Clinical Concepts in

MULTIPLE SCLEROSIS

Emerging Trends in Imaging, Immunology and Therapeutics

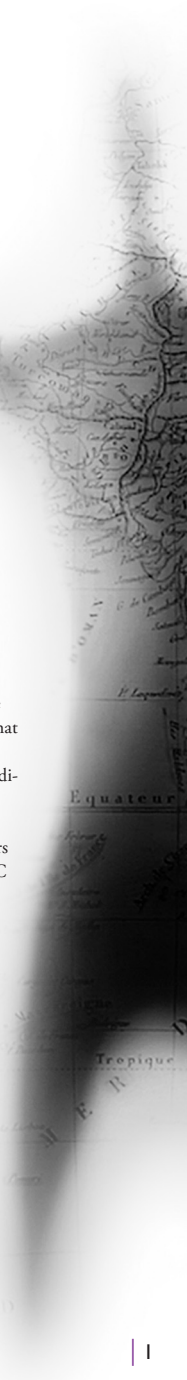
UNIVERSITY of NORTH TEXAS
HEALTH SCIENCE CENTER

In the fall of 2006 and January 2007, the University of North Texas Health Science Center at Fort Worth hosted 4 continuing education conferences titled: "Clinical Concepts in Multiple Sclerosis: Emerging Trends in Imaging, Immunology, and Therapeutics."

Conference presenters provided attendees with the latest research and clinical applications relating to the immunopathogenesis of multiple sclerosis (MS) and the role of MRI in the diagnosis and management of MS, and provided information to enable clinicians to develop a clinical frame of reference for optimizing therapy in relapsing MS.

The following article summarizes the topics presented at the conferences and offers the opportunity for readers to earn continuing medical education (CME) credit.

This CME exercise is accredited by the University of North Texas Health Science Center at Fort Worth Office of Continuing Education.



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THE IMMUNOLOGY OF MULTIPLE SCLEROSIS AND DISEASE-MODIFYING THERAPIES

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Learning Objectives:

After completing this activity, participants will be able to:

- Describe the immunology of multiple sclerosis
- Describe the likely immunological mechanism of action of interferons
- Describe the likely immunological mechanism of action of natalizumab
- Describe the likely immunological mechanisms of action of glatiramer acetate

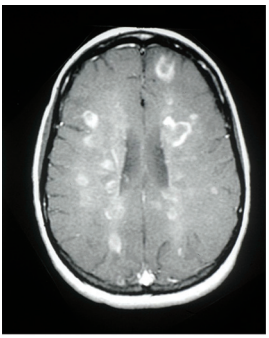
Multiple sclerosis (MS) is a chronic condition of the central nervous system marked by inflammation, demyelination, and axonal degeneration. The disease affects between 350,000 to 400,000 people in North America, with an estimated 10,000 new cases diagnosed annually.[1] It is the most common neurological condition diagnosed in young people, with the majority of diagnoses occurring in patients' twenties and thirties. The condition is more common in Caucasians than other ethnicities, and about twice as common in women than men.[1]

Early Medical History

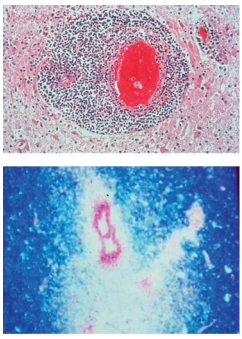
For years, MS was primarily considered an inflammatory demyelinating disease. Today, however, it is clear that the pathology includes a degenerative element, with acute lesion axonal transection occurring early in the inflammatory process (Figure 1).

This axonal and neuronal loss correlates more closely with disability than inflammation alone, particularly with cognitive impairment. The inflammation is believed to be the result of autoreactive T cells (CD4+ or CD8+) that react with myelin and appear more inflammatory than T cells in normal populations.[4 5]

Figure 1: Pathology of MRI Gd+ Lesion.



Gd+Enhancing Lesions



Perivascular Inflamation and Demyelination

UNDERSTANDING THE UNDERLYING PATHOPHYSIOLOGY OF MS

Understanding the pathophysiology of MS begins with an understanding of different T cell phenotypes. A naïve T cell may differentiate into a proinflammatory T_h1 cell or a T_h2 regulatory cell. The differentiation depends on several factors, including the antigen the T cell initially encounters. Viral and bacterial antigens tend to drive a Th1 response while parasitic infections tend to drive a T_h2 response. Given that MS is typically driven by a T_h1 response, it may explain the lower MS incidence in geographic regions with a greater prevalence of parasitic infections. Co-stimulatory molecules on naïve T cells and environmental cytokines also help determine T cell differentiation.

If the T cell response moves in the Th1 direction, inflammatory cytokines such as interferon (IFN)-γ, interleukin (IL)2, IL12, and tumor necrosis factor (TNF) trigger macrophages, which mediate tissue damage. If the response proceeds in the Th2 direction, it drives humoral immunity and generates regulatory T cells, which regulate the proinflammatory T_h1 cells. In this manner, homeostasis is maintained.

Problems occur when one T cell phenotype becomes dominant. If T_h1 cells are dominant, it may lead to inflammatory-mediated diseases such as MS or autoimmune diabetes. If T_h2 becomes overactive, patients may develop antibody-medicated diseases, such as rheumatoid arthritis.

The balance between inflammatory T_h1 and anti-inflammatory T_h2 cells is maintained through a regulatory cell belonging to the T_h2 phenotypes CD4+ CD25+. However, this subtype of T cells appears deficient in patients with MS.3 Thus, a therapeutic goal in MS is to enhance T_h2 activity or otherwise restore the balance between T_h1 and T_h2 cells.

WHAT TRIGGERS THE INFLAMMATORY PROCESS?

There are several hypotheses regarding the triggering event of the T cell inflammatory response that leads to MS.

Myelin Antigens Trigger Inflammation

One leading hypothesis is that myelin antigens act as an inflammatory trigger. This theory comes from a transgenic animal model of MS in which autoimmune encephalomyelitis (EAE), a paralytic disease similar to MS, develops when a purified myelin protein with adjuvant is injected. Studies find the animals' spleen cells contain T_h1 cells. These T_h1 cells are pathogenic; transferring them into naïve mice results in EAE.[6]

Evidence for the myelin-antigen theory in humans comes from the presence of myelin-activated T cells in the blood, spinal fluid, and brain tissue of MS patients. These T cells recognize dominant myelin antigens such as myelin basic protein amino acid 85-99. They also manifest epitope spreading. In this process, the initial myelin-destroying inflammatory response exposes T cells to additional myelin antigens, yielding higher levels of T cell cross reactivity. Epitope spreading becomes more common as the disease progresses.[6]

The Altered Peptide Ligand (APL) study showed the extent of epitope spreading in MS. In this study, amino acids in myelin basic proteins were modified to create a synthetic peptide designed to induce a protective T cell response rather the disease. Although the compound showed great promise in animal models, several clinical trial participants developed severe disease 1 week after starting treatment and the trials were halted early. The patients experiencing relapse exhibited a significant increase in T cells that recognized the myelin basic protein as well as in T cells that recognized the altered peptide itself.[7, 8] These findings strengthened the hypothesis for the myelin antigen as a trigger for relapses, if not for the disease itself.

A specific myelin antigen thought to play a role in the disease process in MS is myelin oligodendrocyte glycoprotein (MOG), which can induce both a T cell and antibody response. This is important given the current understanding of MS as not just a T cell disease, but as one that also includes an antibody element. Since MOG can do both, this suggests the possibility that at least some cases of MS might be triggered by a humoral response to MOG.

Such a response is possible because MOG is located on the surface of the myelin sheath, making it accessible to autoantibodies.

It is expressed almost exclusively in the central nervous system (CNS) and MOG autoantibodies have been found in MS lesions.[6] MOG is also the only myelin antigen that can induce T and B cell mechanisms of demyelination in an EAE animal model. Finally, serum levels of MOG immunoglobulin M (IgM) predict a conversion from clinically isolated syndrome (CIS) to clinically definite MS (CDMS), although this finding has been recently challenged.[6]

The Molecular Mimicry Theory

The molecular mimicry theory suggests that T cells cannot always distinguish foreign antigens from self antigens. This may be an underlying factor in MS since protein chemistry analysis shows similarities between several viral antigens and myelin proteins. Thus, infectious viruses or bacteria in individuals already predisposed to MS could produce proteins that cross-react with myelin antigens, "fooling" T cells. Driven by the infection, T cells cross the blood-brain barrier (BBB) and attack neuronal myelin, mistakenly believing it to be a foreign invader.[9]

Toll-Like Receptors (TLR)

The contribution of toll-like receptors (TLR) also excites interest in MS researchers. These receptors appear on immune cells such as macrophages and T cells and are the first to encounter invading infections. Thus, they are the first to recognize viral antigens and drive immunity, particularly the release of IFNα and IFNγ, inflammatory chemicals that could trigger the disease process.

Crossing the Blood-Brain Barrier

Just how do T cells infiltrate the BBB? The disease is thought to begin in the periphery of the lymphatic system with the activation of CD4+ cells by APCs (macrophages, dendritic or B cells) presenting an unknown antigen. This results in the aforementioned T cell differentiation into T_h1 phenotypes. The release of cytokines by the T_h1 cells and upregulation of very late antigen-4 (VLA-4), vascular cell adhesion molecules (VCAM-1) and intercellular adhesion molecules (ICAM-1) on endothelial cells of the BBB, enabling T_h1 cells to adhere to endothelial cells.[10]

T_h1 cells then release matrix metalloproteinase 2/9 (MMP-2/9) enzymes, which digest components of the extracellular collagen matrix that is a part of the BBB, enabling T_h1 cell penetration into the CNS.[10]

Once there, microglia (similar to macrophages) stimulate T_h1 cells, inducing expression of inflammatory cytokines and chemokines, which help maintain T_h1 cells in the CNS. This ongoing inflammatory process within the brain appears to be self-sustaining.

Next, T_h1 cells activate astrocytes in the CNS that either directly damage the myelin sheath or release molecules such as nitric oxide (NO) that damage the sheath.[10] This process may be stimulated by the release of glutamate from microglia. Glutamate is a potent antioxidant that is neurotoxic in large quantities. It damages the oligodendrocytes that maintain the myelin sheath by the overactivation of AMPA/kainate receptors, leading to neurodegeneration. Thus, therapies that inhibit glutamate, such as the Alzheimer's drug memantine, may eventually be found to play a role in MS.[11-13]

Antibody-Mediated Response to Myelin

A third component of the underlying the pathology of MS is an antibody-mediated response to myelin. Under certain circumstances, peripheral CD4+ cells may differentiate into T_h2 cells, driving B cell immunity. Activated B cells enter the brain similarly to T cells, albeit with certain differences. Once beyond the BBB, B cells differentiate into plasma cells that release antibodies which, along with complement, bind to the myelin sheath, causing destruction.[10]

The Heterogeneity of MS

Given the variety of potential initiating events, evidence suggests a heterogeneous initiating event for MS and, possibly, for the mechanism of myelin damage.

Indeed, the disease itself is thought to be heterogeneous with four patterns of mutually exclusive pathology (Table 1). Patterns 1 and 2 are primarily inflammatory in which the oligodendrocyte is preserved, enabling remyelination. Pattern 2 involves greater involvement of antibodies, complement, and plasma cells. It is the most common pattern, prevalent in approximately 60% of MS patients.[14]

Patterns 3 and 4 involve less inflammation but greater destruction of oligodendrocytes, reducing remyelination and patients' ability to recover from attacks. It is also possible that patterns 1 and 2 are common in relapsing-remitting MS (RRMS) patients who respond well to anti-inflammatory drugs, while patterns 3 and 4 are observed in progressive patients, who do not respond as well over the course of the disease.[14]

Table 1: Pathologic Heterogeneity in Multiple Sclerosis

Inflammation	Pattern I	Pattern II	Pattern III	Pattern IV
CD3+ T cells	+++	++	++	++
Plasma cells/Ab	++	+++	++	+
Complement (C9 neo)	-	++	-	-
Macrophages	++	+	+	+++

Demyelination	Perivenous	Perivenous	Ill-defined Concentric	Perivenous
Oligodendrocytes #	+++	+++	+	+
DNA fragment/ apoptosis	+/-	+/-	++ (Apo)	++
Myelin loss	Even	Even	MAG↓	Even
Remyelination	++	++	-	-
Estimated prevalence	3.7%	59.3%	25.9%	11.1%

Adapted from Luchinetti, et al. *Ann of Neur*; 2000.

However, Dr. Dhib-Jalbut cautioned that it remains unclear whether the patterns are mutually exclusive or if patients' disease patterns change over the course of the disease. The answer to both questions could significantly impact treatment. For instance, if MS is a heterogeneous disease then patients should not be expected to respond similarly to a single therapy and targeted therapies based on the pathological mechanism of the disease will become even more important.

THE IMMUNOLOGY OF DISEASE-MODIFYING THERAPIES IN MS

Interferons

Although several explanations exist for the mechanism of interferon therapy in MS patients, two appear to be most important: cytokine shifts and the BBB.[5]

Treatment with INFβ can reduce the inflammatory response, reestablishing a balance between T_h1 and T_h2 cells. It does this by suppressing interleukin (IL)12, a key cytokine driving INFγ. This suppression is mediated by a concomitant increase in the anti-inflammatory cytokine IL10.[15]

These findings were confirmed in a study of 15 RRMS patients receiving INFβ-1a for 24 weeks. IL10 levels were maintained and increased in clinical responders, while poor responders experienced a precipitous decrease in IL-10, which continued to fall during treatment.[16] This suggests that IL-10 levels may be a good biomarker of treatment response.

Meanwhile, an in vitro study of INFβ-1b on cell lines of MS and healthy subjects showed a significant inhibitory effect on IL12 production dependent on increased IL10 levels, suggesting that an IL10:IL12 ratio may provide a potential marker of treatment response.[15]

MRI showing reduced Gd+ lesions also suggests that INFβ works at the BBB. IFNβ appears to downregulate VLA-4 on T cells, reducing adhesion of T cells to endothelial cells and suppressing MMP-9. Together, the two effects limit the infiltration of T cells into the CNS.[5, 17] In addition, the serum of patients treated with INFβ-1a shows a dose-dependent increase in soluble VCAM (sVCAM), as well as a significant inverse relationship between serum sVCAM levels and MRI activity.[18]

These findings suggest that INFβ increases the turnover of VCAM on endothelial cells, leading to shedding of sVCAM into the circulation. Since sVCAM binds to VLA-4 on T cells, it prevents T cells from binding to VCAM on BBB endothelial cells, reducing the likelihood that they will adhere to the BBB.[5]

Natalizumab

Natalizumab is a humanized monoclonal antibody that binds to VLA-4 on T cells, inhibiting the infiltration of T cells into the CNS. Natalizumab probably has other immunological effects, such as interfering with the activation of T cells in secondary lymphoid organs and their reactivation in the CNS.[19]

There is some evidence that natalizumab may influence T_h1 cell apoptosis. These potential mechanisms of action are consistent with MRI findings, which depict a substantial decrease in Gd+ lesion activity superseding that seen with other immunomodulatory agents.[20]

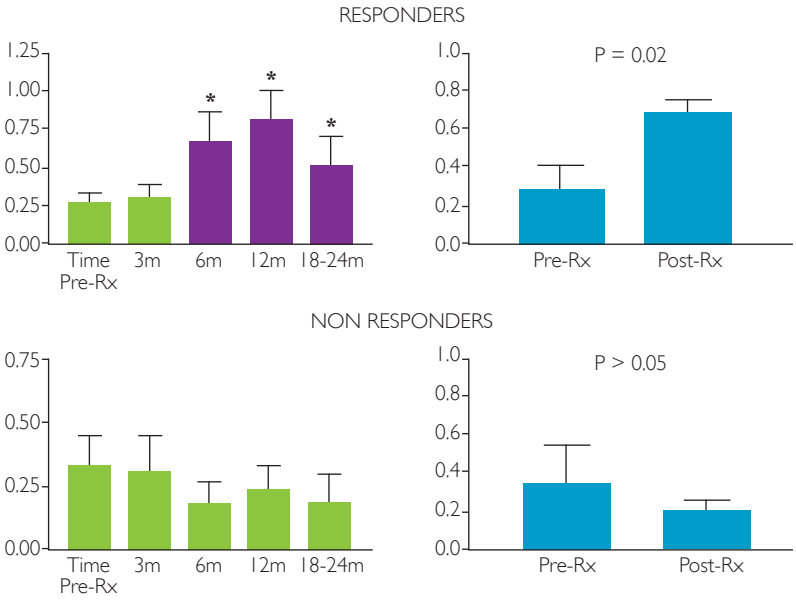
Glatiramer Acetate

Glatiramer acetate (GA) is a synthetic polypeptide engineered 30 years ago to study the chemistry of myelin destruction and the immune response to myelin proteins. Although the expectation was that this synthetic polypeptide would induce disease in animals, it turned out to be beneficial.

Glatiramer acetate consists of 4 amino acids: glutamate, lysine, alanine, and tyrosine. While the type and ratio of amino acids are fixed, the sequence is variable among peptides.

The primary mechanism of action of GA is its ability to bind to the HLA class II molecule on the APC, triggering a T cell response of the anti-inflammatory T_h2 /regulatory phenotype (Figure 2).[21]

Figure 2: Correlation of Th2 Shift with Clinical Response to GA.



The GA-reactive T_h2 cells appear to work primarily within the CNS, where they are re-activated by myelin antigens, triggering the release of anti-inflammatory cytokines such as IL10 and TGFβ.[22] These T cells also produce brain-derived neurotrophic factor (BDNF), which is involved in lesion resolution and recovery.[23] This helps explain earlier work demonstrating a 50% reduction in the development of Gd+ lesions into black holes (which correlate with axonal and neuronal damage) with the use of GA.[24,25] Such evidence suggests that GA intercepts the pathway leading from Gd-enhancement to black hole, suggesting a neuroprotective capability.

Summary

In conclusion, it is clear that INFβ works systemically by modulating inflammatory cytokines, blocking T cell adhesion to the BBB, and by blocking MMP-9, thus preventing T cell infiltration in the CNS. Natalizumab works by binding to VLA-4 and intercepting Th1 cells before they can attach to endothelial cells on the BBB, while GA stimulates the production of T_h2 and regulatory cells peripherally, which then migrate to the CNS where they modulate the immune response by producing anti-inflammatory cytokines and BDNF, possibly providing a neuroprotective effect.

UPDATE ON NEUROIMAGING OF MULTIPLE SCLEROSIS

Patricia K. Coyle, MD

Dr. Coyle is professor and acting chair of Neurology, and director of the Multiple Sclerosis Comprehensive Care Center, at Stony Brook University Medical Center in New York.

Learning Objectives

After completing this activity, participants will be able to:

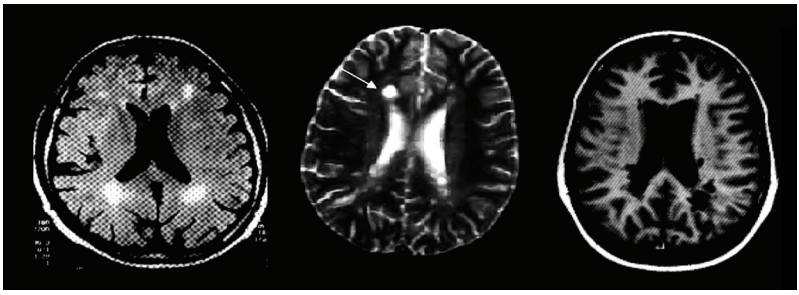
- Describe the role of conventional MRI in the diagnosis and prognosis of MS
- Describe 3 nonconventional MRI techniques that may be used in the prognosis of MS
- Identify the effect of interferons, glatiramer acetate and natalizumab as seen on MR

Conventional MRI in MS

Magnetic resonance imaging (MRI) with contrast agents is the gold standard among neurological consensus groups and physicians in the diagnosis of MS.[26] It is also considered the best disease activity marker for RRMS and, to a lesser extent, SPMS. Overall, MRI is more sensitive than any other clinical marker, including immunological markers.

Conventional MRI techniques typically used for MS diagnosis include T2-weighted (T2) with or without proton density (PD), T1-weighted (T1) with and without gadolinium (Gd) administration, and PD and fluid-attenuated inversion recovery (FLAIR) (Figure 3). All provide different information about the disease.

Figure 3: Images of RRMS Patient.

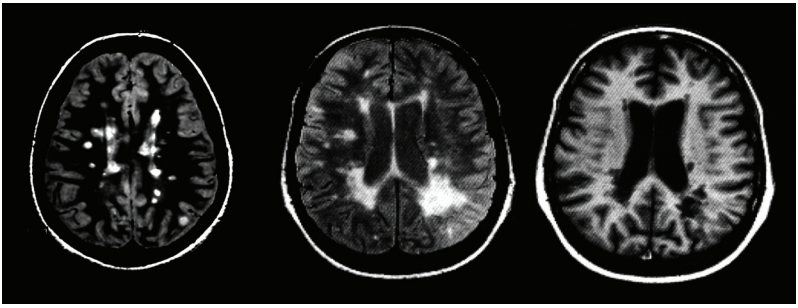


Gd+T1 SCAN T2 WEIGHTED T1 HYPOINTENSE

T2–Weighted Images

T2 is the hallmark imaging modality for MS diagnosis. Lesions imaged with T2-weighting appear as hyperintense, "white snowballs," with the total volume of T2-weighted lesions indicating the burden of disease. The hyperintensity represents an abnormality in tissue water. Thus, spinal fluid appears hyperintense on T2, preventing visualization of lesions in that area. FLAIR suppresses the signal from spinal fluid and "nulls" out the fluid, increasing the conspicuity of lesions adjacent to the spinal fluid (Figure 4).

Figure 4: FLAIR Images.



FLAIR
Fluid Attenuated Inversion Recovery

FLAIR

T1
Black Holes

However, T2 lesions provide little information about the pathology of the abnormal area. Thus, a remyelinated plaque in MS looks identical on T2 to a destructive plaque. Another disadvantage to T2-weighted images is that they do not provide significant prognostic value. In addition, increasing brain T2-lesion load correlates better with cognitive than physical disability.*

T2 MRI is most valuable early in the disease state, when increasing lesion number and size indicates a poor prognosis.

For these reasons, T2 MRI has never reached clinical expectations in terms of its ability to correlate disease activity with disease severity.

T1–Weighted MRI

In T1 MRI images, T2 lesions appear isotense, invisible, or hypointense, forming grey-to-black holes. These black holes reflect chronic axon and tissue matrix damage, acute extracellular edema, and/or myelin disruption. The degree of hypointesity indicates axon density, with greater axon loss and disability correlating with greater hypointensity.

Certain T1–weighted MR images predict advancement to a black hole. These include:

- Lesions > 6 mm
- Ring-enhancing lesions
- Prolonged enhancement > 4 weeks
- New lesions in SPMS

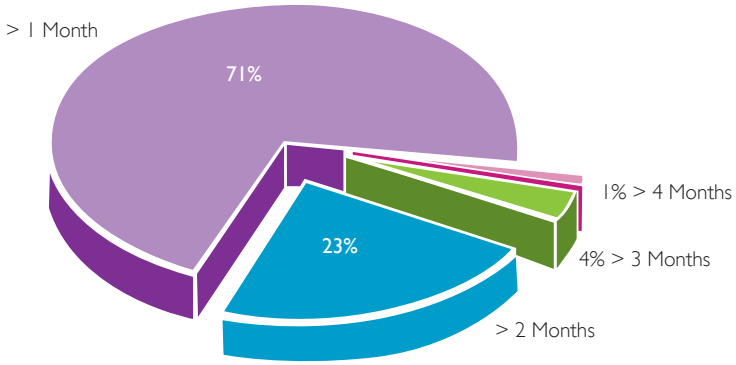
Overall, T1 lesion load correlates more closely with disability than T2 lesion load, particularly in SPMS.

Contrast Enhancement

Although several contrasting substances are available, Gd is the only one used for MS MRI. The typical dose is 0.1 mmol/kg, although some researchers use a double or even triple dose for spinal cord imaging.

A Gd+ lesion provides clinical evidence of a focal BBB breach and active inflammation. It likely indicates an active lesion ≤ 6 weeks old, while a ring enhancement indicates an old lesion that has reactivated, while nodular enhancement indicates a new lesion. The majority of lesions enhance for < 4 weeks, with an average enhancement of 3 weeks. Just 1% enhance for longer than 16 weeks (Figure 5).*

Figure 5: Duration of Enhancing Lesions (n=579).

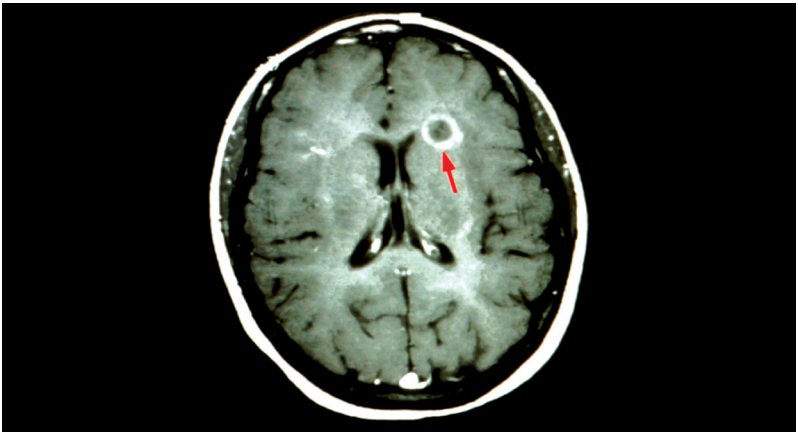


It is clear that contrast enhancement correlates with relapses, clinical symptoms, T2 burden of disease, and future enhancing lesions at a young age. Enhancement is typically greater in the early relapsing phase, becoming less common with age and as patients move into the secondary progressive phase of the disease. Enhancement does not seem to correlate well with atrophy, disability, and disease progression.*

Ring Enhancement

Ring enhancement (Figure 6) has typically been considered a sign of disease severity.[27] However, when the lesions are biopsied, it appears that ring enhancement represents extensive oligodendrocyte recruitment and remyelinization.* If, as noted earlier, this pattern is also a marker of MS lesion pattern 2, there may be a significant antibody and complement-mediated component to the destruction process, which could influence therapeutic approaches.

Figure 6: Ring Enhancement.



MRI IN THE DIAGNOSIS OF MS

An essential requirement for an MS diagnosis is objective evidence of CNS white matter lesions disseminated in time and space. The McDonald International Panel Criteria released in 2001 provided the first criteria that outlined the use of MRI evidence in patients who experienced a clinically isolated syndrome (CIS). Those criteria were revised in 2005 (Table 2).[28]

For dissemination in space, the revisions required that 3 of the following conditions be met:

1. ≥ 1 Gd+ lesion, or 9 T2 lesions
2. ≥ 1 infratentorial lesion
3. ≥ 1 juxacortical lesion
4. ≥ 3 periventricular lesions

The revision clarified the role of spinal cord focal lesions as an infratentorial lesion. If the focal spinal cord MR lesion is also enhancing, it is considered both a contrast lesion and an infratentorial lesion. The new criteria did not endorse routine serial spinal MR follow-ups unless there are symptomatic criteria.

The revisions also provided criteria for dissemination in time. A Gd+ lesion detected at an independent site ≥ 3 mos after a clinical event, or a new T2 lesion detected at any time compared to a reference MRI performed ≥ 30 days after a clinical event meets dissemination in time criteria.[28] Still, an MRI scan is not required for a clinical diagnosis under the International Panel guidelines.

Table 2: 2005 McDonald International Panel Criteria

Presentation	Additional data needed
▪ ≥ 2 attacks ▪ Objective clinical evidence of ≥ 2 lesions	None
▪ ≥ 2 attacks ▪ 1 lesion	▪ Dissemination in space by MRI OR ▪ ≥ 2 MRI lesions + positive CSF OR ▪ Clinical attack at new site
▪ 1 attack ▪ ≥ 2 lesions	▪ Dissemination in time by MRI OR ▪ Second attack
▪ 1 attack ▪ 1 lesion (monosymptomatic CIS)	▪ Dissemination in space (MRI or ≥ 2 MRI lesions and +CSF AND ▪ Dissemination in time (MRI or second attack)

Even with the revisions, the McDonald criteria are rarely used by practicing neurologists because they are considered too stringent and complex, with limited sensitivity for early diagnosis.[29]

In 2006, a panel of British researchers recommended the following additional revisions:[29]

Modified dissemination in space

- ≥ 1 T2 lesion in ≥ 2 regions: periventricular, juxacortical, infratentorial (excluded in brain stem CIS), spinal cord (excluded in cord CIS)

Modified dissemination in time

- ≥ 1 new T2 lesion

The modifications make the criteria less complex and improve the overall accuracy of diagnosing MS in patients with CIS. It also does not require Gd+ lesions on MRI, leading to significant time and cost savings. The recommendations also note that diagnosis of CIS should involve experienced clinicians; that the CIS should be "unambiguously typical"; and that the criteria should only be applied to patients aged 16 to 50 years.[29]

Other MRI-based criteria for an MS diagnosis come from an evidence-based review on the role of MRI in CIS. Frohman et al. concluded that 3 or more T2 white matter lesions were a sensitive predictor of further clinical disease activity in the next decade, and that if a follow-up MRI scan after 3 months depicted a new T2-weighted or contrast-enhanced lesion, it strongly predicted further clinical attacks in the near future. The review concluded that once alternative diagnoses were excluded, CIS with any of these MRI findings were most likely to be MS.[30]

Other suggestive features for an MS diagnosis include numerous white-matter ovoid-shaped lesions >3 mm in size; Dawson's fingers, lesions extending off ventricles in the brain that are oriented perpendicularly to the long axis of the brain; corpus callosum involvement; and enhancing lesions, particularly open-ring enhancing lesions.

Confronting MRI-based Challenges in MS Diagnosis

Challenges with using MRI for diagnosis center around a lack of consensus on the optimal machine technique and analysis, including Tesla strength, slice thickness, placement, and sequences; and a lack of uniform interpretive readout criteria and consensus on when to use Gd, as well as when to image the spinal cord. However, a consensus statement from the Consortium of Multiple Sclerosis Centers published in 2006 offers recommendations and guidelines to address these issues. They include:[31]

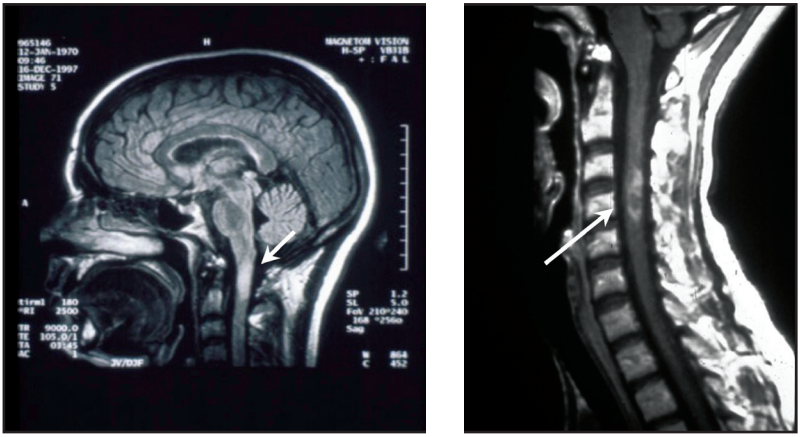
- When available, an MRI study that meets standardized protocol should be conducted as part of the initial evaluation for MS.
- Patients already diagnosed with MS should undergo a baseline evaluation that includes an MRI meeting a standardized protocol in addition to a complete neurologic history and examination.
- If the main presenting symptoms are at the level of the spinal cord and have not been resolved, spinal cord MRI and brain MRI are recommended.
- If the results of the brain MRI are equivocal and the diagnosis of MS is still under consideration, spinal cord imaging may be justified.
- In the absence of clinical indications, routine follow-up MRI scans are not recommended, regardless of treatment status
- Clinical indications for follow-up MRI include:
  - — Unexpected clinical worsening or clinical concern about the patient's course
  - — Reassessment of disease burden for initiation of treatment
  - — Suspicion of secondary diagnosis
- Gd-enhanced MRI is recommended for suspected MS for diagnosis and initial diagnostic evaluation.
- Contrast-enhanced MRI is considered optional for baseline evaluation in those already diagnosed with MS.
- MR imaging of the brain or spinal cord should be performed when possible at ≥1 Tesla (T) to optimize image quality and tissue contrast.

Spinal MRI in Diagnosis

Physicians should be cautious about relying on MRI for diagnosis in patients over age 50 since brain lesions often start appearing in healthy controls after age 50. However, spinal cord lesions are abnormal regardless of age, leading to her recommendation that the spinal cord be imaged in those over 50. In fact, recent data suggests that during the first 2 years of MS, >80% of patients will have abnormal spinal cord MRI scans.[32]

In the spinal cord, focal T2 or PD hyperintense lesions in the cervical and thoracic region are highly suggestive of MS, as are diffuse PD abnormalities, focal or diffuse atrophy, mid-cervical and thoracic lesions, and asymmetrical involvement with multiple, scattered lesions, as well as peripheral lesions. Lesions involving 3 or more vertebral segments or a single long, large lesion tend to be more suggestive of neuromyelitis optica (NMO) than MS. Lesions typically associated with MS are lateral and dorsal, involving fewer than 2 segments and less than half the cross-sectional area, and are edemic only within acute plaques (Figure 7).

Figure 7: Spinal MRI in MS: Cord Lesion.



Using MRI for Prognosis

Conventional MRI parameters offer prognostic utility early, at the time of CIS, and n early relapsing MS more so than in the later, progressive phase. Poor prognostic features on MRI include high lesion burden and contrast lesion activity, high T1:T2 ratio, obvious atrophy and, possibly, brain stem and spinal cord lesions.

Data from Queen Square, a 14-year follow up of CIS patients who met chronological parameters and who had optic neuritis and incomplete transverse myelitis and isolated brain stem cerebellar syndrome, show that over 14 years, 75% developed definite or probably clinical MS. But if one initial MRI was abnormal, 98% had further clinical attacks and/or new MR lesion activity. Conversely, if the initial

brain MRI was normal, 38% experienced further attacks and 19% developed MRI lesions. Quantity and size of lesions correlated with disability over 14 years, with the development of lesion burden in the first 5 years predicting later disability.[33]

The Queen Square data strengthen the concept that there is a "window of opportunity" for early treatment of MS that can affect later disability.[34]

MRI Role in Therapy

Conventional MR techniques can be used to provide outcome information in drug trials. They evaluate disease activity by tracking new and active T2 and Gd+ lesions and T2/T1 lesion burden. In clinical practice, they are often used annually or biannually to follow treatment response and assess relapse.

Different therapies have different profiles on imaging.

- **Glatiramer acetate:** Reduces contrast lesion activity approximately 35% and stabilizes T2 lesion burden by about 6 months. It can reduce the advancement of new lesions to black holes by 50%, and has an effect on brain atrophy.[24,35]
- **Interferons.** The IFNs decrease Gd+ lesions 70% to 80% and shrink T2 lesion burden, although they do not affect lesion evolution. They most likely also reduce atrophy.[36]
- **Natalizumab.** Natalizumab reduces Gd+ lesions 70% to 80%, reduces T2 lesion burden, affects lesion evolution, and most likely reduces atrophy.[37,38]

Nonconventional MRI Techniques

Given the problems with T2/T1 imaging, including poor pathologic specificity, limited clinical correlations, and relatively low sensitivity, researchers are exploring newer imaging approaches. These include water-suppressed, proton MR spectroscopy (MRS), magnetization transfer imaging (MTI), and diffusion-weighted imaging. All are capable of detecting microscopic lesions and all may be used as an adjunct to traditional MR imaging.[39]

There are also several unconventional global neurodegenerative measures, including T1 lesion burden; brain or cervical cord atrophy (global or segmental); quantitative analysis of the brain using MTI to produce a magnetization transfer histogram; and diffuser tensor measurement of the brain to create a diffusion tensor histogram.

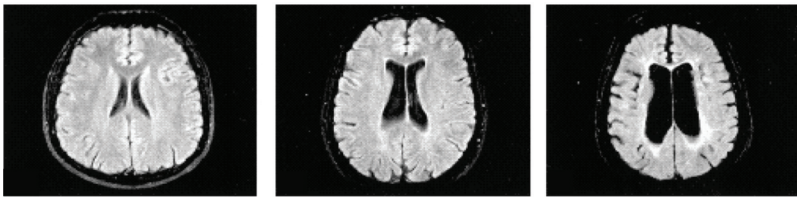
Atrophy as Marker of Disease Progression in MS

Atrophy may be measured by SIENA using brain parenchymal fraction (BPF); or with lesion evolution studies using MRI through mag transfer. Measuring atrophy holds great promise for calculating the burden of disease in MS because it enables clinicians to identify microscopic abnormalities as well as macroscopic abnormalities, and both brain and cervical cord atrophy can be measured.

Atrophy also correlates better with disability and cognitive problems than T2 or T1 lesion load, particularly when evaluated in the spinal cord. Atrophy is 3 to 10 times higher in an MS population than matched controls and appears despite stable examination and lack of relapse.[40] Imaging processes enable the segmentation of grey vs white matter atrophy, important since it appears that gray matter atrophy may be more prominent early in the disease.

Figure 8 depicts the process of brain atrophy through axial cranial MRI scans in a healthy 31-year-old man (A), a 36-year-old woman with RRMS of 2 years' duration (B), and a 43-year-old woman with SPMS of 19 years' duration.[41] They clearly show increasing ventricular size with decreasing BPF.

Figure 8: Brain Atrophy



A B C

One challenge with relying on atrophy as a marker for disease progression is that numerous factors influence atrophy, including age, sex, nutrition, hydration, health status, and drugs. This results in significant variability between patients and even within the same patient. Nonetheless, while there is no agreed-upon method of measuring atrophy, atrophy measurement will eventually become the standard for determining disease progression.

Mag transfer imaging (MTI). This form of nonconventional imaging provides information on lesion evolution via signals from fixed and fluid phase proton populations in the same tissue area. Thus it provides an MT ratio (MTR). The lower the MTR, the greater the tissue destruction. In MS, the MTR is abnormal in brain and spinal cord, even in normal-appearing white matter and brain tissue. In addition, MTR changes can be seen up to 2 years before Gd+ lesions occur, suggesting ongoing microscopic changes developing well before lesions appear.

MTI also allows evaluation of lesion heterogeneity, providing a closer correlate of disability and cognitive dysfunction than conventional MRI. The method also provides MT histogram patterns of RRMS and PPMS, with PPMS showing very abnormal MT histograms despite low T2 lesion loads.

The problem with using this approach is a lack of standardization of MTI across centers, although it can be standardized within centers.

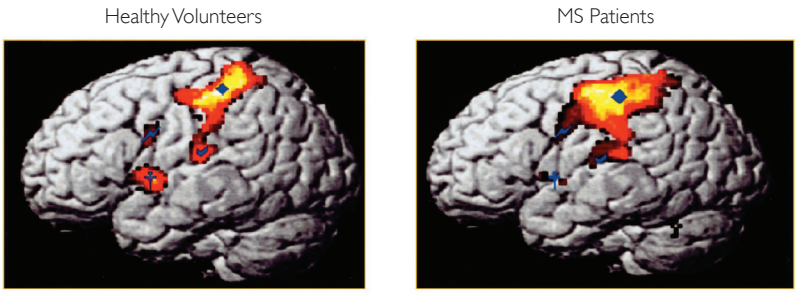
MR Spectroscopy (MRS). This imaging method evaluates chemical levels in the brain. Permanently decreased levels of n-acetylaspartate (NAA) represents axon/neuronal damage, while increased choline peaks are associated with membrane turnover, inflammation, myelin breakdown, gliosis, and destructive pathology. Lipid peaks correlate with myelin damage and increased lactate with inflammation, local ischemia, and neuronal mitochondrial dysfunction. Increased myoinositol correlates with gliosis.

However, the time required to analyze MR-SPEC studies and uncertainties about the best way to use it mean MR-SPEC is not yet ready for clinical use.

Diffusion weighted/tensor imaging. This imaging method provides information on the loss of structural organizations, detecting abnormalities in normal-appearing brain tissue in MS and providing a window into microscopic damage regardless of the macroscopic damage detected by current imaging techniques. Recent studies support correlations with clinical disease, although the best methods for acquisition and post-processing strategies remain unclear.[42]

Functional MRI. This imaging method detects activation circuits in the brain by tracking changes in regional blood perfusion and blood deoxyhemoglobin to depict hyperintense signals. Figure 9 shows a functional MRI of a healthy individual and of an individual with MS. The abnormality suggests enough damage has occurred to cause disarray of the normal neuronal circuitry that would be activated for that particular cognitive task. Although functional MRI provides a good tool for studying motor, visual, and sensory symptoms in MS, as well as a method of studying study baseline circuitry in the disease and the way in which individuals recover from acute vs chronic injury, it is still not appropriate for general clinical use.

Figure 9: Brain Patterns of Cortical Activation During Performance of a Simple Motor Task.



Summary

In conclusion, conventional MRI remains a key diagnostic tool in MS. While nonconventional MRI techniques hold great promise as improved disease biomarkers, they require further development for clinical use. Ultimately, Dr. Coyle predicted, a battery of imaging approaches rather than one MR technique will be used to diagnose and follow patients with the disease.

MAKING A DIFFERENCE THEN AND NOW: A CLINICAL UPDATE

Howard Zwibel, MD

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Learning Objectives

After completing this exercise, participants will be able to:

- Describe the long-term clinical outcome of early treatment of CIS in patients suspected of having MS
- Describe parameters for following patients diagnosed with MS
- Describe parameters for determining efficacy of disease modifying therapies

Early History of MS

Multiple sclerosis is a disease with a long history. In the 1920s, it was felt to be spirochetal or toxic in origin, and treated with mercury and silver nitrate. In the 1930s, an infectious etiology view emerged, with treatment focused on syphilis treatments and tonsillectomy/adenoidectomy. In the 1940s, the disease was attributed to tubercular and vascular aspects, and treated with immunoglobulin and antithrombotics. In the 1950s, the disease was believed to an allergic condition, leading to the use of histamine treatment and the development of the Procarin patch. The 1960s saw dietary and environmental factors move to the forefront of suspected causes, with prednisone and low-fat diets, including the Swank diet, touted as beneficial.

By the 1970s, adrenocorticotrophic hormone (ACTH) and chemotherapy was used to treat the inflammation known to underlie the disease. Finally, by the end of the 20th century, researchers realized the importance of the immune system in MS and began treating it with disease-modifying therapies (DMT), the interferons and glatiramer acetate (GA).

Since then, overall understanding of disease progression in MS has expanded, clearly showing that early relapses affect long-term disability and making it critical that patients are treated early and aggressively (Figures 10 and 11).[43]

Figure 10: Clinical Course of MS. Disease Progression.

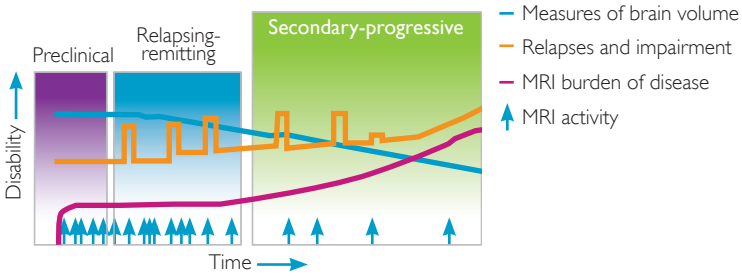
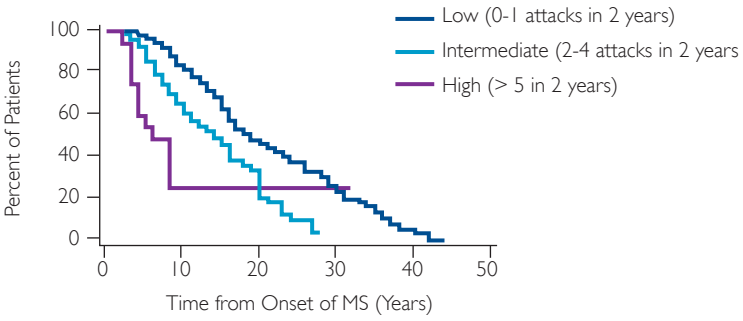


Figure 11: Clinical Disability Over Time in MS. Early Relapses affect Long-term Disability.



Clinical Evidence for Early Treatment

The National Multiple Sclerosis Society recommends initiating treatment with an immunomodulator as soon as possible following a definitive diagnosis of MS with a relapsing course, and for selected patients with a first attack who have a high risk of MS.[44]

Data supporting this statement come from several studies, including the following, several of which now have long-term data available (Table 3):

The Early Treatment of Multiple Sclerosis (ETOMS) trial. In this trial, treatment with 22 mcg of IFNβ-1a weekly delayed progression to clinically definite MS (CDMS) by 24%, with a delay < 300 days.[45]

The Controlled High Risk Avonex Multiple Sclerosis Trial (CHAMPS). This study was designed to evaluate the effect of INFβ 1a treatment on CIS patients with a high likelihood of future MS-like events. The treatment group experienced a 44% reduction in the 3-year cumulative probability of developing CDMS. After 18 months, treatment was associated with a significant reduction of new T2 lesions, Gd+ lesions, and T2 lesion volume.[46]

Betaferon/Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) study. BENEFIT showed that treatment with high-dose, high-frequency INFβ-1b for 2 years beginning with the first clinically identifiable manifestation of the disease reduced the risk of CDMS 50% percent compared with placebo.[47]

The Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis (PRISMS). In this trial, treatment with IFNβ-1b on patients with RRMS resulted in a significantly reduced relapse rate in years 1 and 2 (27% and 33% respectively) than with placebo, while the proportion of relapse-free patients significantly increased.[48]

A single long-term follow-up visit at 7 to 8 years after baseline included 68.2% of the original 560 patients (n=382), 72% of whom were receiving IFNβ-1b. In the original cohort, 19.7% (110/557) progressed to an EDSS score ≥ 6, with progression delayed in those randomized to high-dose IFNβ.[49]

Copaxone Study Group. The Copaxone study launched in October 1991 and now includes up to 12 years of patient involvement and is still ongoing. After 10 years, 47% of patients were still in the trial (n=108), receiving examinations every 6 months. The study showed that 92% of patients receiving GA remained ambulatory, with just 8% progressing to a score ≥ 6 on the Kurtzke Expanded Disability Status Scale (EDSS) after a mean of 10 years on therapy and 18 years' disease duration.[50] This compares to 50% of patients in the Weinshenker natural history cohort (London, Ontario) (n=1099) who progressed to EDSS ≥ 6 at 15 years.[43]

Betaseron Long-Term Follow-up (LTF) Study. Sixteen-year data on IFN-1b presented in 2006 showed 45% of patients in the ongoing cohort (>80) had progressed to ≥ 6 on the Kurtzke Expanded Disability Status Scale (EDSS). This retrospective analysis also showed lower doses produced greater efficacy with fewer deaths over the 16-year period.[51] This is one of the few long-term studies to examine mortality in MS patients.

It is generally accepted that these medications should be used in CIS in patients at risk of developing MS. And with the long-term data now available on most of these therapies, these treatments should be viewed as altering the course of disease in most of patients.

Table 3: Landmark Clinical Studies in MS Treatment

Trial	Treatment Used	Follow-up Period	% progressing to EDSS ≥ 6
Natural progression[43]	NA	15 years	50%
CHAMPS[52]	IFNβ-1a	8 years	35%
Long-term BENEFIT[51]	IFNβ-1b	16 years	45%
PRISMS[49]	IFNβ-1b	7.2	19.7%
Copaxone Study Group[50]	Glatiramer acetate	10–12 years	8%

CURRENT ISSUES IN MS TREATMENT

Neutralizing Antibodies in Current Therapies

Neutralizing antibodies (NABs) continue to be a major issue related to the use of interferons in MS. Early evidence suggested NABs appeared within 6 to 24 months after initiation of INFβ.[53]

In March 2007, American Association of Neurology released guidelines on neutralizing antibodies. The report of the Therapeutics and Technology Assessment Subcommittee noted that:

1. Treatment of MS with IFNβ (Avonex, Betaseron, or Rebif) is associated with the production of NAbs to the IFNβ molecule (Level A).
2. It is probable that the presence of NAbs, especially in persistently high titers, is associated with a reduction in the radiographic and clinical effectiveness of IFNβ treatment (Level B).
3. It is probable that the rate of NAb production is less with IFNß-1a treatment compared to IFNβ-1b treatment (Level B). However, because of the variability of the prevalence data, and because NAbs disappear in the majority of patients even with continued treatment (especially in those with low-titer NAbs), the magnitude and persistence of any difference in seroprevalence between these forms of IFNβ is difficult to determine.
4. It is probable that the seroprevalence of NAbs to IFNβ is affected by one or more of the following: its formulation, dose, route of administration, or frequency of administration (Level B). Regardless of the explanation, it seems clear that IFNβ-1a (as it is currently formulated for IM injection) is less immunogenic than the current IFNβ preparations (either IFNβ-1a or IFNβ-1b) given multiple times per week subcutaneously (Level A). Because NAbs may disappear in many patients with continued therapy, the persistence of this difference is difficult to determine (Level B).
5. Although the finding of sustained high-titer NAbs (>100 to 200 NU/mL) has been associated with a reduction in the therapeutic effects of IFNβ on radiographic and clinical measures of MS disease activity, there is insufficient information on the utilization of NAb testing to provide specific recommendations regarding when to test, which test to use, how many tests are necessary, and which cutoff titer to apply (Level U).[54]

Pregnancy and MS

It is clear that MS has no effect on conception and typically has no negative effect on the course of MS in the mother. However, Dahl et al., evaluating data from the Norway Registry of Live Births, concluded that women with MS had a higher proportion of small-for-gestational age infants and more frequent inductions and interventions (forceps and surgical) during delivery.[55]

The U.S. Food and Drug Administration currently assigns medications to one of five pregnancy categories: A, B, C, D, and X (Table 1). Glatiramer acetate carries a pregnancy labeling of B, while the interferons have a pregnancy labeling of C. Given evidence suggesting that women exposed to INFβ in the first trimester of pregnancy have a slightly greater risk of miscarriage and small-for-gestational-age neonates, disease-modifying therapies should be discontinued for 1 to 2 menstrual cycles prior to conception whenever possible, and relapses during pregnancy treated with high-dose steroids.[56]

IDENTIFYING PATIENTS WITH SUBOPTIMAL RESPONSE TO DISEASE-MODIFYING THERAPY

The following criteria can help clinicians identify individuals with suboptimal responses to disease-modifying therapy:

- Individuals who have attack rates of more than 1/year, or who fail to show reduction in relapse rate after continuous therapy with disease modifying treatment for at least 6–12 months;
- Individuals who have incomplete recovery from repeated attacks, particularly in terms of EDSS score increase;
- Individuals with new or recurrent brainstem or spinal cord lesions;
- Individuals who develop polyregional disease affecting multiple neurologic systems;
- Individuals who have progressive motor or cognitive impairment sufficient to disrupt their daily activities irrespective of changes on neurologic examination, provided the influence of depression, medications, or superimposed concurrent disease is eliminated.

Table 1: Food and Drug Administration Pregnancy Category System[57]

Category A:	Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
Category B:	No evidence of risk in humans. Either animal study shows risk, but human findings do not; or, if no adequate human studies have been performed, animal findings are negative for risk.
Category C:	Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify potential risk.
Category D:	Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.
Category X:	Contraindicated in pregnancy. Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk, which clearly outweighs any possible benefit to the patients.

Source: Food and Drug Administration

Relapses generally decline during pregnancy, likely as a result of changing estriol levels and altered immune function. The relapse rate may increase in the first 3 to 6 months postpartum, however, before returning to pre-pregnancy level.[58] One small study (n=12) suggests that intravenous immunoglobulin may reduce the possibility of relapse in the postpartum period.[59]

Epidural anesthesia and breastfeeding are not contraindicated in women with MS and do not appear to have any effect on relapse rate.[58] However, disease-modifying therapies should not be restarted until after breastfeeding ends.

Optimizing Immunomodulatory Therapy

Given that currently available treatments are only partially effective and that disease progression may not be well controlled in large numbers of patients, possibly due to the development of neutralizing antibodies and suboptimal response to therapy, many clinicians today change patients' therapies or combine therapies despite limited data. In his practice, he switches the majority of RRMS patients who do not respond to GA to an interferon, and patients who do not respond to interferons to GA.

Optimizing therapies in patients requires following patients more closely than many clinicians now do. A recommended follow-up schedule follows:

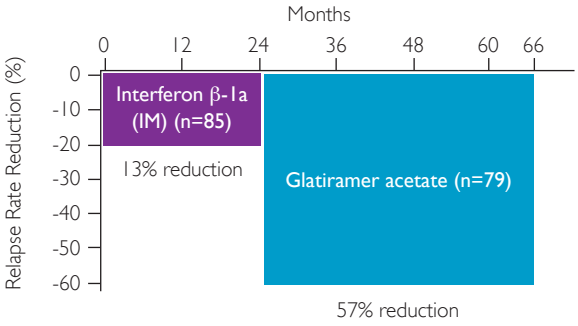
- Regular clinical assessment of patients every 3 to 6 months for the first 2 years after diagnosis and treatment initiation
- Quantitative neurological examination at every visit
- Appropriate laboratory tests
- Consider neutralizing antibody titer if appropriate

Switching Therapies

Although no significant data have been published regarding when to switch from an interferon to GA, two published articles provide recommendations. The first describes an open-label study of approximately 800 RRMS patients, 548 treatment naïve and 247 who previously received INFβ-1b. The reasons for switching were adverse events (67.6%) and perceived lack of efficacy (34.6%). Median duration of GA treatment was 36 and 24 months in treatment naïve and prior interferon patients, respectively. Overall, both cohorts showed a similar relapse rate reduction of 75% compared to baseline, with 68% of patients in each group remaining relapse free, while disability remained stable in both groups. The annualized relapse rate in the 2 years prior to study entry was 2.8 for the treatment-naïve group and 3.1 for patients previously treated with INFβ-1b.[60]

A second, prospective study followed 85 patients who received INFβ-1a for 18 to 24 months and who were then switched to GA because of persistently active disease (76%) or adverse events (24%) and followed for 36 to 42 months.[61]

Figure 12: Experience with Switching to Glatiramer Acetate from Low-dose Interferon.



Caon et al. Eur J Neur. 2006;13(5):471-474.

MULTIPLE SCLEROSIS SOCIETY CLINICAL GUIDELINES REGARDING SUBOPTIMAL TREATMENT[2]

Treatment

- Consider treatment change if attacks continue at a rate greater than before starting treatment.
- Do not declare treatment failure based on a single attack.
- Do not declare treatment failure within a few months of initiating treatment.

Disability

- Do not use change in EDSS during attack or in isolation as determinant of treatment failure.
- An annual increase in EDSS of ≥1 in patients with previous score of 3.0 to 5.5 or ≥ 0.5 with previous score of ≥ 6.0 should raise concern.
- Measurement of change in very low EDSS ranges (≤ 3.0) is too variable to be used in isolation to define treatment failure.

MRI Activity

- Findings on random MRI, on arbitrarily performed MRI, or at predetermined intervals in the absence of clinical activity, are difficult to interpret.
- High-enhancing activity, or substantial new lesion formation after attack subsides, likely indicates treatment failure.

Treatment with GA reduced the mean annualized relapse rate (ARR) from 1.23 to 0.53. In those switched due to lack of efficacy (n = 62), the rate fell from 1.32 while on INFβ-1a to 0.52 on GA. A much smaller, nonsignificant ARR reduction was seen in those switched because of persistent toxicity (n=23).[61]

Safety Issues with Mitoxantrone and Natalizumab

Only when patients fail both the interferons and GA should clinicians consider mitoxantrone or natalizumab for patients.

Natalizumab. This humanized monoclonal antibody was approved on the basis of one-year data from 2 clinical trials.[38, 62-64] It requires monthly infusions, and shows a 65% reduction in relapse rate, an 86% reduction in Gd+ lesions, and a positive effect on disability.

However, significant questions remain regarding its long-term safety. Specific concerns include hypersensitivity reactions, which occur in < 1% of patients, and neutralizing antibodies, which occur in 6% of patients. Also of concern is the risk of progressive multifocal leukoencephalopathy (PML).[62] Although the drug is now available again under strict restrictions, its voluntary withdrawal in early 2006 led Dr. Zwibel to moderate his criteria for its use until more safety data are available.

Mitoxantrone. Clinicians using mitoxantrone should be aware of labeling changes calling for left ventricular ejection fraction evaluation by echocardiogram or multi-gated radionuclide angiography between each dose.[65]

Future Therapies

New therapies on the horizon include:

Fingolimod. This oral agent was previously called FTY720. A phase II, 18-month trial showed that patients taking fingolimod 1.25 mg and 5 mg who experienced more than a 50% reduction in ARR during the trial's first 6 months compared to placebo maintained the low relapse rate during the subsequent 12-month extension. Fingolimod's mechanism of action differs from currently approved drugs in that its agonistic action causes T cells to be sequestered in secondary lymph organs, reducing the number available to infiltrate the CNS.[66]

Estriol. The hormonal therapy estriol has been shown to have a positive effect on Gd+ enhancing-lesions on MRI scans.[67] Another trial is currently underway evaluating its effect in conjunction with GA.

Statins. The immunomodulating effects of statins have been shown in animal studies to affect the course of an MS-like disease. A small, open-label trial of simvastatin in 30 individuals with RRMS showed a mean reduction in number of Gd+ lesions of 44% and in volume of lesions of 41% after 6 months of treatment.[68]

Rituximab. This monoclonal antibody primarily works by deleting B cells. It is being studied in relapsing/remitting MS, progressive MS, and neuromyelitis optica.

Other compounds under investigation include minocycline, shown to reduce Gd+ lesions and relapses, and to affect immunological changes related to the disease;[69, 70] T cell vaccines such as NeuroVax and the oral immunological agents teriflunomide and laquinimod.

Several trials investigating various dosages with existing therapies are also underway, including double-dose INFβ-1b and GA dosing with 40 mg. This latter study showed a 38% reduction in Gd+ enhanced lesions over 9 months, with effectiveness seen as early as 3 months.[71]

Summary

In conclusion, clinicians should follow patients closely, push for early treatment given recent long-term data, and be aware of the possible benefits of switching or combining treatments.

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* Dr. Patricia Coyle provided the information during her live presentation.

INTERACTIVE CASE STUDIES FOR CME CREDIT

Case One — Kelly

A 28-year-old previously healthy female presents with a 4-day history of double vision, horizontal gaze palsy and nystagmus. Upon questioning, she admits to a previous episode of bilateral numbness and tingling in her right leg several months ago and to recent fatigue. She denies pain or any loss of visual acuity, or any other neurologic symptoms. Examination reveals nothing else extraordinary. Subsequent MRI of the brain and cervical spinal cord show 3 lesions in the periventricular and spinal cord areas. Serologic testing for connective tissue disorders, sarcoidosis, vitamin B12 deficiency, and CNS infections are negative, although cerebrospinal fluid analysis is positive for oligoclonal bands. Three months later, her symptoms have abated and a follow-up MRI reveals an additional lesion on the thoracic spine, although there is no postcontrast enhancement.

1. You diagnose the patient with CIS. Your next step is:

A. Initiate treatment immediately with glatiramer acetate (GA) or other immunomodulatory therapy and schedule a follow-up within 3 months.

B. Hold off on immediate treatment pending further incidents.

2. By treating her early with DMT, you are minimizing the risk of:

A. Inflammation

B. Demyelination

C. Neurodegeneration

D. All of the above

Case Two — Pauline

Patient B is a 33-year-old woman who was diagnosed with RRMS 23 months ago. She has been receiving weekly injections of IFNβ-1a (Rebif) ever since. Although she has done well, in the past 8 months she has had 1 clinically relevant event. Her EDSS score has increased from 1 to 1.5, and MRI revealed no reduction in Gd+ lesions or T2 lesion burden, although the number and volume of T1 hypointense lesions have increased. You're considering switching her to GA.

1. What test should you conduct first before making a final decision on a new therapy?

A. Depression screen

B. CSF evaluation

C. Neutralizing antibody titer

D. Spinal MRI

Case Three — Stephanie

Patient C is a 38-year-old woman you have been treating for RMSS for 7 years. She presents with symptoms consistent with optic neuritis and some memory loss. She has been maintained fairly well for 6 years now on GA after an initial course of IFNβ-1a was discontinued due to increasing NABs. Other than her MS, she is otherwise healthy. Upon close questioning and examination of her chart, you realize that her relapse rate has increased. Once her attack subsides, you order a brain and spinal cord MRI.

1. What clinical signs are you looking for on the MRI to help you in your decision to switch her to either mitoxantrone or natalizumab?

A. New or recurrent brainstem or spinal cord lesions

B. Increase in Gd+ lesions

C. Increase in T2 lesion load

D. All of the above

CME ATTENDANCE VERIFICATION, EVALUATION AND CREDIT REQUEST FORM

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Evaluation/Case Study Responses

Case Study One — Kelly
Question 1: A B C D
Question 2: A B C D

Case Study Two — Pauline
Question 1: A B C D

Case Study Three — Stephanie
Question 1: A B C D

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