

# Counseling Points™

Enhancing Patient Communication for the MS Nurse

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## Use of Nonconventional Imaging Techniques in Multiple Sclerosis

*A Roundtable Discussion*

It wasn't long ago that magnetic resonance imaging (MRI) was considered high-tech. Today, however, MRI is a basic tool in multiple sclerosis (MS) management, with a growing trend toward use of higher Tesla (T)-strength scans. There is little question that standard T1- and T2-weighted MRI studies remain an important part of MS diagnosis and treatment, but a growing body of evidence shows that newer technologies can provide additional information that is currently missing from conventional MRIs.

For this issue of *Multiple Sclerosis Counseling Points™*, moderator Amy Perrin Ross, two MS nurse practitioners, and a neurologist discussed how newer imaging techniques may affect current and future approaches to MS patient care.



### What is the Role of Conventional MRI in MS?

The most recent diagnostic criteria in MS clearly delineate the importance of MRI in the diagnosis of the disease. The revised

McDonald criteria released in 2005 outline specific MRI criteria consistent with the clinical diagnosis of MS (Table 1).<sup>1</sup>

In addition, standard MRI remains an important tool in monitoring disease pro-

*Continued on page 3*

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# Welcome to MS Counseling Points™

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Dear Colleague,

If you have worked in the field of multiple sclerosis (MS) for a while, you may remember when ordering a magnetic resonance imaging (MRI) scan for a patient seemed like high-tech science. Today, MRI is considered commonplace in MS management. Many of our patients are well-versed in its terminology and are familiar with the inside of “the tube.”

MRI magnet strengths have grown progressively stronger, but there is even more to this technology on the horizon. Nonconventional imaging techniques with more acronyms than a computer manual (MRS, MTR, DTI) are cropping up in research studies and at academic and MS centers near you. Still, how these technologies work and what they can do for your patients remains a source of confusion for many MS practitioners.

For this edition of *Counseling Points™*, two MS nurse specialists, a neurologist, and I discussed advanced imaging approaches in MS. The result was a learning experience for the group that we hope you will find as enlightening as we did. This exciting subject area will warrant frequent updates as the technology continues to advance and the clinical use of these techniques expands. Until then, we hope that this article will give you a taste of what is to come. The next time you study a standard T1- or T2-weighted MRI image from an MS patient, you will have a greater appreciation that much more can be revealed about the pathology of this disease than meets the eye.



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**Table 1. Summary of Current MRI Diagnostic Criteria in MS<sup>1</sup>**

- $\geq 2$  attacks with objective clinical evidence of  $\geq 2$  disseminated lesions
- $\geq 2$  attacks with objective clinical evidence of 1 lesion, *plus*
  - dissemination in space shown on MRI
  - *or*  $\geq 2$  MRI lesions consistent with MS and positive CSF finding
  - *or* 2nd clinical attack implicating a different site
- 1 attack with objective clinical evidence of  $\geq 2$  lesions, *plus*
  - dissemination in time on MRI (gadolinium + spaced by 30 days from initial attack or new T2 lesion based on at least 2 previous MRIs)
  - *or* 2nd clinical attack
- 1 attack with objective clinical evidence of 1 lesion (monosymptomatic presentation, clinically isolated syndrome), *plus both*
  - dissemination in space shown on MRI *or*  $\geq 2$  MRI lesions consistent with MS and a positive CSF finding
  - dissemination in time shown on MRI *or* 2nd clinical attack
- Insidious neurologic progression suggestive of MS *plus*
  - 1 year of disease progression determined retrospectively or prospectively *and* 2 of the following:
    - positive brain MRI result (9 T2 lesions or  $\geq 4$  T2 lesions with positive visual evoked potential)
    - positive spinal cord MRI result with 2 focal T2 lesions
    - positive CSF findings

CSF=cerebrospinal fluid.

Source: Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald criteria." *Ann Neurol.* 2005;58:840-846. Adapted with permission from John Wiley & Sons, Inc.

gression. According to the Consortium of Multiple Sclerosis Centers (CMSC) MRI guidelines, (currently undergoing revisions based on a recent update meeting), follow-up MRI studies after diagnosis of MS and clinically isolated syndrome (CIS) are recommended:

- in cases of CIS for diagnostic purposes;
- in cases where there is unexpected clinical worsening;
- for reassessment of disease burden before starting or modifying therapy; or
- to evaluate suspicion of a secondary diagnosis.<sup>2</sup>

The mechanisms of MRI are extremely complex. Put simply, MRI measures the behavior of hydrogen atoms (also called protons) in water in the body's tissues during exposure to a powerful magnetic field. MRI technology allows targeted areas, including soft tissue, to be converted into three-dimensional images and can help determine the type of tissue that is present.<sup>3</sup>

The trend toward use of higher-field MRI offers a much clearer picture of MS pathology than earlier, lower-strength magnets.

Thus the 3T-strength MRI is gradually replacing 1.5T studies for the evaluation of MS. A 3T scan can identify lesions too small to be detected on a 1.5T scan, in white matter that is normal-appearing on the lower-field scan. In addition, 3T magnets (and far-stronger ones used in research settings) can reveal the presence of inflammatory infiltrates, which show up as small hyperintensities that would be invisible on a 1.5T MRI. These distinctions may be particularly important in the classification of patients with a CIS.<sup>4</sup>

***A 3T scan can identify lesions too small to be detected on a 1.5T scan, in white matter that is normal-appearing on the lower-field scan.***

In addition, it's important for the clinician comparing current and old MRI films to take magnet strength into account. A 3T MRI may show more lesions, but that should not be

## Table 2. Disadvantages of Conventional MRI in MS

- Lack of correlation between MRI findings and clinical outcomes
- Tendency to overlook gray-matter pathology
- Lack of specificity for degree of inflammation, demyelination, and neurodegenerative changes
- Less specificity for identifying remyelinated lesions
- May miss microscopic pathology in normal-appearing white matter and gray matter
- Incomplete picture of total burden of CNS disease

CNS=central nervous system; MRI=magnetic resonance imaging; MS=multiple sclerosis.

taken to indicate increased burden of disease if it is being compared against a 1.5T scan.

### What Is Missing From Conventional MRI?

With the evolution of newer, more specific measures of disease onset, progression, and neuroprotection, conventional MRI falls short in a number of areas (Table 2). For example, conventional MRI can provide a great deal of information about specific lesions, but there is a puzzling lack of correlation between lesion volume and the patient's level of clinical disability.<sup>5,6</sup> In addition to lesion volume, normal-appearing brain tissue may not show the extent of neuronal loss and thus can appear quite similar in two MS patients who exhibit very different levels of disability.<sup>7</sup>

Normal-appearing white matter and gray matter—areas of the brain without visible lesions—are a subject of growing interest in MS research. “Normal-appearing” is the operative term, because they are not unaffected by the disease process. Gray-matter atrophy, in particular, is believed to be the source of much of the disability seen in MS, yet it appears normal on conventional MRI images.<sup>8,9</sup>

***Normal-appearing white matter and gray matter—areas of the brain without visible lesions—are a subject of growing interest in MS research.***

In addition, conventional MRI does not differentiate between inflammatory and demyelinating conditions. At one time, it was believed that inflammation was the primary or even the sole mechanism in early MS. Chronic demyelination and tissue atro-

phy were thought to occur only after a prolonged inflammatory stage. However, newer imaging approaches show evidence that structural changes in myelin, neurons—including the cell body, dendrites, axons, and myelin sheath—occur earlier in the disease process than previously believed.<sup>10,11</sup>

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***Conventional MRI does not differentiate between inflammatory and demyelinating conditions.***

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Finally, what about remyelination? This aspect of MS pathology is not well understood, including which lesions will remyelinate and how they function after remyelination. Some researchers have suggested that the reason there is little correlation between MRI and clinical findings is because standard T1- and T2-weighted scans do not show the difference between demyelinated lesions and those that are partly or even fully remyelinated.<sup>6</sup>

### What Is Nonconventional Imaging?

Newer imaging technologies used in MS are often grouped together under the term “nonconventional” or “unconventional” imaging. The technologies discussed in this article are outlined in Table 3. Most of the imaging techniques we call nonconventional are actually based on MRI principles.

Each of these technologies offers advanced information about the neuropathology of MS. One feature they have in common is their ability to identify prelesional damage; that is, damage in normal-appearing white matter and gray matter that will eventually turn into a visible MS lesion. In addition, since these technologies are more specific to the pathological

substrate in MS, they correlate better with clinical disability and disease progression than do conventional MRI metrics.

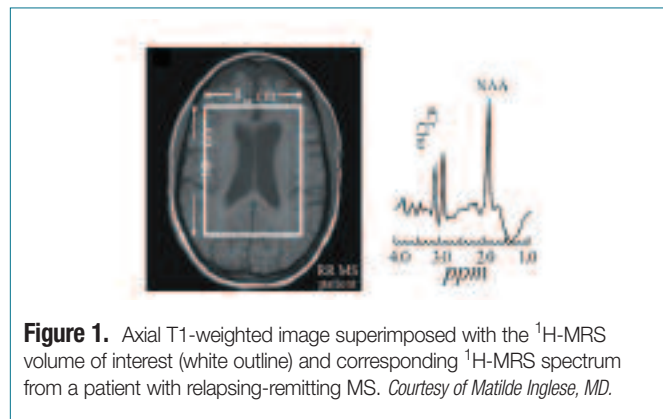
### Proton Magnetic Resonance Spectroscopy (<sup>1</sup>H-MRS)

MRS technology is similar to that of MRI, except that the signal received is not based on protons in water, but on protons in other molecules found in human tissue. In MS patients, one of the most interesting metabolites being measured via MRS is N-acetylaspartate (NAA), a metabolite that is located exclusively in neurons, dendrites, and axons (**Figure 1**).

We now know that NAA levels are an accurate surrogate marker for neuronal loss and/or dysfunction in MS lesions, normal-appearing white matter, and normal-appearing gray matter.<sup>11</sup> Levels of NAA in the brains of people with MS tend to decrease by approximately 4% to 6% per year.<sup>12</sup> A common way to quantify NAA is in relation to creatine (Cr) since it has a constant measure: NAA/Cr is a ratio that has been shown to correlate strongly with disability in MS.<sup>13</sup> <sup>1</sup>H-MRS can be used to determine whether NAA quantities have increased, decreased, or remained stable following the introduction of a disease-modifying therapy (DMT).

Decreased levels of NAA in the brain may reflect not only loss of neurons (cell body, dendrites, and axons), but also dysfunction in the mitochondria of these neurons and axons. This means that the structures are still present but may not be functioning properly.<sup>14</sup>

Some DMTs for MS have been shown to partially reverse this decrease of NAA at the stage of neuroaxonal dysfunction—while the cells are injured but not gone. Data presented



**Figure 1.** Axial T1-weighted image superimposed with the <sup>1</sup>H-MRS volume of interest (white outline) and corresponding <sup>1</sup>H-MRS spectrum from a patient with relapsing-remitting MS. *Courtesy of Matilde Inglese, MD.*

by Arnold and colleagues at the 2008 European Committee for Treatment and Research in MS (ECTRIMS) meeting in Montreal showed that treatment with glatiramer acetate (GA) helped to maintain NAA levels in a subgroup of patients with CIS.<sup>15</sup> Treated patients had increased NAA levels at 12 months that were maintained at 24 months, compared with a loss of NAA seen in the placebo group at 12 and 24 months.<sup>15</sup> Thus, MRS findings support the concept that DMTs offer tissue-protective as well as anti-inflammatory effects that minimize the progression of disease and disability.

<sup>1</sup>H-MRS studies are notoriously challenging to perform and to interpret, but progress has been made recently in standardizing results across centers.<sup>15</sup>

### Magnetization Transfer Imaging (MTI)

MTI is a technique based on MRI principles, but with modifications that allow for differentiation between protons that are relatively fixed (such as to myelin) and those that are free in surrounding tis-

**Table 3. What Techniques Are Considered Nonconventional?**

Proton MR spectroscopy	<sup>1</sup> H-MRS	<ul style="list-style-type: none"> <li>Measures brain metabolites such as NAA, a marker of neuroaxonal integrity</li> </ul>
Functional MRI	fMRI	<ul style="list-style-type: none"> <li>Measures changes in blood oxygenation</li> <li>Shows brain adaptation from injured areas</li> </ul>
Diffusion tensor imaging	DTI	<ul style="list-style-type: none"> <li>Identifies early neuronal/myelin injury in MS</li> </ul>
Magnetization transfer imaging	MTI	<ul style="list-style-type: none"> <li>Measures myelin integrity imaging</li> </ul>

NAA= N-acetylaspartate.

sue. From the acquired MTI images, it is possible to calculate the magnetization transfer ratio (MTR) which is an index of tissue integrity. MTR maps can be evaluated with two approaches: by drawing specific areas of interest in brain regions or by evaluating the whole brain by means of histogram analysis.

MTR results in MS patients reflect the state-of-tissue integrity in myelin and its associated structures. Post-mortem studies have shown that MTR values correlate well with myelin content in brain tissue from MS patients.<sup>16,17</sup> Changes on MTR have also been shown to correlate with clinical disability in MS.<sup>18,19</sup> Importantly, MTR may allow for prediction of MS lesion development several months before these areas of injury are visible using conventional imaging. Interestingly, unlike conventional MRI scans, MTR has the specificity to distinguish between MS lesions that are undergoing remyelination and those that are demyelinating.<sup>20</sup> MTR can also be used to identify areas of demyelination outside of MS lesions, in the normal-appearing white matter and gray matter.

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### *Post-mortem studies have shown that MTR values correlate well with myelin content in brain tissue from MS patients.*

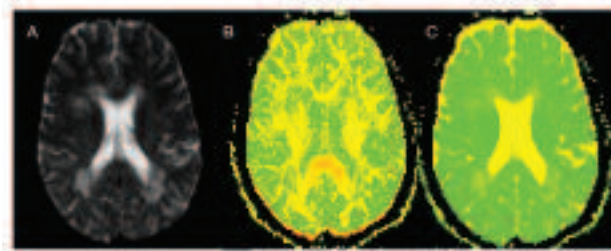
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MTR can be used to determine whether lesion evolution is altered by disease-modifying drugs. In a study conducted at the National Institutes of Health, MTR values of 225 contrast-enhancing lesions in four RRMS patients treated with either interferon  $\beta$ -1b (IFN $\beta$ -1b) or intravenous methylprednisolone (IVMP) were compared at baseline and serially for 12 months.<sup>21</sup> Lesion recovery following treatment with either drug was significantly higher compared to baseline, demonstrating that IFN $\beta$ -1b and IVMP reduce tissue damage and promote lesion recovery in RRMS.<sup>21</sup>

From a technical standpoint, MTR studies are easier to perform and more straightforward to interpret than <sup>1</sup>H-MRS studies.

#### **Diffusion Tensor Imaging (DTI)**

DTI (similar to diffusion-weighted imaging, or DWI) is another technology stemming from standard MRI approaches. In some centers, DTI is already part of the conventional MRI protocol for MS and thus does not add to the cost of ordering or



**Figure 2.** Axial T2-weighted image (A), color-coded fractional anisotropy (FA) map (B), and mean diffusivity (MD) map (C) from a patient with MS. FA and MD are derived from diffusion tensor images (DTI) and reflect fiber and cell integrity, respectively. *Courtesy of Matilde Inglese, MD.*

the acquisition time. DTI involves scanning from a number of different directions to determine the average diffusivity profile of the tissue, which is expressed as entropy. This technology is well known for its application in patients with suspected stroke, to detect brain changes earlier than would be possible using computed tomography (CT) scanning.

DTI offers a broad range of clinical applications in MS. As an adjunct to conventional MRI, these additional views provide a more complete picture of white matter, gray matter, and the whole brain to evaluate overall tissue impairment, with higher diffusivity correlating with greater tissue injury (**Figure 2**).

Recent studies suggest that DTI may be useful in predicting cognitive impairment in MS, an important aspect of MS that does not always correlate well with other radiological or physical findings in MS. Benedict and colleagues studied 60 MS patients (mean disease duration of  $12.8 \pm 8.7$  years) and found significant correlations between DTI results and performance on all cognitive domains of standard neuropsychological tests.<sup>22</sup> The area most strongly associated with DTI entropy was that of processing speed and working memory.

#### **Functional MRI (fMRI)**

The fMRI is an imaging technique with important applications in MS. During the MRI scan, the patient is asked to perform mentally challenging or small-motor tasks while alterations in blood oxygenation are measured.

As with other emerging techniques, fMRI is another tool that helps to bridge the gap between conventional MRI and clinical outcomes. It shows that patients with MS activate several areas of the brain to accomplish simple physical tasks, while normal control subjects might activate only one area (showing cortical activity) for the same task. This is evidence of neuronal recruitment, in which the MS patient compensates for deficits by acti-

vating gray-matter “reserves” in the brain. This phenomenon helps explain why some MS patients with large lesion volumes can still function relatively well.<sup>8</sup>

Unfortunately, when these compensatory reserves run out, rapid functional decline often occurs in a patient who was previously doing well. Thus, fMRI might help to identify patients who are candidates for more aggressive DMT even if they appear to be stable clinically.

## What Advantages Do New Imaging Technologies Offer Our MS Patients?

It's not difficult to see how information from nonconventional imaging methods contribute to the body of MS research, but what are their applications in day-to-day clinical practice?

Much of the diagnostic process for MS is still firmly based on conventional MRI studies, but nonconventional approaches may be particularly useful for further evaluation of patients with CIS (Table 4). As many as 80% of young people with MS have an early disease process characterized by CIS, and advanced imaging techniques may reveal abnormalities in the white and gray matter of these patients that are not evident with standard studies.<sup>23</sup>

Nonconventional imaging approaches also offer intriguing possibilities for patient follow-up, especially for managing those patients with an incomplete response to treatment. One of the frustrating aspects of studying DMTs in MS has been their inconsistent correlation with clinical outcomes, as well as the inability to predict which patients will do well on a particular therapy. For patients who are not responding well to a specific DMT, being able to more closely examine the burden of

disease and the behavior of individual lesions may allow clinicians to better tailor therapies.

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*fMRI might help to identify patients who are candidates for more aggressive DMT even if they appear to be stable clinically.*

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Advanced imaging will continue to build our knowledge about the mechanisms of DMTs and their role in neuroprotection.<sup>24</sup> <sup>1</sup>H-MRS, in particular, is of interest for this purpose because of its ability to show changes in disease markers such as NAA as a result of treatment. For example, using a combination of standard MRI and <sup>1</sup>H-MRS, Khan and colleagues were able to demonstrate axonal metabolic recovery and neuroprotection from administration of GA.<sup>12</sup>

## Clinical Use of Nonconventional Imaging: What Does the Future Hold?

Despite their great potential, there are several limitations to the technologies discussed here (Table 5). Many are not widely available outside of major academic centers, and in some cases their use may be more appropriate in research settings involving large numbers of patients than for evaluating individual patients. Some techniques require a high degree of skill and experience on the part of the technicians conducting the tests and the clinicians who interpret the results. Furthermore, the cost of performing additional, sophisticated testing will clearly

### Table 4. Potential Advantages of Nonconventional Imaging

- Evaluation of patients with CIS
- Better correlation with clinical outcomes in MS, including cognitive impairment
- Detect changes in myelin and axonal structures earlier in disease course
- Quantify remyelination and demyelination in lesions
- Quantify gray-matter atrophy
- Quantify tissue injury in whole brain or in small areas
- Provide quantitative surrogate markers of disease
- Show compensatory recruitment of gray-matter reserves

CIS=clinically isolated syndrome.

## Table 5. Limitations to Nonconventional Imaging

- Availability
- Cost
- A high degree of skill is required for performing and interpreting them
- Results are not standardized across different centers
- Their use is not reflected in clinical practice guidelines
- They may be better suited for trials with larger numbers of patients than the clinical setting

be an important factor to consider. Costs of these tests will have to be weighed against their potential benefit in improving the delivery and selection of DMTs and/or helping to reduce costly and devastating disability among patients with MS.

It may be too early to reach a consensus as to how and when these techniques should be used and incorporated into the current treatment recommendations for MS. Given the potential value of the new information they can provide, however, it is likely that their availability and standardization will expand quickly to complement existing MRI protocols. Therefore, clinicians need to understand what these nonconventional imaging are, as well as recognize their tremendous potential for providing valuable information to maximize and individually tailor patient care.

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# MS Counseling Points™

## Use of Nonconventional Imaging Techniques in Multiple Sclerosis

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- A growing body of evidence shows that newer technologies can provide additional information that is currently missing from conventional magnetic resonance imaging (MRI).
- 3 Tesla-strength MRI can identify lesions too small to be detected with a 1.5T MRI and can reveal the presence of inflammatory infiltrates.
- Conventional MRI does not correlate well with clinical disability in multiple sclerosis (MS), does not show minute damage in “normal-appearing” white and gray matter, and cannot distinguish between demyelinated and remyelinating lesions.
- Proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS) is used to measure levels of N-acetylaspartate (NAA), a brain-specific metabolite that is an accurate surrogate marker for neuronal loss in MS.
- Decreased NAA levels represent greater tissue loss in MS, but these levels may be partially reversed by disease-modifying therapies (DMTs).
- Magnetization transfer ratio (MTR) measures tissue integrity in myelin and associated structures. MTR may allow for prediction of lesion development months before these areas are visible on conventional images.
- Diffusion tensor imaging (DTI) has a range of clinical applications and is part of the standard MRI protocol for MS in some centers. One interesting application of this technology is in the evaluation of cognitive impairment.
- Functional MRI (fMRI) can be used to identify how gray-matter reserves help to compensate for damage in other brain regions. Some patients may function well clinically despite an extensive lesion load, but when gray-matter reserves are depleted there may be a rapid clinical decline.
- Clinically isolated syndrome (CIS) and incomplete response to a DMT are some settings for which advanced imaging techniques seem to hold particular promise.
- Updates of MS practice guidelines may someday need to incorporate use of non-conventional imaging.

## Proton magnetic resonance ( $^1\text{H-MR}$ ) spectroscopy detects metabolic changes in normal-appearing white matter

A total of 51 subjects—including 31 patients with a clinically isolated syndrome (CIS) and 20 healthy controls—participated in a study to detect metabolic changes in normal-appearing white matter (NAWM) and correlate them with magnetic resonance imaging (MRI) findings. Multisequence 3.0 Tesla MRI of the brain was performed, along with single-voxel  $^1\text{H-MR}$  spectroscopy of the parietal NAWM, which can detect concentrations of the metabolites N-acetyl-aspartate (NAA), decreases in which indicate axonal damage, and myoinositol (Ins), increases in which suggest inflammatory disease activity.

Although Ins concentrations were normal,  $^1\text{H-MRS}$  showed CIS patients had lower NAA concentrations than controls (-8.1%;  $P=0.012$ ); NAA levels were decreased in the ratio to other metabolites, such as choline (-11.6%;  $P=0.035$ ) and creatine (-8.9%  $P=0.010$ ). MRI showed 2 CIS patients with no lesions, and 29 patients with inflammatory lesions. There were no significant correlations in metabolite concentrations among patients with and without a lesion dissemination in space.

The authors state that conventional MRI and diagnostic criteria do not necessarily correspond with disease activity in its early stages. If the findings that metabolic changes can demonstrate early MS activity in the NAWM are corroborated in additional studies, spectroscopy may prove useful for supporting the diagnosis of definitive MS in patients with CIS.

Wattjes MP, Harzheim M, Lutterbey GG, et al. High field MR imaging and  $^1\text{H-MR}$  spectroscopy in clinically isolated syndromes suggestive of multiple sclerosis. *Journal of Neurology*, 2008;255:56-63.

## New oral agent for MS in clinical testing

Participants from 51 centers in nine countries ( $N=306$ ) with RRMS and at least one gadolinium-enhancing (GdE) lesion during the past year were randomly assigned to receive either 0.6 mg or 0.3 mg of laquinimod, a new oral agent, or placebo daily for 36 weeks in a double-blind, placebo-controlled, phase-IIb study.

The adjusted mean cumulative number of GdE lesions on MRI in the laquinimod 0.6 mg arm was 40.4% lower than in the placebo group (mean=4.2 vs. 2.6,  $P=0.0048$ ) between weeks 12 and 36. The 0.3 mg dose of laquinimod did not reduce the rate relative to placebo. The annual relapse rate in the 0.6 mg laquinimod group was 0.52 vs. 0.77 for the placebo group ( $P=0.3297$ ).

Both laquinimod doses were well tolerated, although slight, dose-dependent increases in liver enzymes occurred.

The authors concluded that 0.6 mg of laquinimod is a promising, convenient treatment for MS that effectively slows MRI-measured disease activity and tissue destruction without increasing serious risks or side effects over the 0.3 mg dosage. A phase III trial is further assessing its benefits and costs.

Comi G, Pulizzi A, Rovaris M, et al. Effect of laquinimod on MRI-monitored disease activity in patients with relapsing-remitting multiple sclerosis: A multicentre, randomised, double-blind, placebo-controlled phase IIb study. *The Lancet*. 2008;371:2085-2092.

## Osteopontin may play important role in CNS inflammation

Elevated levels of osteopontin, a phosphoprotein, are associated with MS disease progression and relapse in animal models. A case-control study was conducted to evaluate osteopontin levels in the cerebrospinal fluid (CSF) of MS patients and in those with other inflammatory neurological diseases and compare them to CSF levels in case-control patients with non-inflammatory neurological disorders.

Of the 62 patients who participated, 27 had MS, 11 had another neurological inflammatory disorder, such as neurosarcoidosis, and 24 had a non-inflammatory neurological disease, such as intracranial hypertension. No patient was having an active relapse at the time of osteopontin measurement. CSF samples were also tested for other pro- and anti-inflammatory cytokines, including interleukin-12 (IL-12), IL-10, and metalloproteinase 9 (MMP9).

The levels of osteopontin in the CSF of both the MS group and those with other inflammatory neurological disorders were significantly higher than the osteopontin levels in the CSF of patients with non-inflammatory neurological disorders (415 ng/mL, 563 ng/mL, and 286 ng/mL, respectively). Osteopontin levels correlated with the pro-inflammatory IL-12 cytokine but not with the anti-inflammatory IL-10. MMP9 could not be detected. Furthermore, there was no correlation between osteopontin levels in the plasma and the CSF, Expanded Disability Status Scale score, or time since last relapse.

These findings suggest that increased levels of osteopontin in the CSF of MS patients may play an important role in central nervous system inflammation.

Bratic M, Nunan R, Niepel G, et al. Increased osteopontin levels in the cerebrospinal fluid of patients with multiple sclerosis. *Archives of Neurology*. 2008; 65:633-635.

# MS Counseling Points™

## Use of Nonconventional Imaging Techniques in Multiple Sclerosis

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