLAIR</td>
<td>Recommended</td>
<td>Sagittal FLAIR sensitive to early MS pathology such as in corpus callosum</td>
</tr>
<tr>
<td>3</td>
<td>Axial FSE PD/T2</td>
<td>Recommended</td>
<td>TE, minimum (eg, ≤ 30 ms) TE1 (usually ≥ 80 ms) PD series sensitive to infratentorial lesions that may be missed by FLAIR series</td>
</tr>
<tr>
<td>4</td>
<td>Axial fast FLAIR</td>
<td>Recommended</td>
<td>Sensitive to WM lesions and especially juxtacortical-cortical lesions</td>
</tr>
<tr>
<td>5</td>
<td>Axial pre-Gd T1</td>
<td>Optional</td>
<td>Considered routine for most neuroimaging studies</td>
</tr>
<tr>
<td>6</td>
<td>3D T1</td>
<td>Optional</td>
<td>Some centers use this for atrophy measures</td>
</tr>
<tr>
<td>7</td>
<td>Axial Gd-enhanced T1</td>
<td>Recommended</td>
<td>Standard dose of 0.1 mmol/kg injected over 30 s; scan starting minimum 5 min after start of injection</td>
</tr>
</tbody>
</table>

FSE = fast spin echo (or turbo spin echo); PD = proton density-weighted (long TR, short TE sequence); T2 = T2-weighted (long TR, long TE sequence); T1 = T1-weighted (short TR, short TE sequence). Section thickness for sequences 3-6 is ≤ 3 mm with no intersection gaps when feasible. Partition thickness for 3D sequence 6 is ≤ 1.5 mm. In-plane resolution is approximately ≤ 1 x 1 mm.

*The subcallosal line joins the undersurface of the front (rostrum) and back (sphenium) of the corpus callosum.

### Spinal Cord MRI Protocol

#### When Acquired Immediately Following an Enhanced Brain MRI*

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 plane (or other scout)</td>
</tr>
<tr>
<td>2</td>
<td>Postcontrast sagittal T1</td>
</tr>
<tr>
<td>3</td>
<td>Postcontrast sagittal FSE PD/T2†</td>
</tr>
<tr>
<td>4</td>
<td>Postcontrast axial T1</td>
</tr>
<tr>
<td>5</td>
<td>Postcontrast axial FSE PD/T2‡</td>
</tr>
<tr>
<td>6</td>
<td>Postcontrast 3D T1§</td>
</tr>
</tbody>
</table>

#### When Acquired Without a Preceding Enhanced Brain MRI

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 plane (or other scout)</td>
</tr>
<tr>
<td>2</td>
<td>Precontrast sagittal T1</td>
</tr>
<tr>
<td>3</td>
<td>Precontrast sagittal FSE PD/T2†</td>
</tr>
<tr>
<td>4</td>
<td>Precontrast axial FSE PD/T2‡</td>
</tr>
<tr>
<td>5</td>
<td>3D T1§</td>
</tr>
<tr>
<td>6</td>
<td>Postcontrast-enhanced sagittal T1*</td>
</tr>
<tr>
<td>7</td>
<td>Postcontrast-enhanced axial T1</td>
</tr>
</tbody>
</table>

*Indications are 1) main presenting symptoms are at the level of the spinal cord, and these have not resolved 2) if the brain MRI results are equivocal. No additional IV contrast is required if the spinal cord study immediately follows the contrast-enhanced brain MRI, as gain is very limited. The segment to be studied (cervical and/or thoracic) is based on clinical findings. Sagittal section thickness is 3 mm (no gap).

†PD series may depict lesions less apparent on heavily T2-weighted series.
‡Increases confidence in the findings of sagittal series; may provide classic lesion characteristics.
§For volumetric analysis if desired.

Table 3: Baseline Lesion Number and Clinical Outcome at 20 Years

<table>
<thead>
<tr>
<th>At 20 years</th>
<th>Number of Brain T2 Lesions at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (N = 34)</td>
</tr>
<tr>
<td>No. of CIS</td>
<td>27 (79%)</td>
</tr>
<tr>
<td>No. of CDMS</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>No. of patients with EDSS &gt; 3</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>No. of patients with EDSS ≥ 6</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

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mild disability. CIS patients who develop SPMS usually have greater T2 lesion volumes at baseline and a greater increase in T2 lesion volumes over the first 5 years compared with RRMS patients who continue to SPMS.36

**Advanced MRI**
Nonconventional (advanced) quantitative MRI techniques, including magnetization transfer imaging (MTI), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS), may be more sensitive and specific for assessing and monitoring disease activity in MS and CIS patients compared with cMRI (Table 4, page 18).14,88,122,128,150,160-169 Advanced MRI techniques may provide detailed insight into the pathogenesis and the degenerative and reparative processes involved in MS in the future.14

There is some evidence demonstrating the value of these advanced techniques in predicting conversion to MS.161,170 Wattjes and colleagues170 found significantly lower N-acetylaspartate (NAA) concentrations at baseline (indicating evidence of axonal damage) on MRS in CIS patients who converted to MS than in CIS patients who did not develop MS within the follow-up period (up to 7 months). However, this study was small with a very short follow-up period. In another study, subtle changes outside T2-visible lesions on MTI were predictive of subsequent MS in CIS patients. This study also was small, and patients developing MS had a significantly higher T2 lesion volume than those who did not.161

By detecting early occult tissue damage in a CIS, advanced MRI techniques may have a future role in facilitating an earlier diagnosis of MS.88,162 Yet, no study at present has demonstrated the clear diagnostic usefulness of these techniques, and additional studies are needed to confirm a prognostic role for advanced MRI. Some advanced methods are more time consuming than cMRI techniques and have limited availability in routine practice. Currently, cMRI remains the most clinically relevant and accessible tool to predict conversion to MS.170,171 Advanced MRI findings and their clinical implications in a CIS are described in Table 5, page 19.18,42,90,122,127,128,150,152,160-163,170,172-179

**Cerebrospinal Fluid**
Examination of the CSF can indicate inflammation, aid in the diagnosis of MS, and help to exclude alternative diagnoses. The laboratory technique and method of analysis are important for the quality of CSF results as is the reproducibility of the test. The CSF contains < 6 white blood cells (WBCs)/mm³ and normal protein content (usually < 100 mg/dL) in most patients with a CIS or established MS. A mild lymphocytic pleocytosis or elevated protein level is seen in approximately 35% of patients. More than 50 WBCs/mm³ or a protein content > 100 mg/dL rarely is observed and raises the possibility of an alternative diagnosis.68,180

**Oligoclonal Bands (OCBs)**
Abnormal IgG synthesis is detected by isoelectric focusing followed by immunoblotting and shows OCBs in the CSF that are present in the serum in 60%-70% of CIS patients and > 90% of patients with MS.15 OCBs in the CSF of all types of CIS patients indicate a risk for developing MS.15,100,181-188 Elevated OCBs are generated by a B-cell response and produced by plasma blasts and plasma cells in the CSF or CSF compartment. Two or more OCBs detected in the CSF that are not present in the serum (drawn at the same time) are considered abnormal. Isoelectric focusing followed by immunoblotting is the most sensitive measure of detecting OCBs. However, other less sensitive methods often are still used in the United States.15,100,181-188

The IgG index, which measures intrathecal production of IgG, is elevated in > 70%-90% of patients with MS. If OCBs are absent from the CSF, the IgG index usually is normal.181,189 Studies show that the IgG index is less sensitive and specific than detection of OCBs for the diagnosis of MS.181

Detection of OCBs in the CSF in conjunction with MRI findings can improve predictive accuracy for the development of MS.181,182,190 However, studies on CSF findings independent of MRI lesions in relation to the development of MS have yielded conflicting results. It is important to note that an elevated IgG index or the presence of OCBs is not specific to MS and may be seen in numerous inflammatory and noninflammatory neurological disorders.181 Furthermore, the absence of an elevated IgG index or OCBs in CSF does not exclude the possibility of demyelinating disease. Therefore, CSF abnormalities always should be considered in conjunction with clinical and MRI findings, as well as with the results of other paraclinical tests (eg, VEP).
*Considered a conventional technique by some. Spinal cord atrophy also can be measured, and atrophy is correlated with motor disability.

**TABLE 4: Advanced MRI Techniques***

<table>
<thead>
<tr>
<th>Technique</th>
<th>What It Measures</th>
<th>How It Is Measured</th>
<th>Correlations and How It Is Used Clinically</th>
</tr>
</thead>
</table>
| **Brain atrophy***              | Loss of brain volume                                                           | Quantitative automated or semi-automated methods such as regional 3D measurements | • Better or best predictor of disability (EDSS)  
• Predictor of cognitive impairment, disease course, and HRQoL  
• Minimizes the clinical-MRI paradox, as brain-tissue loss contributes to clinical findings to a greater extent than findings on cMRI  
• Surrogate measure of the efficacy of drug therapy in MS |
| **Magnetization transfer imaging (MTI)** | Interactions between protons in free fluids and protons bound to macromolecules by means of the MTR  
A low MTR is an indicator of damage to myelin and axonal membranes  
Low MTR has been detected in NAWM, NAGM, and whole brain of MS patients vs controls | MTR can be determined by gradient-echo or spin-echo pulse sequence; 3D gradient echo with short TE of at 1.5T has been preferred  
MTR data often expressed as histograms, with analysis of peak height, peak position, and mean  
Newer methods under investigation | • Sensitive method to detect disease activity and monitor disease progression (a biomarker)  
• Able to assess abnormalities in normal-appearing brain tissue (WM, GM, whole brain) not seen with cMRI  
• Decreases in MTR have been good predictors of disability in longitudinal studies  
• Recovery of MTR may reflect remyelination  
• Degree of reduction in MTR at time of Gad-enhancing lesion predicts whether lesion will evolve into black hole  
• Monitor efficacy of therapeutic modalities |
| **Diffusion tensor imaging (DTI)** | More recent technique of DWI allowing determination of not only the magnitude but also the directionality of water diffusion in tissues (anisotropy)  
Anisotropy is high in normal WM tracts; a decrease represents structural damage in fiber pathway, which is seen in MS | Initially, collection of DW images along several gradient directions to determine the DT; done by using diffusion-sensitized MRI pulse sequences (eg, echo planar imaging)  
For complete data acquisition and processing details, see Le Bihan et al, 2001  
Newer method is DT tractography (DTT), where WM trajectories are noninvasively reconstructed by tracking direction of the fastest diffusion | • Detects status of/damage to WM tracts in MS  
• DWI and DTI also enable study of subtle GM changes  
• Quantitative variables derived from DTI correlate with disability in RRMS and PPMS  
• DTI useful in predicting cognitive impairment in MS  
• Longitudinal changes in diffusion in MS patients suggest use as treatment outcome measure  
• DTI provides insights into WM integrity and fiber connectivity and prognosis |
| **Magnetic resonance spectroscopy (MRS)** | Measures tissue metabolites in lesions and NAWM, changes of which reflect pathologic processes in MS; image segmentation techniques enable study of GM  
Important metabolites are NAA, myoinositol, glutamate, choline, and creatine  
Reduced NAA levels are indicative of axonal/neuronal damage; increases in myoinositol occur as NAA levels fall, suggesting astrogliosis and chronic neuronal injury; increased choline suggests inflammation and demyelination | Tissue water overrides signals from protons; MRS samples the signals from protons associated with tissue neuro-metabolites by suppression of water  
Methods can capture anatomically correlated data by use of single voxel and 2D and 3D multivoxel procedures or as an unlocalized signal from whole brain | • Decline in NAA/creatine ratio correlates moderately with disability, cognitive dysfunction, and disease duration  
• NAA reductions and myoinositol elevations seen in NAWM in early MS  
• Regional reductions in NAA correlate with cognitive dysfunction, T2 lesion load, extent of brain atrophy, and extent of tissue damage reflected by T1 hypointense BOD  
• May be useful for therapeutic monitoring (eg, increased NAA/creatine ratio with IFN beta), but results are conflicting |
| **Functional MRI (fMRI)**          | Enables study of neuronal mechanisms underlying CNS function, brain plasticity, and cortical adaptive reorganization in response to brain injury  
fMRI signal depends upon blood-oxygenation-level-dependent (BOLD) contrast mechanism; this is secondary to differences in blood deoxyhemoglobin concentrations in activated areas as consequence of variations in neuronal activity | Brain activation in response to applied visual or motor stimuli is assayed by alterations in signal intensity resulting from the changes in blood deoxyhemoglobin | • fMRI has shown that cortical reorganization occurs in response to a given task after brain injury, which can limit clinical consequences of widespread tissue damage  
• Magnitude of fMRI activation correlated with lesion burden on cMRI  
• Brain-reserve capacity is exceeded as disease worsens with lesser fMRI activation  
• Functional cortical changes on fMRI may play adaptive role in limiting MS-related cognitive impairment  
• fMRI may be useful for monitoring effects of motor or cognitive rehabilitation or symptomatic MS therapies (eg, rivastigmine) |

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*BOD=burden of disease; DT=diffusion tensor; PW=diffusion weighted; DW=diffusion weighted imaging; MTR=magnetization transfer ratio; NAA=N-acetylaspartate; TE=echo time.
Clinically Isolated Syndrome

or Fazekas (Table 6, Panel A, page 20, discussed further) for predicting conversion to MS. Some studies have indicated that combining OCB detection with other diagnostic criteria such as MRI criteria may improve the predictive value in assessing risk for MS. The Masjuan et al study reported that simultaneous use of OCBs and Barkhof/Tintore criteria had greater sensitivity (97%) and negative predictive value (94%) with similar specificity than either criteria used alone. However, 5-year follow-up data from the ONTT (Optic Neuritis Treatment Trial) demonstrated that the presence of OCBs increased the risk of CDMS in patients with a normal brain MRI but not in those with abnormal brain MRI findings (discussed further). Examining the CSF may be most helpful in CIS patients with vague neurological symptoms and nonspecific MRI findings. Yet, as mentioned above, normal CSF does not exclude the possibility of demyelinating disease.

Evoked Potentials

Visual evoked potentials are sensitive for detecting clinically silent lesions in the anterior visual pathway. VEPs are

### Table 5: Advanced MRI Findings in a CIS

| MTI/DTI | • Low MT ratios (MTRs) in NAWM and NAGM of patients with a CIS, indicative of occult tissue damage. Reduced NAA concentrations did not correlate with lesion volumes or cMRI-visible inflammation, suggesting that neuronal/axonal damage occurs independently of axonal transection within Wm lesions and that axonal pathology is separate from inflammatory processes. Low NAA concentrations recently confirmed in NAWM of CIS patients. Significant reductions in whole-brain NAA in normal-appearing brains of patients presenting with a CIS, reflecting axonal damage or loss. The thalamus and other deep Gm structures particularly affected in 1 study. However, brain-volume loss at CIS presentation is not a universal finding. Detectable atrophy appears more commonly during the first year post-CIS presentation or in the follow-up period in those patients who go on to develop MS. Long-term follow-up study of CIS patients: GM atrophy correlated better with disability than WM atrophy. fMRI has shown cortical adaptation in ON patients, which may contribute to visual recovery. Performance of simple motor tasks in CIS patients has been associated with functional cortical changes (reorganization) on fMRI; patients progressing to MS have different activation patterns on motor tasks than those not progressing. Overall, studies with fMRI in a CIS suggest that cortical reorganization does occur, even in this early stage, and this has the potential to improve long-term outcomes. |
| MRS | • Significant reductions in whole-brain NAA in normal-appearing brains of patients presenting with a CIS, reflecting axonal damage or loss. Reduced NAA concentrations did not correlate with lesion volumes or cMRI-visible inflammation, suggesting that neuronal/axonal damage occurs independently of axonal transection within Wm lesions and that axonal pathology is separate from inflammatory processes. Low NAA concentrations recently confirmed in NAWM of CIS patients. Baseline NAA concentrations in NAWM have been significantly lower (and myo-inositol levels higher) in CIS patients converting to MS than in those who did not, suggesting NAA may be a prognostic marker for conversion to MS. However, this study was small; further confirmatory assessments are needed. No differences in NAA concentrations found in patients with or without lesion-determined DIS, suggesting limited application of MRS in MS diagnosis. |
tests useful for identifying CIS patients at increased risk for developing MS. Therefore, they are not included in the current MS diagnostic criteria.

**DIAGNOSTIC CRITERIA**

Over the past 50 years, all MS diagnostic criteria (including those proposed by Barkhof/Tintore, Poser, McDonald 2001, revised McDonald 2005, and Swanton 2006) have been based on the demonstration of CNS lesions disseminated in space and time and the reasonable exclusion of alternative diagnoses. In addition to information gained from a detailed clinical history and neurological examination, paraclinical information obtained from MRI, VEPs, and examination of the CSF can help demonstrate DIS, and MRI changes can be used to demonstrate DID in CIS patients. The following overview of each set of diagnostic criteria for MS is designed to provide a summary of criteria that have been used in key clinical trials and therefore have direct relevance to clinical practice.

**Barkhof/Tintore MRI Criteria**

Three sets of MRI criteria were described by Paty, Fazekas, and Barkhof (Table A, Panel A) and subsequently were reviewed by Tintore et al in 2000. The original Barkhof criteria were modified by Tintore et al, who demonstrated that abnormal, with a prolonged P100 latency (a nominal latency of approximately 100 m/sec being normal) in approximately 30% of patients with clinically isolated syndromes other than ON and in more than 50% of MS patients despite having no history of visual symptoms or clinical evidence of optic nerve dysfunction. Abnormal VEPs (specifically consisting of a delayed but well-preserved waveform) can be used in combination with findings on a neurological examination to fulfill MS diagnostic criteria for DIS (see below). However, abnormal pattern reversal on VEPs, while highly sensitive to demyelination, are not specific to MS and may be observed in patients with other disorders, including compressive lesions of the optic nerve or chiasm; glaucoma; retinal disease; vitamin B12 deficiency; infectious diseases (e.g., neuroborreliosis, neurosyphilis); systemic lupus erythematosus; or neurosarcoidosis.

VEPs are prolonged in most patients with a recent episode of ON, and routine testing for diagnostic purposes is not indicated. However, pattern-shift VEP is a sensitive indicator of optic nerve demyelination and can indicate asymptomatic and otherwise clinically undetectable lesions.

Other neurophysiologic studies, including somatosensory and brainstem auditory evoked potentials, largely have been supplanted by MRI, and studies have not found these
these criteria had greatest accuracy when 3 of the 4 parameters were fulfilled. The risk of MS increased 4-fold in patients fulfilling 3 out of 4 parameters compared with patients not fulfilling these criteria. This finding offered superior specificity, positive predictive value (PPV; chance of subsequent MS), and accuracy of the Barkhof/Tintore criteria compared with other available diagnostic criteria (Table 6, Panel B).

The Barkhof/Tintore criteria were included in the 2001 McDonald criteria and the 2005 revised McDonald criteria for demonstrating DIS. In studies assessing the accuracy of the 2001 McDonald criteria to predict which patients will develop MS in 1-3 years, high sensitivities, specificities, and accuracies were observed (74%-83%, 83%-86%, and 80%-83%, respectively). In 2003, Tintore and colleagues compared the usefulness of the 2001 McDonald criteria with the older Poser diagnostic criteria (discussed below) in patients with a CIS suggestive of MS (n = 139). At 1 year, 37% had developed MS according to the McDonald criteria compared to 11% with the Poser criteria. Within a mean of 49 months, 80% of those fulfilling the McDonald criteria had developed a second clinical attack. Therefore, although physicians are not necessarily able to diagnose more patients using the McDonald criteria compared with the Poser criteria, they are able to diagnose them earlier, which has important implications for early initiation of DMTs and disease outcomes. MRI criteria for each of the following diagnostic guidelines are shown in Table 7. These include the 2001 McDonald criteria, the revised 2005 McDonald criteria, and the 2006 Swanton criteria in CIS patients.

**Poser and McDonald 2001 Criteria**

The Poser criteria, which were published in 1983, were considered the standard for MS diagnosis. These original criteria specified the presence of 2 separate lesions in the CNS defined primarily by history and evidence of clinical events; however, they failed to recognize MRI-detected subclinical disease activity. New diagnostic criteria proposed by McDonald et al were established in 2001. These criteria formally incorporated the use of MRI into the diagnostic scheme and, providing the patient had an episode of neurological dysfunction consistent with CNS demyelination, allowed for earlier diagnosis of MS prior to a second clinical event. Studies demonstrate that these criteria have approximately 80% sensitivity and 85% specificity for diagnosing MS within 3 years. The use of the 2001 McDonald criteria in CIS patients more than doubled the rate of diagnosing MS within the first year compared with use of the Poser criteria.

**McDonald 2005 Criteria**

The McDonald 2001 criteria (Table 7) were revised in 2005 (Table 8, Panel A, page 22) to simplify and clarify key definitions and concepts in the diagnosis of MS.

---

### TABLE 7: MRI Criteria for Dissemination in Space and Time for MS

<table>
<thead>
<tr>
<th>DIS (on either baseline or follow-up MRI)</th>
<th>McDonald 2001</th>
<th>McDonald 2005</th>
<th>Swanton 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 or more of:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 9 T2 lesions or 1 Gd-enhancing lesion</td>
<td></td>
<td>3 or more of:</td>
<td></td>
</tr>
<tr>
<td>• 3 or more PV lesions</td>
<td></td>
<td>3 or more PV lesions</td>
<td></td>
</tr>
<tr>
<td>• 1 or more JC lesions</td>
<td></td>
<td>1 or more JC lesions</td>
<td></td>
</tr>
<tr>
<td>• 1 or more PP lesions</td>
<td></td>
<td>1 or more PP lesions</td>
<td></td>
</tr>
<tr>
<td>• 1 cord lesion can replace 1 brain lesion</td>
<td></td>
<td>A SC lesion can replace an infratentorial lesion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>An enhancing SC lesion is equivalent to an enhancing brain lesion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any number of SC lesions can be included in total lesion count</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DIT</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) A Gd-enhancing lesion at least 3 months after CIS onset</td>
<td></td>
<td>(i) A Gd-enhancing lesion at least 3 months after CIS onset</td>
<td></td>
</tr>
<tr>
<td>(ii) With reference to a prior scan, a new T2 lesion at least 3 months after CIS onset</td>
<td></td>
<td>(ii) With reference to a baseline scan, a new T2 lesion obtained at least 30 days after CIS onset</td>
<td></td>
</tr>
</tbody>
</table>

BS=brainstem; JC=juxtacortical; PP=posterior fossa; PV=periventricular; SC=spinal cord

Note: posterior fossa also refers to infratentorial.
The 2001 McDonald diagnostic criteria for MS were revised in 2005 (Panel A). Main differences in 2001 and 2005 criteria are discussed in text. If an individual has had 1 episode of neurological dysfunction consistent with demyelinating disease, MRI abnormalities may be used to demonstrate DIT and DIS. This allows for an earlier diagnosis, since approximately 80% of patients diagnosed with MS based on MRI criteria will develop CDMS over 14 years.

- It should be noted that CDMS is a term not widely used in clinical practice today. It was used formerly to indicate 2 clinical demyelinating attacks separated in time and space (ie, 2 noncontiguous neuroanatomical locations and events).
- Lesions characteristic of MS at times are discovered on MRI in individuals with no history of neurological symptoms and a normal examination (RIS). However, a diagnosis of MS cannot be established in the absence of clinical evidence of demyelination, according to diagnostic criteria, even if MRI abnormalities are accompanied by the presence of CSF OCBs, an elevated IgG index, and delayed VEPs.
- The 2005 McDonald criteria indicate that when all specified criteria are fulfilled and alternative diagnoses have been excluded, the diagnosis is MS. If there is a suspicion of MS, but only some of the criteria are met, the diagnosis is “possible MS.” The third possibility is no MS.

### TABLE 8: Diagnosis of MS With McDonald Criteria

**Panel A. Revised 2005 McDonald Diagnostic Criteria**

<table>
<thead>
<tr>
<th>Attacks</th>
<th>Objective Lesions</th>
<th>Additional Data Needed for MS Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>DIS by:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Positive MRI†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- MRI (≥ 2 T2 lesions consistent with MS) plus positive CSF*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Second attack involving a different CNS site</td>
</tr>
<tr>
<td>1</td>
<td>≥ 2 (multifocal presentation)</td>
<td>DIT by:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- MRI§</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Second attack</td>
</tr>
<tr>
<td>1</td>
<td>1 (monofocal presentation)</td>
<td>DIS by:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Positive MRI†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- MRI (≥ 2 T2 lesions consistent with MS) plus positive CSF*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and DIT by:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- MRI§</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Second attack</td>
</tr>
<tr>
<td>Insidious progression suggestive of MS</td>
<td>Sustained disease progression ≥ 1 year (retrospectively or prospectively determined) and 2 of the following:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Positive MRI (9 T2 lesions or ≥ 4 T2 lesions with positive VEP)**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Positive spinal cord MRI (≥ 2 T2 lesions)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Positive CSF</td>
</tr>
</tbody>
</table>

†Refer to MRI criteria for DIS in Table 7 (center column, McDonald 2005).
§Refer to MRI criteria for DIT in Table 7 (center column, McDonald 2005).
*Positive CSF: raised IgG index or IgG oligoclonal bands in CSF but not in serum.
**Positive VEP: delay with a well-preserved waveform, as seen in MS.

**Panel B. Application of 2005 McDonald Criteria**

- The 2001 McDonald diagnostic criteria for MS were revised in 2005 (Panel A). Main differences in 2001 and 2005 criteria are discussed in text. If an individual has had 1 episode of neurological dysfunction consistent with demyelinating disease, MRI abnormalities may be used to demonstrate DIT and DIS. This allows for an earlier diagnosis, since approximately 80% of patients diagnosed with MS based on MRI criteria will develop CDMS over 14 years.
- It should be noted that CDMS is a term not widely used in clinical practice today. It was used formerly to indicate 2 clinical demyelinating attacks separated in time and space (ie, 2 noncontiguous neuroanatomical locations and events).
- Lesions characteristic of MS at times are discovered on MRI in individuals with no history of neurological symptoms and a normal examination (RIS). However, a diagnosis of MS cannot be established in the absence of clinical evidence of demyelination, according to diagnostic criteria, even if MRI abnormalities are accompanied by the presence of CSF OCBs, an elevated IgG index, and delayed VEPs.
- The 2005 McDonald criteria indicate that when all specified criteria are fulfilled and alternative diagnoses have been excluded, the diagnosis is MS. If there is a suspicion of MS, but only some of the criteria are met, the diagnosis is "possible MS." The third possibility is no MS.

of MS. The 2 important changes from the 2001 criteria included (1) better-defined use of spinal cord lesions to fulfill DIS (ie, a spinal cord lesion can replace an infratentorial lesion, an enhancing spinal cord lesion is equivalent to an enhancing brain lesion, spinal cord lesions can be included in the total lesion count) and (2) allowance of a new T2 lesion(s) on brain MRI at any time compared with a reference scan performed at least 30 days after an initial clinical demyelinating event to fulfill criteria for DIT.

According to the McDonald 2005 criteria, a diagnosis of RRMS requires at least 1 episode of neurologic dysfunction consistent with inflammation and demyelination lasting ≥ 24 hours that occurs in the absence of fever or infection and is accompanied by objective evidence of lesions disseminated in space and time. DIS may be demonstrated by 2 anatomically distinct lesions on examination consistent with CNS demyelination (eg, optic atrophy and an extensor plantar response) or a focal lesion on examination plus various combinations of MRI, CSF, and VEP abnormalities (Table 8, Panel B). In the absence of 2 clinical attacks separated by more than 30 days, DIT may be demonstrated by subclinical disease evolution on MRI. The MRI criteria for DIS and DIT are
shown in Table 7, page 21. **Figure 2** provides an example of the use of cMRI to fulfill DIS and DIT in a patient presenting with ON.

**Swanton Criteria**
In 2006, Swanton et al. proposed new MRI guidelines for the diagnosis of MS (Table 7, page 21) with no requirement of a Gd-enhancing lesion. In a retrospective analysis study of CIS patients (N = 208), the Swanton 2006 criteria demonstrated higher sensitivity than the 2005 McDonald criteria (72% vs 60%) and similar specificity (about 90%). Diagnostic reliability of the Swanton criteria compared with the 2005 McDonald criteria were supported by the nearly identical PPVs in this study (approximately 78%), suggesting that most patients fulfilling either of these criteria will develop MS within 3 years.

In 2007, Swanton et al. published a study applying the 2001 and 2005 McDonald criteria as well as the 2006 Swanton new criteria to a cohort of CIS patients in order to assess their utility for conversion to CDMS. Results showed the specificity of all criteria was high (2001, 91%; 2005, 88%; 2006, 87%). The sensitivity of the Swanton criteria (72%) and the 2005 McDonald criteria (60%) were higher than the 2001 criteria (47%). Only the Swanton criteria had an independent significant effect on conversion risk when all 3 criteria were included in the model. The authors concluded that the 2006 criteria were simpler than the 2001 and 2005 McDonald criteria without compromising specificity and accuracy. The evidence of both DIS and DIT on 2 MRI scans has higher specificity and predicts risk of CDMS than either DIS or DIT alone.

A 2009 comparison using retrospective baseline MRI studies also showed the similar specificity of the revised 2005 McDonald criteria and Swanton criteria, with slightly greater (but non-significant) sensitivity and accuracy for the Swanton criteria. Further studies are needed to assess the Swanton criteria more completely, and a prospective comparative study of Swanton vs McDonald criteria also is needed.

**American Academy of Neurology Criteria**
The American Academy of Neurology (AAN) criteria, published by Frohman et al in 2003, are prognostic rather than diagnostic. These criteria are based on an extensive literature review of evidence for use of baseline and follow-up MRI in predicting and diagnosing MS in CIS patients. Final recommendations emerging from this review include:

- A finding of ≥ 3 T2 WM lesions on baseline MRI is very sensitive predictor (> 80%) of subsequent CDMS within 7-10 years.
- The presence of ≥ 2 Gd-enhancing lesions at baseline is highly predictive of future CDMS.
- The appearance of new T2 lesions or new Gd-enhancing lesions ≥ 3 months after a CIS (and after baseline MRI assessment) is highly predictive of subsequent CDMS in near future.
Although the AAN criteria have good sensitivity, their specificity is relatively low, which carries the risk of a false-positive diagnosis. Therefore, they are not widely used in clinical practice.

**Magnetic Imaging in MS (MAGNIMS) Criteria**

In 2007, MAGNIMS, a European multicenter collaborative research network, met to review existing criteria for MS in CIS patients. They specified DIS and DIT criteria and proposed a new diagnostic algorithm based on MRI findings. This algorithm is propriety; please visit www.neurology.org for further information.

The new MAGNIMS algorithm and criteria likely will have important implications in the clinical management of CIS patients in the future. In conclusion, the McDonald 2005 criteria currently are the most widely accepted diagnostic criteria in clinical practice, but this could change in the future.

**DIFFERENTIAL DIAGNOSIS**

The diagnosis of a CIS is based on a clinical presentation consistent with CNS demyelination in combination with MRI findings. Examination of other paraclinical parameters such as CSF analysis may provide evidence to support a diagnosis of demyelinating disease. However, no test is specific for a CIS, and excluding other illnesses that could have similar clinical and MRI findings is of paramount importance.

Differential diagnosis is complex and involves the use of clinical, MRI, laboratory, and other paraclinical findings to exclude a wide range of other diseases and disorders that can mimic a clinical demyelinating event. These include infectious, autoimmune, inflammatory, genetic, metabolic, anatomical/structural, and neoplastic conditions as well as MS variants and other neurological conditions. The prevalence of other disorders in a specific population, geographic location, or demographic also should be considered.

In 2008, Miller et al published proposed guidelines for the differential diagnosis of MS developed by the International Task Force. These guidelines provide a clear definition of a CIS; categorize clinical and paraclinical features of a CIS that are most typical of patients eventually diagnosed with MS as well as red flags (features compatible with MS but could occur in other diseases); provide specific consensus-based algorithms for the differential diagnosis of the 3 most common CIS presentations related to MS (ON, spinal cord, and brainstem-cerebellar syndromes) (Figure 4); and offer a classification system and diagnostic criteria for idiopathic disorders of the CNS.

Furthermore, this review provides detailed guidelines to differentiate MS in CIS patients from other IIIDs, such as NMO and ADEM. This detailed guideline serves as an important clinical tool in the differential diagnosis of a CIS and MS.

A workshop of the European MAGNIMS also provided a series of MRI red flags that suggest a diagnosis other than MS, which also are useful in the differential diagnosis of a CIS. Courtney and colleagues also compiled a list of disorders that mimic MS and provided ways to distinguish them from MS. The complexities of differential diagnosis in CIS patients highlights the need for sensitive and accurate disease biomarkers for patient assessment and monitoring.

**CONCLUSION**

Conventional MRI is of great value in the assessment and diagnosis of CIS and MS in patients and subsequently for monitoring disease progression and response to DMTs. Diagnostic criteria incorporating cMRI clarify the use of imaging in the diagnosis of MS. Standardized cMRI protocols facilitate comparisons of serial cMRI images over time. Both brain and spinal cord imaging have key roles in the assessment of CIS and MS patients. Advanced MRI technologies are evolving and may offer greater insight into the pathology of MS and an opportunity for earlier diagnosis. CSF analysis and evoked potential testing offer additional important information in the assessment of selected patients with a CIS or suspected MS. Diseases and disorders that can mimic the clinical presentation of a patient with a suspected CIS should be excluded. Once a CIS is diagnosed, it is important to understand the prognosis of a CIS and MS and to make appropriate treatment decisions.
TABLE 9: CIS Clinical Features and Likelihood of Signaling an MS Diagnosis

<table>
<thead>
<tr>
<th>CIS Features Typically Seen in MS</th>
<th>Less Common CIS Features That May Be Seen in MS</th>
<th>Atypical CIS Features Not Expected in MS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Optic Nerve</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral ON</td>
<td>Bilateral simultaneous ON</td>
<td>Progressive optic neuropathy</td>
</tr>
<tr>
<td>Pain on eye movement</td>
<td>No pain</td>
<td>Severe, continuous orbital pain</td>
</tr>
<tr>
<td>Partial and mainly central visual blurring</td>
<td>No light perception</td>
<td>Persistent complete loss of vision</td>
</tr>
<tr>
<td>Normal disc or mild disc swelling</td>
<td>Moderate to severe disc swelling with no hemorrhages</td>
<td>Neuromyelitis (optic disc swelling with macular star)</td>
</tr>
<tr>
<td></td>
<td>Optic neuritis (mild, posterior)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optic neuritis (severe, anterior)</td>
<td></td>
</tr>
<tr>
<td><strong>Brainstem-Cerebellar</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral internuclear ophthalmoplegia</td>
<td>Unilateral internuclear ophthalmoplegia, facial palsy, facial myokymia</td>
<td>Complete external ophthalmoplegia, vertical gaze palsies</td>
</tr>
<tr>
<td>Ataxia and multidirectional nystagmus</td>
<td>Deafness</td>
<td>Vascular territory syndrome, eg, lateral medullary</td>
</tr>
<tr>
<td>Sixth nerve palsy</td>
<td>One-and-a-half syndrome</td>
<td>Third nerve palsy</td>
</tr>
<tr>
<td>Facial numbness</td>
<td>Trigeminal neuralgia</td>
<td>Progressive trigeminal sensory neuropathy</td>
</tr>
<tr>
<td></td>
<td>Paroxysmal tonic spasms</td>
<td>Focal dystonia, torticollis</td>
</tr>
<tr>
<td><strong>Spinal Cord</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial myelopathy</td>
<td>Complete transverse myelitis</td>
<td>Anterior spinal artery territory lesion (sparing posterior columns only)</td>
</tr>
<tr>
<td>Lhermitte's symptom</td>
<td>Radiculopathy, areflexia</td>
<td>Cauda equina syndrome</td>
</tr>
<tr>
<td>Deafferented hand</td>
<td>Segmental loss of pain and temperature sensation</td>
<td>Sharp sensory level to all modalities and localized spinal pain</td>
</tr>
<tr>
<td>Numbness</td>
<td>Partial Brown-Sequard syndrome (sparing posterior columns)</td>
<td>Complete Brown-Sequard syndrome</td>
</tr>
<tr>
<td>Urinary urgency, incontinence, erectile dysfunction</td>
<td>Fecal incontinence</td>
<td>Acute urinary retention</td>
</tr>
<tr>
<td>Progressive spastic paraplegia (asymmetrical)</td>
<td>Progressive spastic paraplegia (symmetrical)</td>
<td>Progressive sensory ataxia (posterior columns)</td>
</tr>
<tr>
<td><strong>Cerebral Hemispheres</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild subcortical cognitive impairment</td>
<td>Epilepsy</td>
<td>Encephalopathy (obtundation, confusion, drowsiness)*</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>Hemianopia</td>
<td>Cortical blindness</td>
</tr>
</tbody>
</table>

*Although encephalopathy is required for ADEM, it also may be seen at presentation and/or during the course of MS.

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Effective, long-term management of CIS patients requires a reliable risk assessment for the development of future MS, an accurate prognosis to identify those who may be candidates for early treatment with DMTs, and appropriate counseling and education for patients.25
Figure 4. Differential Diagnosis of Common Types of Clinically Isolated Syndromes

Panel A. CIS Presentation With Demyelinating Optic Neuritis

**OPTIC NEURITIS**

- **Typical MS**
  - (Unilateral visual loss, pain, afferent pupil defect, retrobulbar or mild disc swelling, visual loss does not progress beyond 2 weeks)

- **Atypical for MS**
  - (No pain, retinal exudates, retinal hemorrhages, severe disc swelling, no visual recovery after 1 month or bilateral visual loss)

**Brain MRI**

- Normal
- Abnormal lesions consistent with demyelination

**MRI, CSF, OCT neurophysiological, serologic, and other studies as appropriate**

- Consider other diagnoses

Panel B. CIS Presentation With Demyelinating Brainstem Syndrome

**ISOLATED BRAINSTEM SYNDROME**

- **Typical for MS**
  - Internuclear ophthalmoplegia; 6th nerve palsy; multifocal signs (eg, facial sensory loss and vertigo or hearing loss)

- **Atypical for MS**
  - Hyperacute onset; vascular territory signs (eg, lateral medullary syndrome); age > 50; isolated trigeminal neuralgia; fluctuating ocular/bulbar weakness; nonremitting; fever; meningism

**Brain MRI**

- Normal
- Abnormal lesions consistent with demyelination

**MRI, CSF neurophysiological, serologic, and other studies as appropriate**

Panel C. CIS Presentation With Demyelinating Spinal Cord Syndrome

**ISOLATED SPINAL CORD SYNDROME**

- **Typical for MS**
  - Evolution over hours to days
  - Partial myelitis
  - Purely sensory
  - Deafferented upper limb
  - Lhermitte’s sign
  - Partial Brown-Séquard
  - Spontaneous remission

**Brain and spinal cord MRI**

- Normal
- Abnormal lesions consistent with demyelination

**MRI clearly indicates a non-MS diagnosis, eg, spinal cord compression**

- Consider other diagnoses

- **Atypical for MS**
  - Hyperacute onset or insidiously progressive
  - Complete transverse myelitis
  - Sharp sensory level
  - Radicular pain
  - Areflexia
  - Failure to remit

- Compression eg, intervertebral disc, tumor
- Ischemia/infarction
- Other inflammatory eg, neuromyelitis optica, sarcoid, lupus, Sjögren’s
- Infection eg, syphilis, Lyme, viral, tuberculosis
- Toxic/nutritional/metabolic eg, B12 deficiency, nitrous oxide toxicity, copper deficiency
- Arteriovenous malformation
- Non-cord “mimics” eg, Guillain-Barré syndrome, myasthenia gravis

**MRI, CSF neurophysiological, serologic, and other studies as appropriate**
NATURAL-HISTORY COHORTS AND PLACEBO ARMS OF SHORT-TERM TRIALS

The prognosis for outcomes in CIS patients without DMTs has been studied in natural-history cohorts and placebo arms of short-term clinical trials. In general, natural-history studies are representative of natural outcomes and provide good, long-term data, whereas short-term clinical studies are highly reliable within the follow-up period of the study. Overall, results from the placebo arms of the relatively short-term IFN and GA CIS clinical trials show that approximately 40%-50% of untreated CIS patients with at least a minimally abnormal baseline brain MRI will develop MS, and approximately 85% will fulfill McDonald criteria for MS within 2-3 years (Table 10, Panel A, page 28).

BENEFIT

In BENEFIT (Betaferon in Newly Emerging MS for Initial Treatment),66 CIS patients were randomized to receive SC IFN beta-1b or placebo. Eighty-five percent of placebo-treated patients fulfilled the 2001 McDonald criteria for MS during the 2-year observation period.101 The risk of progressing to CDMS was higher in younger patients (those < 30 years of age had a 60% risk; those > 30 years of age had a 33% risk), patients who were treated with steroids (48% vs 38% who were not), and those with positive CSF findings (positive for OCBs or increased IgG index 49% vs 36% with negative findings). There was no difference in the risk of developing CDMS among patients with different clinical presentations of a CIS—ON, spinal cord syndrome, or brainstem-cerebellar syndrome. However, the risk of CDMS was higher in patients with ≥ 9 T2 lesions on baseline brain MRI (55% vs 31% for < 9 lesions) and ≥ 1 Gd-enhancing lesions (63% vs 41% with no Gd-enhancing lesions). The highest risk for CDMS was found in patients with monofocal presentation plus > 9 T2 lesions (55%) or 1 Gd-enhancing lesion (63%) at baseline, and the risk was 75% for those with both MRI abnormalities.101,211

CHAMPS

In CHAMPS, 383 CIS patients were randomized to receive treatment with IM IFN beta-1a once weekly or placebo. In a follow-up analysis of the CHAMPS placebo group, the clinical/MRI findings associated with a higher risk for conversion to CDMS were younger age and the presence of Gd-enhancing lesions at baseline.97,158,159 In patients with ≥ 2 Gd-enhancing lesions at baseline, 52% reached CDMS by 18 months compared with 24% of patients who had < 2 enhancing lesions (P = 0.01).97,98,159

ETOMS

In ETOMS (Early Treatment of MS), 309 CIS patients were randomized to receive treatment with SC IFN beta-1a every week or placebo. MRI and clinical parameters predictive of higher conversion to CDMS included multifocal presentation, > 9 T2 lesions, and presence of Gd-enhancing lesions on baseline cMRI.99 Twenty percent of placebo-treated patients (baseline median EDSS score = 1.0; no disability but minimal signs in 1 FS) had confirmed EDSS progression of at least 1 point, and 6% of patients worsened by 2 points within 2 years.99 These data confirm that irreversible disability occurs early in the course of the disease.

PreCISe

In PreCISe (Early GA Treatment in Delaying Conversion to Clinically Definite MS in Subjects Presenting with a Clinically Isolated Syndrome), 481 CIS patients were randomized to receive either SC GA every day or placebo. The trial was stopped prematurely after a pre-planned interim analysis. Patients had received treatment for a mean of 2.3 years. The risk of more rapid conversion to CDMS was higher in CIS patients in the placebo group vs the treatment group. In 25% of the CIS patients studied, those in the placebo group converted to CDMS in 336 days vs 722 days in the treatment group.102 Furthermore, the placebo group had an increase in T2 lesion load (at last observed value [LOV], 9.8 lesions in the placebo group vs 4.2 in the treatment group [P < 0.0001]). Other MRI activity also was increased in the placebo group, with the cumulative number of T1 hypointense lesions on MRI being significantly higher in the placebo group compared with the treatment group (3.6 lesions vs 1.7 lesions at LOV [P < 0.0001]). The decrease in brain volume was higher in the placebo group (-0.38% vs -0.33% in the treatment group).102
### TABLE 10. Natural History of a CIS

#### Panel A. Progression to CDMS in Placebo Groups of Short-term Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (years)</th>
<th>Number of Placebo-Treated Patients</th>
<th>Progression to CDMS</th>
<th>Time to CDMS (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHamps97,98</td>
<td>3***</td>
<td>190</td>
<td>50%</td>
<td>397*</td>
</tr>
<tr>
<td>ETOMS99</td>
<td>2</td>
<td>154</td>
<td>45%</td>
<td>252**</td>
</tr>
<tr>
<td>BENEFIT101</td>
<td>2</td>
<td>176</td>
<td>45%</td>
<td>255*</td>
</tr>
<tr>
<td>PreCISE102</td>
<td>2.3</td>
<td>238</td>
<td>43%</td>
<td>336*</td>
</tr>
</tbody>
</table>

*25th percentile
**30th percentile
***The CHamps trial ran from April 1996 to March 2000 and was terminated early due to the interim analysis results that showed treatment with IFN beta-1a was significantly better than placebo and met the criteria for stopping the trial, including a P value of 0.029. Patients were followed up to 3 years.

#### Panel B. Natural-History Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyons MS cohort†‡§ (Lyon, France)</td>
<td>1844*</td>
<td>• Median time to second relapse after MS onset, 1.9 years; longer in subgroup presenting with unilateral ON compared with a brainstem or spinal cord presentation</td>
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<td>• Median times to EDSS scores of 4.0, 6.0, and 7.0 also more prolonged in ON presentation vs other CIS types</td>
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<td>• Median time from onset of MS to an EDSS score of 4.0 was 14.1 years in those who presented initially with ON compared with 6.0-10.5 years in other types</td>
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<td></td>
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<td>• Although treatment was given to many patients (mainly azathioprine), it did not appear to affect outcomes</td>
</tr>
<tr>
<td>European MAGNIMS cohort†‡§</td>
<td>532†</td>
<td>• This cohort was more representative of the general population of CIS patients seen in the clinical setting as patients were included irrespective of MRI, including those without asymptomatic lesions at baseline</td>
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<td>• 33% converted to CDMS over a period of 1 month to 8.6 years (mean 20 months)</td>
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<td>• McDonald criteria for DIS fulfilled in 30% of cases</td>
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<td>• At a survival time of 2 years after the initial event, 45% of patients fulfilling baseline criteria for DIS (at least 3 of 4 Barkhof/Tintore criteria) converted to CDMS, compared to only 10% with no asymptomatic lesions at baseline (most often no lesions at all)</td>
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<td></td>
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<td>• Risk for CDMS also lower in patients with only 2 of the 4 Barkhof criteria or minimally abnormal MRI scan</td>
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<td>• Risk for conversion to CDMS independent of type of CIS presentation</td>
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<td></td>
<td>• Essentially no patients in study had received DMT before conversion to CDMS</td>
</tr>
<tr>
<td>Rocca et al†‡</td>
<td>208‡</td>
<td>• Similar lenient entry criteria as European MAGNIMS cohort, without prespecified MRI criteria</td>
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<tr>
<td></td>
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<td>• Conversion to CDMS in 43% of patients over 1-49 months</td>
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<td></td>
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<td>• Fulfillment of DIS at baseline significantly increased this risk</td>
</tr>
<tr>
<td>Gothenburg study (Sweden)‡</td>
<td>109</td>
<td>• Decline in the number of patients at various time points of assessment, from 109 at baseline to 71 at a mean of 14.1 years follow-up</td>
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<td>• For the CIS group as a whole (with or without baseline MRI abnormalities), 43%, 59%, and 68% developed CDMS at follow-up assessments of 5.3 years, 9.7 years, and 14.1 years, respectively</td>
</tr>
<tr>
<td></td>
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<td>• At 14-year follow-up visit, CDMS had developed in 69% of patients who presented with ON, 67% with spinal cord syndromes, and 64% with brainstem syndromes; median EDSS score of patients with CDMS, 3.25</td>
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<tr>
<td></td>
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<td>• Baseline MRI clearly predictive of development of CDMS, which occurred in 88% of patients with abnormal baseline MRI scans (T2 lesions) and 19% with a normal baseline MRI</td>
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<td>• Disability also predicted by baseline MRI findings; worse outcomes observed in patients with larger lesion numbers and lesion volumes and larger increases in lesion volume over time</td>
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<td></td>
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<td>• EDSS scores at 14 years significantly correlated with number of lesions on baseline and 5-year and 10-year MRI scans</td>
</tr>
<tr>
<td>Fisniku et al (Queen Square Group, London)‡</td>
<td>107</td>
<td>• See text</td>
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<td></td>
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<td>• In the group as a whole, CDMS developed in 63% after 20 years (median EDSS at CDMS, 4.0),</td>
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<td>• Overall conversion rates at this time similar in patients who initially presented with ON, brainstem syndrome, or spinal cord syndrome; however, risk greater in patients with abnormal baseline MRI</td>
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<tr>
<td>Optic Neuritis Treatment Trial†</td>
<td>126 (PL)</td>
<td>• See text</td>
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<td>• At 2 years, CDMS developed in 16.7% of the 126 placebo-treated patients</td>
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<td>• At 15 years, cumulative probability of CDMS was 53% in the original placebo recipients, which did not differ significantly from patients who had received steroid treatment at presentation</td>
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<tr>
<td></td>
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<td>• Risk of CDMS greater in patients with abnormal baseline MRI at all time points</td>
</tr>
</tbody>
</table>

*Includes 1562 with a relapsing-remitting onset and 282 with PPMS onset and median duration of MS of 9 years. CIS type at onset was ON, 18%; brainstem, 9%; long-tracts dysfunction, 52%; combination of symptoms, 21%.
†Patients with a CIS from 7 European centers.
‡Patients with a CIS from 4 European centers.
PL=placebo
LONG-TERM NATURAL-HISTORY STUDIES
Key long-term natural-history studies in CIS patients also were performed by Brex et al and Fisniku et al (Table 10, Panel B). Brex et al examined 71 CIS patients at 14 years with serial MRIs and reported that 88% (44 out of 50) of patients with abnormal baseline MRI findings developed MS compared with 19% (4 out of 21 patients) of those with normal baseline MRI. CIS patients with no asymptomatic baseline MRI brain lesions had only minimal disability after 14 years (EDSS 1-2). Patients with larger numbers and volumes of baseline asymptomatic T2 brain MRI lesions tended to have worse clinical outcomes after 14 years. However, the change in T2 lesion volume in the first 5 years after a CIS had the strongest correlation (r = 0.61, P < 0.001) with the EDSS score at 14 years, suggesting that lesion development early in the course of the disease influences long-term disability.16

Fisniku et al subsequently followed the same cohort of patients from the above Brex study with both clinical and MRI assessments up to 20 years from the start of the Brex study. The Fisniku study offers the longest and most comprehensive natural-history data for CIS patients to date (Table 10, Panel B). Of 140 patients initially enrolled, 107 were included in this study (104 of whom were alive at the time of the 20-year assessment). Of note, ascertainment was better at year 20 in the Fisniku cohort compared with the Brex cohort due to improved abilities in locating patients at year 20 compared with year 14. In the Fisniku study, CDMS was diagnosed by Poser criteria and was based solely on clinical criteria (second clinical episode separated in time and space).34

Results at year 20 revealed that CDMS developed in 63% of all untreated CIS patients (median EDSS score at CDMS diagnosis was 4.0). Overall conversion rates at this time were similar in patients who initially presented with ON (65%), spinal cord syndrome (61%), or brainstem syndrome (60%). CDMS developed in 82% of CIS patients who had abnormal baseline brain MRI (median time to conversion was 2 years) compared with only 21% in those with a normal baseline scan (median time to conversion was 6 years). However, there was no difference in the conversion rate to CDMS for patients with 1-3 lesions at baseline and those with ≥ 10 lesions at baseline.36

In the Fisniku study, 58% of patients had RRMS (including benign MS in 39%, defined as EDSS < 3), and SPMS developed in 42% of patients. A key finding of this study is that those progressing to SPMS had larger baseline T2 lesion volumes and a greater increase in lesion volume over time, especially over the first 5 years. The EDSS at 20 years correlated well with the number of baseline T2 lesions and lesion volume (Table 3, page 16). Results of this study showed that a greater number of baseline lesions indicated a greater risk of long-term disability (EDSS > 3 at 20 years was seen in 26% of patients with 0 baseline lesions and 65% with ≥ 10 baseline lesions). However, outcomes were shown to be extremely variable: 45% of patients with ≥ 10 baseline MRI brain lesions had an EDSS of > 6 at 20 years, but 35% of patients with at least 10 baseline MRI brain lesions had an EDSS ≤ 3.36

Optic Neuritis Treatment Trial—Long-term Placebo Arm
Another key natural-history study in CIS research was the placebo arm of the ONTT.213 In this trial (N = 457), patient eligibility requirements were 18-46 years of age, presence of acute unilateral ON with visual symptoms ≤ 8 days, presence of relative afferent pupillary defect, and visual field defect in the affected eye. Demographic and clinical characteristics included: 77% females, mean age of 32 years, pain usually worsened by eye movement in 92%, and optic disc swelling in 35%. Visual acuity was 20/40 or better in 35%, 20/50 to 20/190 in 29%, and ≥ 20/200 in 36%. Patients were randomized to receive 1 of the following treatment protocols: intravenous (IV) methylprednisolone (n = 151) 1g/day (250 mg q 6 hours) for 3 days, followed by oral prednisone 1 mg/kg qd for 11 days or oral prednisone 1 mg/kg qd for 14 days (n = 156), or oral placebo (n = 150). Most patients (97%) completed the full treatment course. The main outcome measurements of the trial were visual acuity, visual field, contrast sensitivity, and color vision. Visual function was followed in all patients with a total follow-up of 15 years, ending in 2006.109,156,213

In this study, most ON patients in all 3 groups had rapid improvement of vision during the first 2-4 weeks after onset, regardless of the initial severity of visual loss.107,109 Complete recovery of visual function usually occurred by 4-6 weeks, although gradual improvement...
other CIS types; however, this has been challenged
by other investigators.\textsuperscript{15,108} Some studies demonstrate
that neurologic disability generally is mild in patients
developing MS after presenting with acute ON.\textsuperscript{216,219}
Yet, Fisniku et al\textsuperscript{36} showed that at 20 years, the risk
of CDMS and the median EDSS scores were similar
regardless of the initial CIS.

**PREDICTING THE RISK OF MS FOLLOWING A CIS**

Accurately predicting disease course and long-term out-
comes following a CIS is a major challenge for clinicians.
Consensus-based risks for progression to MS based on the
CIS classification and MRI findings were suggested by the
International Task Force.\textsuperscript{34} In the International Task Force
proposal, CIS types 1 and 2 have a high probability of
progressing to MS, whereas type 3 patients are at relatively
low risk. Type 4 is rare, and these patients require follow-up
to determine if they have MS or another condition. Type 5
CIS or RIS patients should be followed closely, as they
subsequently may develop symptoms or new MRI abnor-
malities consistent with CNS demyelination.

In the ONTT, CDMS developed in approximately 17% and
30% of the placebo-treated patients within 2 and 5 years, respectively.\textsuperscript{217} The risk of conversion to MS
strongly correlated with the number of T2 lesions on
baseline brain MRI. Fifty-one percent of patients with
\( \geq 3 \) T2 lesions developed CDMS compared with only
16% in those with normal MRI.\textsuperscript{216}

In patients without baseline MRI lesions, the risk of
MS was lower in males and in those presenting with
optic-disc swelling and/or atypical ON features, such
as lack of pain, the presence of no light-perception vision,
retinal exudates, severe optic-disc edema, and peripapillary hemorrhages.\textsuperscript{104,216} The presence of OCBs
in the CSF did not increase the 5-year risk of CDMS in
ONTT patients who had MRI brain lesions. However,
the risk was increased nearly 7 fold (27% vs 4%,
\( P = 0.06 \)) in patients with a normal brain MRI.

Independent of brain MRI findings, the presence of
prior, nonspecific neurologic symptoms not considered
to be clinical demyelinating events (mainly brief par-
esthesia) also were predictive of developing CDMS.\textsuperscript{15,218}

Data from the ONTT and other studies suggest that the
prognosis for ON patients may be better with respect to
time to develop MS and disability compared with
Other studies show that clinical features of a CIS indicate the future risk of developing MS. Patients with ON at greater risk of future demyelinating events include those with retro-orbital pain, a normal optic disc on examination, and unilateral symptoms. Clinical features of transverse myelitis predictive of greater risk include incomplete transverse myelitis, asymmetric symptoms, smaller cord lesions, and absence of cord edema.

With regard to focality in CIS presentation and risk of developing MS, findings from BENEFIT, CHAMPS, and ETOMS have varied. In BENEFIT and CHAMPS, there was no overall difference in the risk of CDMS in placebo-treated patients with a monofocal vs multifocal presentation. In BENEFIT, a greater risk for developing MS was seen in monofocal placebo patients with ≥ 1 Gd-enhancing lesion on follow-up MRI at 3 or 6 months. These increased risk patterns were not seen in multifocal patients. In contrast, the ETOMS study found a higher risk for CDMS in multifocal patients.

In summary, accurately predicting disease course and long-term outcomes following a CIS continues to be a major challenge for clinicians. Data from natural-history studies and placebo arms of clinical trials show that baseline cMRI brain lesions in CIS patients offer key prognostic indications for the future development of MS. CIS patients with baseline MRI brain lesions are at a much greater risk of developing MS compared to those with a normal baseline brain MRI. However, patients with normal MRI still are at risk for MS.

CIS is a highly variable disease state. While many patients make a full recovery from the initial event, most then go on to develop MS in the future, ranging from a mild or benign disease course with little or no disability to severe disease with progressive disability. Although the number of lesions on a baseline brain MRI is predictive of the risk of developing MS and, in general, the greater the number of baseline lesions the greater the risk of future disability, there is no reliable way of predicting future disability in an individual CIS patient. Currently, no reliable marker exists to determine which CIS patients will continue to have a mild disease course from outset. Improving technologies may allow better imaging and prognostics in MS in the near future. Because recent data clearly indicate that most CIS patients with baseline lesions progress to MS and are at risk of developing irreversible neurological disability, the new standard of care is to initiate DMT in these patients as early as possible.

**6 TREATMENT**

The current treatment paradigm for CIS management includes treating the acute event and considering initiation of long-term DMT and symptomatic therapies as needed. For more details on symptom management, please refer to the first Primer in this series: Clinician's Primer on Multiple Sclerosis: An In-Depth Overview (2008).

**ACUTE TREATMENT OF A CIS**

Based on data from the ONTT, most neurologists treat clinically isolated syndromes (and MS exacerbations) that occur in functional impairment with 1 gram of IV methylprednisolone per day for 3-5 days, with or without a brief oral steroid taper. Although some neurologists treat clinically isolated syndromes and MS exacerbations with a short course of low-dose (eg, 1 mg/kg) prednisone, the results of the ONTT bring this practice into question (see below).

**Corticosteroid Therapy**

Studies indicate that a short course of IV corticosteroids accelerates the time to recovery of an acute neurological event in a CIS but likely has no impact on long-term clinical outcomes. High-dose corticosteroids also suppress Gd-enhancing lesions in MS patients; the significance of this is unknown in asymptomatic individuals.

In the ONTT, vision improved more rapidly (especially visual field defects) in the IV methylprednisolone group compared with the oral prednisone or placebo-treated groups. However, by 6 months and at 1 year, visual acuity was similar in the 3 groups. There was no difference in the rate of recovery between the placebo- and oral prednisone-treated groups.
Patients treated with oral prednisone were more likely to develop recurrent episodes of ON than patients in the other 2 groups during the initial trial and follow-up period.\textsuperscript{109,213,214} At 5 years, the probability of new attacks of ON in either eye was 2-fold higher in those who had received oral prednisone vs the other 2 groups.\textsuperscript{215} It is unclear if the risk of recurrent ON with oral prednisone may have been related to baseline differences in treatment groups.\textsuperscript{222} However, given the lack of efficacy and concern of recurrent episodes of ON with low doses of oral prednisone (eg, 1 mg/kg/day), most neurologists treat clinically isolated syndromes (and MS exacerbations) with high-dose IV corticosteroids.

An unexpected finding in the ONTT was that the 3-day course of IV methylprednisolone delayed the development of CDMS. Within the first 2 years, MS developed in 7.5% of the IV methylprednisolone group compared with 16.7% and 14.7% of those in the placebo and oral prednisone groups, respectively.\textsuperscript{217}

An analysis of the interval before developing MS showed that the 2-year cumulative incidence of MS was significantly lower in the IV methylprednisolone group than in the placebo and oral prednisone groups ($P = 0.03$), but there was no significant difference between the 2-year cumulative incidences of MS in the placebo and oral prednisone groups ($P = 0.54$).\textsuperscript{220} Most of the benefit of IV methylprednisolone on the development of MS was apparent in high-risk patients (abnormal baseline MRI). This benefit lessened after 2 years, and by the end of 3 years, there was no difference among the 3 groups.\textsuperscript{109,216,217}

This finding was never duplicated, and it is unknown if a short course of IV corticosteroids provides a short-term protective effect against the development of MS in patients with ON or other types of clinically isolated syndromes. Other studies have shown a beneficial effect on relapses and EDSS scores for up to 1 year after a single course of high-dose steroids in RRMS.\textsuperscript{222}

Adverse effects of short-term steroid therapy include sleep disturbances, mood changes, upset stomach, facial flushing, and mild weight gain.\textsuperscript{109,223} Rare serious side effects of short-term corticosteroid use can include transient psychotic depression, acute pancreatitis, or avascular necrosis of bone.\textsuperscript{223}

### Intravenous Immunoglobulin Therapy

Intravenous immunoglobulin (IVIG) use in a CIS is controversial but has been studied and used as a treatment option in patients with ON who are unresponsive to steroids.\textsuperscript{208,222} In 2008, Tselis et al.\textsuperscript{224} studied the use of IVIG in ON patients with severe vision loss. All patients had visual acuity 20/400 or worse in the affected eye. Patients with corticosteroid-refractive ON were treated with IVIG and compared with control patients who received corticosteroids only in an open-label, non-randomized, controlled, prospective study. Results confirmed significant improvement in patients receiving IVIG, with 78% of patients achieving near-normal vision (20/30 or better) compared with the control group (12.5%). The authors concluded that the use of IVIG following corticosteroids may be useful in ON. A larger controlled trial is indicated to confirm these results.

### Plasma Exchange

Plasma exchange is the only other treatment shown to be effective for acute inflammatory demyelinating events. In a small, double-blind, placebo-controlled, crossover trial, patients with severe attacks of inflammatory demyelinating disease (the majority of whom had MS) who failed to improve after at least a 5-day course of high-dose parenteral corticosteroids were randomized to receive either 7 plasma or sham exchanges over 14 days. Approximately 40% of patients had functional improvement during plasma exchange compared with approximately 6% of patients who received sham exchange. Improvement occurred early during treatment and was sustained within 6 months of follow-up. On average, those who responded were treated within 40 days of symptom onset. One patient who was treated 61 days after the onset of symptoms improved. The time to initiation of plasma exchange was similar in those patients who responded to treatment compared with those who did not.\textsuperscript{225}

### DMTs in a CIS

In CIS patients, evidence of early underlying neuro-pathology and a high incidence of conversion to MS in those with abnormal baseline brain MRIs argue strongly in favor of early initiation of DMT in most patients. Well-designed studies have demonstrated that the IFN beta and GA are effective in reducing the development of MS and MRI-identified disease activity in CIS patients (Table 11, page 34) and that early treatment with DMTs may be more
effective in clinically isolated syndromes compared with RRMS. However, although DMTs may limit relapses, disability, and MRI measures of disease in the short term, there are no adequately controlled, long-term studies to definitely determine if these benefits are durable.79,86,126

**Original Short-term Studies of DMTs in a CIS**

**BENEFIT**

BENEFIT, a double-blind, 2-year trial, randomized 468 CIS patients to receive either SC IFN beta-1b 250 μg every other day or placebo.100,101 The MRI inclusion criteria for this trial were occurrence of first demyelinating event plus ≥ 2 clinically silent brain MRI T2 lesions that must be ≥ 3 mm in size (1 of which must be ovoid, periventricular, or infratentorial). The coprimary endpoints included time to CDMS and McDonald MS criteria. Patients in the IFN beta-1b treatment group had a significant reduction in the cumulative probability of developing MS compared with placebo \( P = 0.002 \). The 2-year cumulative probability for developing CDMS was 28% of patients in the IFN beta-1b treatment group compared with 45% of patients in the placebo group \( P < 0.0001 \). The 2-year cumulative probability for developing MS (using the McDonald criteria) was 69% in the IFN beta-1b treatment group compared with 85% in the placebo group.

The time to CDMS was 618 days in the active treatment group and 255 days in the placebo group. In the first 6 months, 51% of patients in the placebo group fulfilled McDonald criteria for MS compared with only 28% in the IFN beta-1b group. There was a significant reduction in MRI disease activity in the IFN-treated group, including new T2 lesions, Gd-enhancing lesions, and Gd-enhancing lesion volume. IFN beta-related adverse events included injection-site reactions, flu-like symptoms, leukopenia, fever, and elevated liver enzymes. The development of neutralizing antibodies (NABs) also occurred.100,101

**CHAMPS**

The CHAMPS trial was a randomized, double-blind, 3-year trial where 383 CIS patients received treatment with IM IFN beta-1a 30 μg/week or placebo.98 The MRI inclusion criteria for this trial were occurrence of first acute demyelinating event plus evidence of prior subclinical demyelination on MRI (ie, ≥ 2 clinically silent lesions on brain MRI that must be ≥ 3 mm in diameter and characteristic of MS; ≥ 1 lesion must be periventricular or ovoid). The primary endpoint was development of CDMS. The trial was stopped prematurely after a pre-planned interim efficacy analysis. There was a significant reduction in the cumulative probability of developing CDMS in the IFN group (rate ratio = 0.56; \( P = 0.02 \)). Thirty-five percent of patients in the IFN group developed CDMS compared with 50% in the placebo group within 3 years. Time to develop CDMS was 809 days in the active treatment group and 397 days in the placebo group \( P = 0.0016 \). Gd-enhancing lesions, new or enlarging T2 lesions, and an increase in lesion volume all were significantly lower in the IFN treatment group \( P < 0.001 \). Adverse events related to the IFN beta-1a included flu-like symptoms and depression; the development of NABs also occurred.98

**ETOMS**

ETOMS was a double-blind, 2-year trial in which 309 CIS patients were randomized to treatment with SC IFN beta-1a 22 μg/week or placebo for up to 2 years.99 The MRI inclusion criteria for this trial were occurrence of a first neurological event suggesting MS in the previous 3 months plus ≥ 1 abnormality on neurological exam plus a positive brain MRI showing 1 of the following: ≥4 WM T2 lesions or ≥ 3 WM lesions if 1 was infratentorial or 1 was Gd enhancing. The primary endpoint of the study was development of CDMS. Thirty-four percent of patients in the IFN beta group developed CDMS compared with 45% in the placebo group \( P = 0.047 \). Time to develop CDMS was 569 days in the active treatment group vs 252 days in the placebo group \( P = 0.034 \). The active treatment group showed a significantly lower number of new T2 lesions and a reduction in lesion load compared with placebo in MRI-measured disease activity.99 The dose of IFN beta-1a used in this trial, which is considerably less than the dosages approved by the FDA for the treatment of RRMS (22 and 44 μg 3 times weekly), had no significant effect on clinical or most MRI outcomes in a separate placebo-controlled RRMS study.127 Adverse events related to SC IFN beta-1a included injection-site reactions, fever, myalgia, and chills.

**PreCISE**

PreCISE, a double-blind, originally planned 3-year trial, 481 CIS patients were randomized to receive SC GA 20 mg/day or placebo. The MRI inclusion criteria for this trial included occurrence of a CIS with unifocal manifestation plus a positive brain MRI at screening (ie, ≥ 2 T2-weighted brain lesions measuring 6 mm in diameter). The primary endpoint was time to CDMS. This trial was
<table>
<thead>
<tr>
<th>Study Design/Duration</th>
<th>N</th>
<th>Primary Endpoint(s)</th>
<th>Treatments</th>
<th>Development of CDMS</th>
<th>Time to CDMS (days)</th>
<th>MRI Changes</th>
<th>Adverse Effects‡</th>
</tr>
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<tbody>
<tr>
<td>CHAMPS&lt;sup&gt;97,98&lt;/sup&gt;</td>
<td>383</td>
<td>CDMS; MRI findings</td>
<td>IM IFN beta-1a 30 µg qw vs PL</td>
<td>35% IFN beta-1a 50% PL (49% RR) Cumulative probability of developing CDMS was significantly lower in the IFN group vs placebo (P = 0.002)</td>
<td>809 IFN beta-1a 397 PL*</td>
<td>Gd-enhancing lesions, new or enlarging T2 lesions, and increase in lesion volume significantly lower with IFN beta-1a (All P &lt; 0.001)</td>
<td>Flu-like syndrome (28%) Depression (7%) NAbs (1%-2%)</td>
</tr>
<tr>
<td>ETOMS&lt;sup&gt;99&lt;/sup&gt;</td>
<td>309</td>
<td>CDMS</td>
<td>SC IFN beta-1a 22 µg once weekly◆ vs PL</td>
<td>34% IFN beta-1a 45% PLΔ Fewer patients developed CDMS in the IFN group vs PL (P = 0.047)</td>
<td>569 IFN beta-1a 252 PL** P = 0.034</td>
<td>New T2 lesions and increase in lesion load significantly lower in IFN beta-1a group§</td>
<td>Injection-site inflammation (48%) Fever (16%) Myalgia (8%) Chills (6%)</td>
</tr>
<tr>
<td>BENEFIT&lt;sup&gt;100,101&lt;/sup&gt;</td>
<td>468</td>
<td>Time to CDMS</td>
<td>SC IFN beta-1b 250 µg qod vs PL</td>
<td>28% IFN beta-1b 45% PL (50% RR) More patients in PL group fulfilled McDonald criteria (85% vs 69%) (see text)</td>
<td>618 IFN beta-1b 255 PL*</td>
<td>IFN beta-1b delayed time to CDMS (P &lt; 0.0001) and McDonald MS (P &lt; 0.00001) New T2 lesions, Gd-enhancing lesions, and volume of Gd-enhancing lesions significantly lower with IFN beta-1b</td>
<td>Injection-site reactions (40%) Flu-like syndrome (26%) Leukopenia (12%) Fever (8%) Hepatic-enzyme elevations (~10%) NAbs (16.0%-25.2%)</td>
</tr>
<tr>
<td>PreCISE&lt;sup&gt;102&lt;/sup&gt;</td>
<td>481</td>
<td>Time to CDMS</td>
<td>SC GA 20 mg daily vs PL</td>
<td>25% GA 43% PL (45% RR) GA reduced risk of developing CDMS (P = 0.0005)</td>
<td>722 GA 336 PL*</td>
<td>Treatment effect of GA in delaying conversion to CDMS (P = 0.0017 in completers cohort and P = 0.0003 in per-protocol cohort) New T2 lesions and volume, Gd-enhancing lesions, and T1 hypointense lesions significantly lower with GA</td>
<td>Injection-site reactions (32%) Immediate post-injection reactions (14%) Lymphadenopathy (5%) Injection-site necrosis (2 patients) Vomiting (3%)</td>
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</table>

‡In descending order of frequency and greater than with placebo; percentages are placebo subtracted.
◆25th percentile
**30th percentile
Δ The benefit of SC IFN beta-1a in delaying conversion to CDMS also was greater in patients fulfilling 3 or 4 Barkhof/Tintore criteria at presentation (35% vs 49% with placebo).<sup>263</sup>
§ Filippi et al.<sup>264</sup> found that IFN beta-1a reduced brain-tissue loss in 2 years by about 30% in ETOMS.
qod=every other day; qw=once weekly; RR=risk reduction.
stopped after a pre-planned interim analysis showed that GA reduced the conversion to CDMS by 45% (P = 0.0005) compared with placebo. There was a 386-day delay in the development of CDMS for the first 25th percentile of patients treated with GA compared with placebo (722 days vs 336 days). The GA treatment group showed a significant reduction in MRI-measured disease activity, including new T2 lesion load and volume, Gd-enhancing lesions, and T1 hypointense lesions. On the basis of these findings, the trial was stopped, and all placebo patients were given the opportunity to receive active treatment. The most common adverse events related to GA were injection-site reactions (56% vs 24%) and immediate post-injection reactions (19% vs 5%).

The results of the IFN and GA CIS trials demonstrate the benefits of early treatment of CIS patients with DMTs to delay the development of MS and reduce MRI measures of disease. However, data to establish the efficacy of DMTs to prevent long-term disability are lacking.

Subgroup Analyses
In a recent subgroup analysis of the BENEFIT trial, IFN beta-1b was found to be effective in reducing conversion to MS regardless of CIS focality, MRI activity at baseline, or other clinical features, with the exception of negative CSF findings and monofocal patients with ≤ 9 T2 baseline lesions (no significant effect on rate of CDMS vs placebo). Early subgroup analyses from CHAMPS indicated that IM IFN beta-1a was effective in reducing conversion to CDMS in all CIS types and that treatment benefits were greater in patients who were at high risk of developing CDMS (≥ 9 T2 lesions or ≥ 1 Gd-enhancing lesions).

A recent reanalysis of patients from CHAMPS indicated that 30% of patients could be classified as having multifocal disease at baseline. Also observed was a difference in treatment effect during the first 2 years of IM IFN beta-1a based on clinical classification of focality at baseline. In the IM IFN beta-1a treated patients, the relative reduction in CDMS conversion over 2 years was statistically significant only in patients with monofocal presentation (P = 0.0013) and not in patients with multifocal presentation. A greater risk reduction also was seen in patients with ≥ 1 Gd-enhancing lesion at baseline (68%) compared to those without Gd-enhancing lesions (42%); whereas CDMS risk reduction was similar in patients with ≥ 9 T2 lesions and < 9 T2 lesions (about 50%). Of note, researchers have suggested that the above subgroup analyses of BENEFIT and CHAMPS may have been underpowered.

Extension Studies
Several extension studies of these pivotal trials have demonstrated the benefit of DMTs in a CIS.

BENEFIT Extension Studies
In the original BENEFIT study, CIS patients with a minimum of 2 clinically silent lesions were randomized to receive either SC IFN beta-1b 250 μg (n = 292) or SC placebo (n = 176) every other day for 2 years or until reaching a diagnosis of CDMS. At that time, patients were eligible to enter the follow-up phase with open-label SC IFN beta-1b 250 μg every other day for up to 5 years from randomization. After 3 total years, CDMS developed in 37% of patients in the immediate-treatment (IT) group compared with 51% of the delayed-treatment (DT) group (original placebo-treated patients who had switched to SC IFN beta-1b after the 2-year study or after a diagnosis of CDMS), representing a reduction in the development of CDMS of 41% (P = 0.0011) in the IT group. In addition, there was less accumulation of MRI-disease activity, and the risk for progression of disability was significantly reduced in the IT group (by 40%; P = 0.022); reduction of disability progression was seen in the IT group with confirmed EDSS progression of 16% and 24% of patients in the IT and DT groups, respectively.

In the 5-year extension of BENEFIT, results showed a sustained reduction of the risk of CDMS (37%; P = 0.003) as well as greater suppression of MRI-disease activity in the IT group. A benefit on cognitive performance (measured by the Paced Auditory Serial Addition Test [PASAT]) also was seen in the IT group vs the DT group. However, the risk for confirmed disability progression at 5 years was not significantly lower in the IT group (25%) compared with the DT group (29%). There were only minimal changes in EDSS scores over 5 years in both groups. Low EDSS values were seen in most patients in both groups at the end of the 5-year observation period (42% and 45%, respectively).
CHAMPIONS
CHAMPIONS (Controlled High-Risk AVONEX Multiple Sclerosis Prevention Study in Ongoing Neurologic Surveillance), the 2-year extension of the CHAMPS trial, evaluated the effect of early vs delayed treatment with IM IFN beta-1a in CIS patients. CHAMPIONS enrolled 53% of the CIS patients from CHAMPS (203 of 383), and all were offered IM IFN beta-1a 30 μg once weekly for up to 5 years. Patients originally randomized to placebo in CHAMPS were designated the DT group, and those originally randomized to IM IFN beta-1a were designated to the IT group. The DT group initiated DMT a median of 29 months after CHAMPS randomization. Over 5 years, the cumulative probability of developing CDMS was significantly lower in the IT group vs the DT group (36% vs 49%; P = 0.03). Further, annualized relapse rates and new/ enlarging T2 lesions were significantly lower in the IT group over 5 years. Disability was similar in the 2 groups, and major disability was minimal. Limitations of CHAMPIONS were that patients who continued in this extension study had a significantly lower rate of CDMS during CHAMPS and were statistically older than those who did not continue in the extension study. A 10-year follow-up of the CHAMPIONS study revealed continued benefits in terms of conversion to CDMS and relapse rates but no significant differences in disability or MRI outcomes in the IT group vs the DT group.233

Direct-Comparison Trials
Although results of the IFN beta and GA CIS trials suggest the DMTs may have similar efficacy, comparing across trials can be misleading due to different study designs, inclusion criteria, baseline characteristics (Table 1, page 10), dropout rates, and variations in placebo-treated patients. However, results of direct-comparative trials in RRMS patients31,32,234 can help guide the choice of initial therapy in CIS patients. Two recently completed, large, randomized, observer-blinded trials—REGARD (Rebif vs Glatiramer Acetate in Relapsing MS Disease)31 and BEYOND (Betaferon Efficacy Yielding Outcomes of a New Dose)32—evaluated clinical efficacy (time to first relapse, annualized relapse rate, proportion relapse-free, and disability progression) and MRI outcome efficacy between the high-dose/frequency IFN betas and GA.

In REGARD, the GA 20 mg/day treatment group was similar to that of SC IFN beta-1a 44 μg 3 times weekly; after 96 weeks, there was no significant difference between the 2 treatment groups for the primary outcome time to first relapse (P = 0.64). Overall, relapse rates were lower than expected with 258 patients having 1 or more relapses (126 in the SC IFN beta-1a group and 132 in the GA group). The expected number of relapses was 460. There were no significant differences in secondary outcomes for the number and change in volume of T2 active lesions or for the change in the volume of Gd-enhancing lesions.

However, patients treated with SC IFN beta-1a had significantly fewer Gd-enhancing lesions (0.24 vs 0.41) per patient per scan compared with the GA group (P = 0.0002). The adverse event frequency and severity was not significantly different between the 2 groups. Of note, SC IFN beta-1a use is off-label for a CIS as it is not currently approved for use in CIS, even though it is used in CIS patients in clinical practice.

In BEYOND, patients were randomized to receive either SC IFN beta-1b 250 μg or 500 μg every other day or 20 mg GA every day. The primary outcome was relapse risk, and secondary outcomes were disability progression (EDSS) and change in T1 hypointense lesion volume. Results revealed no difference in relapse risk, EDSS progression, T1 hypointense lesion volume, or brain volume between the 3 treatment groups in RRMS patients. Flu-like symptoms were more common in patients treated with IFN beta-1b, and injection-site reactions were more common in the GA group. However, the overall tolerability to both drugs was similar.

Two randomized trials, INCOMIN (Independent Comparison of Interferon) and EVIDENCE (Evidence of Interferon Dose-Response-European North American Comparative Efficacy), revealed the significantly greater clinical/MRI efficacy of higher-dose, higher-frequency SC IFN beta formulations (SC IFN beta-1a 44 μg tiw or SC IFN beta-1b 250 μg qod) compared with IM IFN beta-1a 30 μg once weekly.235-237 However, only MRI outcomes were blinded in the INCOMIN study. EVIDENCE was a short study, and the incidence of NABs was much greater with the high-dose IFN compared with incidence of NABs in the low-dose arm in the EVIDENCE trial.229 Results of these studies provide clinicians with data that may help in making informed choices about treatment.238
Safety
In REGARD and BEYOND, the number and severity of adverse effects generally was similar for all agents. However, there are some differences in these trials and other studies reported in the literature, which are provided in Table 12.239-251

TABLE 12: Comparative Adverse Effects of DMTs

<table>
<thead>
<tr>
<th>IFN beta Preparations</th>
<th>20,31,32,235,240-242</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Main adverse effects: Flu-like symptoms, injection-site reactions, hematologic abnormalities (eg, lymphopenia), liver-enzyme elevations, depression, fever, NAbs (except in IFN beta-1a)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glatiramer Acetate</th>
<th>21,242-246</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Main adverse effects: Injection-site reactions, systemic postinjection reaction (several symptoms, including chest tightness, dyspnea, tachycardia, flushing)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>IFN beta: Between-Agent Comparisons</th>
<th>235,236,245-251</th>
</tr>
</thead>
<tbody>
<tr>
<td>- NAbs occur most often with SC IFN beta-1b (23%-47%, appearing at ≥ 3 months), least often with IM IFN beta-1a (2.0%-8.5%, appearing after approximately 9 months); for SC IFN beta-1a, frequency of NAbs is 12%-27%, and they usually appear by 9 months of therapy</td>
<td></td>
</tr>
<tr>
<td>- Higher incidence of flu-like symptoms likely with IM IFN beta-1a compared with SC IFN beta preparations</td>
<td></td>
</tr>
<tr>
<td>- Incidence of injection-site reactions greater with SC IFN beta preparations (especially SC IFN beta-1b) than with IM IFN beta-1a</td>
<td></td>
</tr>
<tr>
<td>- Higher incidence of liver-enzyme elevations and hematologic abnormalities with SC IFN beta preparations than with IM IFN beta-1a</td>
<td></td>
</tr>
</tbody>
</table>

PATIENT COUNSELING AND EDUCATION
Patients with a recent CIS need to be educated about the subsequent risk of MS and the disease itself, natural history of clinically isolated syndromes and MS, prognosis, options for immunomodulatory therapy, and the risks and benefits of initiating early DMTs vs delayed treatment. Patients should be offered information on MS even when formal criteria for diagnosis have not been fulfilled, as a potential diagnosis has important practical implications, such as lifestyle and treatment decisions and access to life and/or disability insurance.162,252 It is important to ensure the patient is educated about specific therapies and participates in the decision process to begin DMT.162,252

CONCLUSION
A review of the literature indicates that a clear majority of MS experts favor early treatment in CIS patients with abnormal baseline MRIs due to the high risk of developing MS and the likelihood of irreversible neurological disability.19,60,253-258 Data from CHAMPIONS and BENEFIT indicate that a delay in treatment with IFN beta preparations for 2-3 years in high-risk CIS patients is associated with a significantly greater long-term risk for CDMS than when patients are treated at the time of presentation.220,231-233 In contrast, some clinicians believe that DMTs should be delayed until there is more certainty that therapy is needed based on subsequent clinical or MRI activity.162,239,260 Differing clinical approaches to managing clinically isolated syndromes are discussed in Table 13, page 38.

Based on data from randomized controlled trials and extension studies, the following summary offers an effective approach to the clinical management of CIS patients:

1. Initial evaluation. Detailed history, full neurological examination, and assessment of clinical and paraclinical findings.
2. Differential diagnosis to exclude other possible diseases/disorders (Figure 4, page 26).
3. Brain MRI. The standardized minimum brain imaging protocol recommended by CMSC for patients presenting with a CIS is:143 (a) 3 plane (or other) scout; (b) sagittal fast FLAIR; (c) axial fast spin echo proton density/T2; (d) axial fast FLAIR; and (e) axial Gd-enhanced T1 image.
4. Spinal cord imaging. If the main presenting symptoms are at the level of the spinal cord and have not resolved, spinal cord MRI and brain MRI are required by the CMSC Standardized Imaging Protocol for MS. If results of the brain MRI are equivocal and the diagnosis of MS still is being considered, then spinal cord imaging may be justified.143 Many neurologists also obtain baseline spinal cord MRI in all CIS patients.
5. Acute treatment of a CIS. When indicated, IV methylprednisolone 1 g/day for 3-5 days with or without a brief prednisone taper is recommended to treat the acute neurological event. Corticosteroids do not seem to affect degree of recovery but may delay the development of MS for several years.
6. Risk evaluation. Determine the risk of progression to MS based on parameters discussed earlier. Detection of asymptomatic cMRI brain lesions is a strong predictor of subsequent MS. At present, no definitive method exists
10. Continuous treatment. DMT should be continuous (ie, without interruption) in patients who have no issues with DMT tolerability and in those who are not suboptimal responders.

11. Regular follow-up to provide frequent monitoring of disease progression and treatment response as well as ongoing safety monitoring and patient support and education.

TABLE 13: Early vs Delayed Treatment of High-Risk CIS Patients: The Arguments

<table>
<thead>
<tr>
<th>Early Treatment Is Indicated11,254–257</th>
<th>Treatment Should Be Delayed162,259,260</th>
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<tbody>
<tr>
<td>- The true onset of MS is unknown, but most patients presenting with a CIS also have MRI lesions, indicative of prior disease activity; thus, ‘early treatment’ is actually late.</td>
<td>- MS may have a favorable natural history in some patients, and these patients do well without treatment. A benign course is evident in many patients with an abnormal MRI or with minimal or no disability for 10-14 years, especially if they are disability-free 5 years after a CIS.</td>
</tr>
<tr>
<td>- Irreversible axonal damage occurs early in MS and is ongoing, including periods between relapses (clinical quiescence). Tissue damage and brain atrophy can accumulate during this time, which is associated with physical and cognitive disability.</td>
<td>- Whether treatment after a first attack (a CIS) has any greater benefit than delaying treatment until a second episode is unknown.</td>
</tr>
<tr>
<td>- Most high-risk patients with a CIS progress to MS, and early DMT can significantly delay its occurrence.</td>
<td>- The long-term efficacy of DMTs on disability is unproven.</td>
</tr>
<tr>
<td>- DMTs are unable to reverse damage that has already occurred, but they are preventive. They can reduce progression of disability in the short term, new MRI-lesion formation, and frequency of relapses. Incomplete recovery from relapses results in irreversible neurological disability. By preventing relapses, DMTs may prevent long-term disability.</td>
<td>- Early DMT in a CIS appears no more effective than delayed treatment in minimizing progression of disability in the long term (eg, at 5 or 10 years post-CIS).</td>
</tr>
<tr>
<td>- Early DMT in a CIS appears more effective than delayed treatment in slowing onset of CDMS, reducing MRI-disease activity, and reducing short-term disability progression (up to 3 years).</td>
<td>- With prolonged treatment, it is difficult to determine if a beneficial outcome is due to a favorable natural history or successful therapy; early treatment runs the risk of treating patients who would have had a good prognosis without it.</td>
</tr>
<tr>
<td>- The BENEFIT extension suggests that cognitive function may be preserved to a greater degree at 5 years with early vs delayed treatment.</td>
<td>- Expense is significant over time to both patients and payers.</td>
</tr>
<tr>
<td>- DMTs work best in early disease, with much less benefit later in the progressive phase of MS.</td>
<td>- MRI and clinical progression can identify patients who need treatment.</td>
</tr>
<tr>
<td>- Natural history studies indicate that 90% of MS patients will progress to significant disability over time, and it is not possible to predict those with “benign” courses (possible only in retrospect).</td>
<td></td>
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</tbody>
</table>

for the prediction of long-term disability in MS patients.

7. Patient counseling and education on diagnosis and natural course of the disease.

8. Establish a treatment plan and selection of a DMT. Initial treatment decisions should be individualized and based on a combination of efficacy, type and frequency of administration, and potential side effects. Initiating a DMT at the time of a CIS is suggested in patients deemed by MRI to be high risk for MS. This can delay the onset of MS, delay disability progression for at least several years, and minimize cumulative MRI measures of disease. Extensions of CIS trials indicate a greater benefit of early vs delayed treatment (eg, up to 2 years from CIS presentation). There also is a potential benefit of early vs delayed treatment on cognitive performance at 5 years.232 Despite arguments for delaying treatment, most neurologists consider starting DMT after an initial clinical demyelinating event in the patient with baseline lesions on brain MRI.

9. Patient counseling and education on DMTs. Patient education on potential side effects as well as type of administration are important. Adverse effect profiles may dictate treatment selection. Patients need counseling on the importance of adherence to long-term injectable therapy with DMTs, which can affect outcomes greatly. Therapy selection based on likely adverse effects may facilitate compliance. Preventing adverse effects of DMT also can help adherence, such as pre-medicating with ibuprofen if needed to lessen flu-like symptoms associated with IFN beta or ensuring proper injection technique in an effort to minimize injection-site reactions in patients treated with GA. If the physician does not recommend a DMT for early treatment or if the patient elects not to begin early therapy, the patient should be followed closely for clinical and subclinical disease activity by MRI.
CONCLUSIONS

At present, there are no specific, universally accepted guidelines for assessing and managing CIS patients. Steps listed in the Summary of Recommendations for Managing CIS Patients (listed previously) offer an approach to managing these patients. Studies show that early axonal damage and loss already is present in CIS patients. Most neurologists favor early treatment with GA or IFN beta in CIS patients with at least minimal MRI findings characteristic of MS. However, current DMTs are only partially effective, and controlled long-term efficacy data are lacking.

Advances in technology and research are identifying new therapeutic targets, and novel agents to treat MS currently are being developed, including oral agents and monoclonal antibodies. In September 2010, fingolimod was approved by the FDA as an oral agent for first-line treatment of relapsing MS, which represents an important new milestone in MS therapeutics.

Other new oral drugs, such as cladribine, laquinimod, and oral fumarate (BG00012), are in late-stage development or are pending FDA approval and likely will emerge as important therapeutic options in patients with early MS if further studies demonstrate at least comparable efficacy and safety to current injectable DMTs. Oral agents also offer potential advantages of improved patient adherence to long-term treatment regimens and clinical outcomes in patients with MS. Novel agents may result in improved treatment options for both clinically isolated syndromes and established MS in the future. Increasing knowledge of the impact of early axonal damage and loss in MS has highlighted the need for developing effective and safe neuroprotective agents and protocols, and these are likely to play an important role in the future of CIS and MS management.

At CIS presentation, MRI is a proven key tool in accurately predicting conversion to CDMS. However, accurately predicting disease course and long-term outcomes following a CIS remains a major challenge for clinicians. Advanced MRI techniques, including functional and quantitative imaging assessments of neuronal function, are still evolving; the future could offer a greater understanding of CIS and MS pathogenesis, earlier detection, improved and individualized management strategies, sensitive monitoring of disease processes and treatment response, as well as more accurate prediction for disease course and development of disability. In the future, clinicians may be able to utilize a combination of chemical and radiological biomarkers at CIS presentation to more accurately determine the risk of developing MS and long-term disability and optimize treatment strategies.

A key challenge for clinicians is to successfully distill relevant findings from clinical trial data and apply this information to therapeutic decision making in individual patients. This Primer offers an approach to making a prompt and accurate diagnosis, assessing risk, determining patient prognosis as best as possible, and developing an early treatment plan in CIS patients in order to reduce the likelihood of disease progression and enhance clinical outcomes.
REFERENCES


Glossary of Terms

Demyelination – occurs when the phospholipid sheath surrounding CNS axons is damaged and stripped away, resulting in slow, disordered, or arrested nerve conduction.

Clinically isolated syndrome – a first clinical and neurological event suggestive of MS lasting ≥ 24 hours caused by inflammation/demyelination in 1 or more sites in the CNS.

Expanded Disability Status Scale – a disability scale using an ordinal scale of 1-10, measuring various functional system scores and ability to walk, with a high score indicating greater disability.

Gadolinium – a chemical compound that can be administered to a person during MRI to help distinguish between new and old lesions.

Gadolinium-enhancing lesion – a lesion appearing on MRI, following injection of gadolinium, that reveals a breakdown in the BBB. This breakdown indicates either a newly active lesion or the re-activation of an old one.

Optic neuritis – inflammation or demyelination of the optic nerve with transient or permanent impairment of vision and occasionally pain.

Neuromyelitis optica – a necrotizing, inflammatory, demyelinating disorder targeting the spinal cord and optic nerves.

Primary progressive MS – a clinical course of MS characterized from the beginning by progressive disease, with no plateaus or remissions or an occasional plateau and very short-lived, minor improvements.

Progressive relapsing MS – a clinical course of MS that shows disease progression from the beginning, but with clear, acute relapses, with or without full recovery from those relapses along the way.

Relapsing-remitting MS – a clinical course of MS characterized by clearly defined, acute attacks with full or partial recovery and no disease progression between attacks.

Secondary progressive MS – a clinical course of MS that is initially relapsing-remitting and becomes progressive at a variable rate, possibly with an occasional relapse and minor remission.

T1-weighted MRI – images show acute MS lesions as hypointense areas due to edema of the damaged brain tissue. It was the first quantitative, volumetric imaging study used in MS.

T2-weighted MRI – images show hyperintense bright lesions representing demyelination, edema, gliosis, or matrix destruction.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ADEM</td>
<td>acute disseminated encephalomyelitis</td>
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<tr>
<td>AAN</td>
<td>American Academy of Neurology</td>
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<tr>
<td>BBB</td>
<td>blood-brain barrier</td>
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<tr>
<td>CDMS</td>
<td>clinically definite MS</td>
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<tr>
<td>CIS</td>
<td>clinically isolated syndrome</td>
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<tr>
<td>cMRI</td>
<td>conventional MRI</td>
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<tr>
<td>CMSC</td>
<td>Consortium of Multiple Sclerosis Centers</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>DIS</td>
<td>dissemination in space</td>
</tr>
<tr>
<td>DIT</td>
<td>dissemination in time</td>
</tr>
<tr>
<td>DMT</td>
<td>disease-modifying therapy</td>
</tr>
<tr>
<td>DT</td>
<td>delayed treatment</td>
</tr>
<tr>
<td>DTI</td>
<td>diffusion tensor imaging</td>
</tr>
<tr>
<td>EDSS</td>
<td>Expanded Disability Status Scale</td>
</tr>
<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
</tr>
<tr>
<td>FLAIR</td>
<td>fluid-attenuated inversion recovery</td>
</tr>
<tr>
<td>FS</td>
<td>functional system</td>
</tr>
<tr>
<td>GA</td>
<td>glatiramer acetate</td>
</tr>
<tr>
<td>Gd</td>
<td>gadolinium</td>
</tr>
<tr>
<td>GM</td>
<td>grey matter</td>
</tr>
<tr>
<td>^3H-MRS</td>
<td>proton magnetic resonance spectroscopy</td>
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<tr>
<td>HRQOL</td>
<td>health-related quality of life</td>
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<tr>
<td>IFN</td>
<td>interferon</td>
</tr>
<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
</tr>
<tr>
<td>IIDD</td>
<td>idiopathic inflammatory demyelinating disease</td>
</tr>
<tr>
<td>IL</td>
<td>interleukin</td>
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<tr>
<td>IM</td>
<td>intramuscular</td>
</tr>
<tr>
<td>IP</td>
<td>International Panel</td>
</tr>
<tr>
<td>IT</td>
<td>immediate treatment</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>IVIG</td>
<td>intravenous immunoglobulin</td>
</tr>
<tr>
<td>LOV</td>
<td>last observed value</td>
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<tr>
<td>MOG</td>
<td>myelin oligodendrocyte glycoprotein</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>MRS</td>
<td>magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>MTI</td>
<td>magnetization transfer imaging</td>
</tr>
<tr>
<td>NAA</td>
<td>N-acetylaspartate</td>
</tr>
<tr>
<td>NAbs</td>
<td>neutralizing antibodies</td>
</tr>
<tr>
<td>NAWM</td>
<td>normal-appearing white matter</td>
</tr>
<tr>
<td>NMO</td>
<td>neuromyelitis optica</td>
</tr>
<tr>
<td>OCB</td>
<td>oligoclonal bands</td>
</tr>
<tr>
<td>ON</td>
<td>optic neuritis</td>
</tr>
<tr>
<td>PASAT</td>
<td>Paced Auditory Serial Addition Test</td>
</tr>
<tr>
<td>PPMS</td>
<td>primary progressive MS</td>
</tr>
<tr>
<td>PPV</td>
<td>positive predictive value</td>
</tr>
<tr>
<td>PRMS</td>
<td>progressive relapsing MS</td>
</tr>
<tr>
<td>RIS</td>
<td>radiologically isolated syndrome</td>
</tr>
<tr>
<td>RRMS</td>
<td>relapsing-remitting MS</td>
</tr>
<tr>
<td>SC</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>SPMS</td>
<td>secondary progressive MS</td>
</tr>
<tr>
<td>VEP</td>
<td>visual evoked potential</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
<tr>
<td>WBNAA</td>
<td>whole-brain N-acetylaspartate</td>
</tr>
<tr>
<td>WM</td>
<td>white matter</td>
</tr>
</tbody>
</table>
POSTTEST

1. A CIS:
   a. is the first event in all types of MS.
   b. indicates a risk for development of RRMS.
   c. rarely is associated with the presence of brain lesions on MRI.
   d. is a first neurological event lasting ≥ 72 hours caused by only 1 lesion in the CNS.

2. Which of the following is true about MS pathophysiology?
   a. Axonal damage is apparent long before presentation of a CIS and is ongoing, which has led to the current recommendation of initiating early DMT in high-risk CIS patients.
   b. WM involvement far exceeds GM involvement.
   c. Axonal damage is a major contributor to permanent disability.
   d. Recent data have excluded early oligodendrocyte apoptosis as a primary event in pathogenesis.
   e. (a) and (c) are correct.

3. All of the following are considered predictors of subsequent development of MS in CIS patients, EXCEPT:
   a. The presence of OCBs in patients with normal brain MRI
   b. T2 lesions on baseline MRI
   c. Older age at time of presentation
   d. CIS types 1 and 2 as defined by the International Task Force

4. Which of the following distinguishes the 2005 McDonald diagnostic criteria from the 2001 McDonald criteria?
   a. The rate of diagnosis of MS within the first year is substantially higher (more than doubled) with use of the 2005 criteria.
   b. In the 2005 criteria, a new T2 lesion or lesions on brain MRI performed at least 30 days after an initial clinical demyelinating event, compared with a reference scan, can be used to fulfill criteria for DIT.
   c. A T2 spinal cord lesion is equivalent to a T2 brain lesion in the 2005 criteria.
   d. In the 2005 criteria, spinal cord lesions can be included in the total lesion count.
   e. (b) and (d) are correct.

5. In the longest and most comprehensive natural-history study of CIS patients published by Brex and Fisniku,
   a. the risk of long-term disability was greatest in patients with greater numbers of lesions on baseline brain MRI.
   b. rates of progression to CDMS were higher in patients presenting with ON compared with brainstem or spinal cord syndromes.
   c. patients progressing to SPMS had smaller baseline lesion T2 volumes.
   d. rates of conversion to CDMS were higher in patients with 10 lesions at baseline compared with only 2 lesions.

6. The ONTT showed that:
   a. oral prednisone for 2 weeks was equally as effective as a 3-day course of IV methylprednisolone.
   b. a 3-day course of IV methylprednisolone accelerated the time to vision improvement and also delayed the time to development of CDMS.
   c. oral prednisone for 2 weeks increased the risk of recurrent episodes of ON.
   d. at 5 years, visual function was significantly better in the IV methylprednisolone group compared with the oral prednisone and placebo groups.
   e. (b) and (c) are correct.

7. Which of the following statements is accurate regarding treatment outcomes of a CIS with IFN beta preparations in BENEFIT, CHAMPS, and ETOMS and glatiramer acetate in PRISQue?
   a. A delay in the development of diagnosed MS and reduced MRI measures of disease activity relative to placebo were shown in BENEFIT and ETOMS but not in CHAMPS or PRISQue.
   b. SC IFN beta-1a was demonstrated superior to IM IFN beta-1a in CHAMPS in delaying the development of diagnosed MS and reducing MRI measures of disease activity.
   c. All trials showed a delay in the development of diagnosed MS and a reduction in MRI measures of disease activity relative to placebo.
   d. All trials showed a delay in the development of diagnosed MS, but MRI measures of disease activity were reduced only in CHAMPS.
8. Which of the following regarding extension studies of pivotal trials using DMT in a CIS is correct?
   a. The 5-year extension of BENEFIT showed no benefit in cognitive performance (measured by the PASAT) in the immediate-treatment group compared with the delayed-treatment group.
   b. The 3-year extension of BENEFIT showed a significant reduction in the risk of progression to disability (measured by EDSS score) in the immediate-treatment group compared with the delayed-treatment group.
   c. The 5-year extension of BENEFIT showed a significant reduction in the risk of progression to disability (measured by EDSS score) in the immediate-treatment group compared with the delayed-treatment group.
   d. The 2-year extension of CHAMPIONS showed no significant difference in annualized relapse rates and new/enlarging T2 lesions in the immediate-treatment group compared with the delayed-treatment group.

9. How do results of the REGARD, BEYOND, INCOMIN, and EVIDENCE trials in patients with RRMS assist in guiding therapy decisions in CIS patients?
   a. REGARD and BEYOND suggest that GA or SC IFN beta preparations have similar clinical efficacy, with a potential advantage of SC IFN beta preparations on some MRI outcome measures, which may help clinicians make informed choices about all aspects of treatment including a CIS.
   b. IM IFN beta-1a demonstrated greater impact on clinical/MRI outcomes than SC IFN beta preparations in INCOMIN and EVIDENCE, which may help clinicians make informed choices about all aspects of treatment including a CIS.
   c. The higher-dose, higher-frequency SC IFN beta preparations demonstrated greater impact on clinical/MRI outcomes than IM IFN beta-1a in INCOMIN and EVIDENCE, which may help clinicians make informed choices about all aspects of treatment including a CIS.
   d. In REGARD and BEYOND, SC IFN beta preparations showed greater clinical and MRI efficacy than GA, which may help clinicians make informed choices about all aspects of treatment including a CIS.
   e. (a) and (c) are correct.

10. Following a CIS promptly with a DMT:
    a. is recommended by most neurologists in young patients, regardless of baseline MRI findings.
    b. should be delayed until there is more certainty that DMT is needed based on subsequent MRI or clinical activity.
    c. is recommended by most neurologists in patients with baseline lesions on MRI.
    d. should be considered only in patients with both baseline MRI activity and other risk factors for the development of CDMS.
EVALUATION FORM

Medical Education Resources and Consensus Medical Communications respect and appreciate your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete the posttest and evaluation form.

There are no prerequisites or fees for participating in and receiving credit for this activity. During the eligibility period of July 2011 and July 2012, participants must 1) study the educational activity, 2) complete the posttest by recording the best answer to each question in the answer key on this form, 3) complete the evaluation form, and 4) mail or fax the completed form to Medical Education Resources at 720-449-0217. A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 70% or better. Statements of credit will be mailed within 4-6 weeks of the activity.

REQUEST FOR CREDIT  Please Print Clearly

Name ___________________________________________ Specialty ________________________________

Organization _____________________________________________________________________________

Degree □ MD □ DO □ PA □ NP □ RN □ RPh □ Other: __________________________________________

Mailing address: □ Hospital/Academic/Office □ Home

Address ________________________________________________________________________________

City ___________________________________________________________________________________

State ________________ Zip __________

Telephone __________________ Fax __________________ Email ________________________________

Signature________________________________________ Date ________________________________

FOR PHYSICIANS ONLY
I certify my actual time spent to complete this educational activity to be:

□ I participated in the entire activity and claim 3.0 credits.

□ I participated in only part of the activity and claim _______ credits.

ACTIVITY POSTTEST
Please circle the appropriate answer:

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Please answer the following questions by circling the appropriate rating.

EXTENT TO WHICH PROGRAM ACTIVITIES MET THE IDENTIFIED OBJECTIVES
After completing this activity, participants should be better able to:

Describe the clinical challenges of accurately diagnosing patients presenting with a CIS ________________________________ 5 4 3 2 1

Discuss the role of MRI in the diagnosis of a CIS and in the risk stratification of patients who develop MS ________________________________ 5 4 3 2 1

Identify common presenting features in CIS patients ________________________________ 5 4 3 2 1
CONT.

Discuss the rationale for early initiation of therapy in CIS patients  
Review disease-modifying therapies shown to improve clinical outcomes in CIS patients  
Please indicate if this activity was free from commercial bias.  Yes  No  
If No, please indicate the topic(s) that were not free from commercial bias.

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity  
Enhanced my current knowledge base  
Will help me improve patient care  
Provided new ideas or information I expect to use  
Was timely and will influence my practice of medicine  
Addressed my most pressing questions  
Please indicate any changes you plan to make in your practice of medicine as a result of information you received from this activity.

Please rate your commitment level to making these changes  
In what time frame do you anticipate making these changes?  Immediately  1-2 months  3-6 months  At some point in the future  
Based on my participation in this CME/CE activity, I will now incorporate the following new clinical strategies:  
(Select all that apply.)  
Increase my knowledge and confidence in diagnosing and treating CIS patients  
Update my practice protocols in response to this knowledge  
Subcategorize CIS patients  
Utilize and interpret MR imaging in CIS patients in order to indicate patients at high risk for developing MS and initiate appropriate therapy  
Initiate DMTs early for appropriate CIS patients  
I already do all these things.  
If this activity did not give you strategies to be better able to practice medicine, please list the factors acting as barriers.

This activity was designed to help the participant master the ABMS/ACGME core competency of patient care, medical knowledge, and practice-based learning and improvement.  How well did this activity address this competency?  
Please provide general comments regarding this activity and suggest how it might be improved.

Please provide any other medical topics that would be of interest to you.