

Counseling Points™

Enhancing Patient Communication for the MS Nurse

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LONG-TERM USE OF DISEASE-MODIFYING THERAPY *A Roundtable Discussion*

One of the definitive studies on the natural history of multiple sclerosis (MS), published in 1995, suggests that 20% to 40% of patients have “benign” or “mild” disease.¹ However, the authors cautioned, this term is somewhat misleading: While it is defined as less than moderate disability after 10 years, many patients with benign or mild disease will eventually become disabled. Indeed, 50% will devel-

op progressive disease within 10 years, and within 15 years of the onset of MS, will require some form of walking aid.¹

Before the introduction of the first disease-modifying therapy (DMT) in 1993, clinicians were limited to treating symptoms and offering ancillary treatments, such as physiotherapy and occupational therapy. Patients had little in the way of hope and were destined to become progressively disabled.

Today, with the use of DMTs, the clinical picture is much brighter.

Positive Effects of DMTs

Data from retrospective analyses and open-label extension of trials of DMTs and anecdotal experience suggest that patients taking these agents experience fewer and less severe relapses and less disability than patients who elect not to initiate therapy. Added benefits of DMT are a reduced

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WELCOME TO MS COUNSELING POINTS™

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Dear Colleague,

When patients with multiple sclerosis (MS) start treatment with a disease-modifying therapy (DMT), it is important they realize they are making a life-time commitment. That is not to say that they may not eventually switch therapies at some point, but whichever drug they are taking, they will probably need to use it for the rest of their lives.



This concept can be quite overwhelming for some patients. Thus, it is important for clinicians to develop a close therapeutic relationship with patients from the outset. Clinicians must emphasize the importance of adherence, and be able to identify as time progresses any concerns or problems patients may experience with their therapy.

When educating patients about therapy, perhaps the most important message is one of hope—DMT has been available for close to 15 years and during that time clinicians have seen these agents change the natural history of the disease, allowing patients to live full and active lives.

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need for the short-term administration of corticosteroids, which are used to dampen the inflammatory processes associated with relapses, and less impact on employment and the activities of daily living.

Many patients with benign or mild disease will eventually become disabled.

Interferon β -1b, administered subcutaneously (SC) every other day was the first agent to be approved for use (1993) in the United States for relapsing-remitting MS (RRMS). Data presented at the annual American Academy of Neurology meeting in 2006 suggested that patients who had been taking the drug for up to 16 years had slower disease progression compared with those who had not been on long-term therapy.² In this study, the researchers were able to locate 328 of 371 patients who had been enrolled in the original pivotal trial.

Pre-injection Warm Compress Reduces Local Site Reactions

Applying a warm compress 5 minutes before administering a glatiramer acetate injection can help relieve local injection-site reactions, according to a study presented at the annual Consortium of Multiple Sclerosis Centers meeting held in June 2006.

Helen Jolly, RN, MSCN, lead investigator on the study, said the warm compress was particularly useful in reducing redness, pain, and swelling around the injection site.

A total of 50 patients were involved in this open-label, randomized, single-crossover study. Patients adhered to their usual injection routine for 14 days, and used Kwik-Heat Instant Hot Packs 5 minutes before injecting for an additional 14 days. The order of regimens was randomized and counter-balanced across patients, and patients were asked to record local injection-site reactions in a diary on a daily basis throughout the trial.

“Overall, using the warm compress resulted in significantly fewer reactions than not using it,” according to Ms. Jolly, clinical nursing manager at the Neurological Institute of South Florida in Miami. When the compress was applied, significantly fewer patients reported redness immediately and at 2 and 5 minutes after injection ($P=0.041$; $P=0.041$; and $P=0.008$, respectively). “Pain was significantly reduced immediately and at 2 minutes, but not at 5 minutes, after injection,” Ms. Jolly noted. Swelling, which was described as a raised area at the injection site, was significantly lessened at both 2 and 5 minutes ($P<0.001$), but not immediately post-injection. “When the compress was used, reactions were described as significantly less bothersome,” Ms. Jolly added.

“A lot of patients prefer to administer glatiramer acetate after a warm shower,” she said. “However, for patients who experience moderate-to-severe local injection-site reactions, we recommend using a warm compress for 5 minutes before injecting.”

Among the patients who reached Expanded Disability Status Scale (EDSS) level 6.0, those on long-term interferon β -1b treatment reached this endpoint after a median of 13 years compared with 7 years for patients on short-term treatment. Long-term treatment was defined as use of interferon β -1b for more than 80% of the time since the start of the pivotal trial (about 12 years or longer), while short-term treatment referred to use for less than 10% of the time (about 1.6 years or less). It should be noted that the patients were not followed after completion of the original trial; rather, the investigators only gained a “snapshot” of how patients were doing at a point in time some years after the trial ended, which has led some clinicians to question the generalizability of these data.

Data from retrospective analyses and open-label extension of trials of DMTs and anecdotal experience suggest that patients taking these agents experience fewer and less severe relapses and less disability than patients who elect not to initiate therapy.

Recently, a retrospective evaluation of patients originally treated in the interferon β -1a administered by intramuscular injection once-weekly pivotal clinical trial was published.³ Among 160 patients at an 8-year follow-up assessment, 42% and 29.1% of the original placebo and treated patients reached an EDSS score of >6 , respectively.

4 The 10-year results of a prospective, open-label study of glatiramer acetate were also published in 2006.⁴ In this ongoing study, patients are examined every 6 months. To gather data for the 10-year results, the researchers performed three separate evaluations. The first was described as a “modified intention to treat” (mITT) analysis and included patients who had received at least one dose of glatiramer acetate since 1991 (n=232). “Ongoing” patients were those who had continued to take the

drug for up to 12 years (mean 10.1 years) through November 2003 (n=108). “Withdrawn” patients were assessed at a 10-year follow-up visit (n=50 of the 124 withdrawals). Mean exposures were 6.99, 10.1, and 4.26 years, respectively. While patients in the mITT group were on glatiramer acetate, relapses decreased from 1.18/year to one relapse every 5 years. The median time to ≥ 1 point increase in EDSS score was 8.8 years. Overall, nearly 60% of these patients were described as having stable or improved EDSS scores, defined as an increase of ≤ 0.5 point, no change, or a decrease in EDSS score from onset of treatment. Among ongoing patients, EDSS scores increased 0.5 points, and 62% were described as stable or improved since starting therapy with glatiramer acetate in 1990 to 1992. Among withdrawn patients, 10-year follow-up revealed an increase in EDSS of 2.24 points, with 28% being described as stable or improved. Ninety-two percent of patients (mean disease duration 15 years) remained ambulatory while taking glatiramer acetate. Because these patients were followed in a prospective fashion, clinicians feel more comfortable with the validity of these data.

While patients in the mITT group were on glatiramer acetate, relapses decreased from 1.18/year to one relapse every 5 years.

In the pivotal trial of interferon β -1a via subcutaneous injection three times weekly, 68% of enrolled patients attended a follow-up visit at 7 to 8 years after baseline.⁵ Of these, 72% were still receiving interferon β -1a. Patients who had originally been randomized to receive 44 mcg three times weekly showed lower EDSS score progression and relapse rates than did those who were originally randomized to receive placebo and were switched to active treatment after 2 years. This follow-up study confirms that the earlier a treatment is started, the greater the benefit. In other words, it’s hard to catch up.

Anecdotal experience confirms the findings of these long-term evaluations. However, it should be

noted that care must be taken when evaluating the results of long-term clinical analyses, as previously stated. Clinicians should be aware of whether the patients were followed prospectively or contacted at a later point to gather information retrospectively or to get a “snapshot” of what is happening with that patient at one point in time.

Practical Issues

Patients newly diagnosed with MS must not only come to terms with the realization that they have a chronic disease, but also the knowledge that they are facing a lifetime of therapy. When initiating discussions about DMTs, it is important to emphasize the positive aspects of treatment first. Clinicians can now confidently tell patients that there is an ever-growing pool of data and anecdotal experience confirming that DMTs reduce the rate of relapses and slow the progression of disease. The first message should be one of hope.

A consensus statement on disease management published by The National Multiple Sclerosis Society recommends that therapy be started as soon as possible following a definite diagnosis of MS.

Getting Started

Naturally, many patients are reluctant to even contemplate beginning a therapy that requires them to self-inject or be injected by a caregiver. Clinicians need to use their powers of persuasion to convince patients that it is advisable to initiate therapy as early as possible after diagnosis and that the idea of self-injecting, once a routine is established, often turns out to be worse than the reality. A consensus statement on disease management published by The National Multiple Sclerosis Society recommends that therapy be started as soon as possible following a definite diagnosis of MS, noting that irreversible damage to nerve axons can occur early in the disease and that central nervous system (CNS) lesions and brain atrophy can occur even in patients without symptoms or relapses.⁶

Managing Expectations

Perhaps the most important task of clinicians caring for patients with MS is setting realistic expectations. Yes, DMTs will reduce the rate of relapses and slow disease progression. The important words to emphasize here are “reduce” and “slow.” These drugs are not a cure, so patients should be made aware that they may occasionally experience a relapse and eventually notice some permanent neurological disability.

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When discussing initiation of therapy with patients, it is important to stress that the success of any DMT will depend on where the patient is in his/her disease course and the specific sites of demyelination within the CNS when the medication is started. Patients who have had MS for several years and/or those who have extensive spinal disease may not respond as well as others.

While expectation-setting is essential when beginning therapy, it also pays to revisit this issue over time.

While expectation-setting is essential when beginning therapy, it also pays to revisit this issue over time. Patients who experience a relapse might become disheartened and less inclined to continue therapy. Others may become overconfident, thinking that because they have not had any flare-ups or problems, they can afford to skip a dose or two, or cut the number of injections from seven to five times weekly, or every other day to every third day, or from three times a week to twice a week. If a patient is experiencing severe side effects, such as flu-like symptoms as seen with interferons, from their medication, it may be pragmatic to reduce the dose, at least temporarily, rather than have the patient stop therapy altogether. Alternatively,

patients may consider, in consultation with their clinician, switching therapy

Importance of Education and Follow-up

From the very first day of diagnosis, clinicians must adopt the role of educator. This is particularly true when DMT is being initiated. Patients who feel confident and competent about self-injection are more likely to adhere to therapy in the long term. A recent study showed that treatment-naïve patients who were judged as being competent in self-injection from the outset of DMT were more likely to remain adherent at 1 year than those who were not rated as competent.⁷ In addition, greater improvement in self-injection competency at 30 days was a predictor of greater adherence at 12 months. This highlights the need for education on appropriate injection techniques and regular reassessment.

Patients who feel confident and competent about self-injection are more likely to adhere to therapy in the long term.

In the first year after initiation of therapy, patients should be followed at 3- and 6-month intervals—not only to check on their physical status, but also to reinforce the importance of correct injection technique, site rotation, and adherence. During the first year, many clinicians ask patients to self-inject during these follow-up visits to evaluate technique. It is probably worthwhile having patients self-inject during a visit at least once a year thereafter. Patients sometimes tend to get complacent and cut corners when injecting, which can lead to problems such as failure to fully inject the medicine or loss of asepsis.

When following up with patients, it is crucial to be specific in questioning them. General questions such as “Are you injecting properly and rotating sites?” will probably not expose any problems patients may be experiencing. Clinicians should not only ask patients to self-inject in the office, but also inspect injection sites to check for any signs of abscesses or reactions. If patients complain of

injection site reactions, there are some simple steps that can be taken to avoid these. A study presented at the 2006 Consortium of Multiple Sclerosis Centers meeting found that using a warm compress 5 minutes prior to injecting glatiramer acetate reduces the incidence of pain, redness, and swelling (see box, page 3).⁸

Many clinicians ask patients to self-inject during follow-up visits to evaluate technique.

If patients are having difficulties with self-injecting, clinicians should ask if there is a family member or other person who can administer injections. If necessary, the clinician can arrange for a visiting nurse to administer injections.

Long-term Side Effects

The side effects of DMTs can be managed. Usually the flu-like symptoms associated with the interferons can be controlled with prophylactic non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, as well as initial dose titration. Over the long-term, it is important for clinicians to ask patients if they are continuing to experience these side effects. Anecdotally, many patients skip interferon injections on the weekends because they do not want to be bothered with flu-like symptoms. Reinforcing the value of premedication may help overcome this problem to some extent. There have also been some reports of depression associated with MS. Thus, clinicians should monitor patients' psychological as well as physical status.

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Some patients taking interferons may experience increases in liver enzyme levels. Patients on interferon therapy should be routinely monitored for laboratory abnormalities, per prescribing instructions. A relatively rare problem associated with use



of interferons in MS is thyroid dysfunction. As well as being used for MS, type I interferons are prescribed to treat chronic viral hepatitis and several hematological and solid tumors. A literature review reveals an overall mean prevalence of incident thyroid dysfunction of 6.2%, hypothyroidism occurring more frequently (3.9%) than hyperthyroidism (2.3%).⁹ Thyroid dysfunction is mainly subclinical, and spontaneous resolution occurs in almost 60% of patients with or without withdrawal of interferon. All patients prescribed interferons should have a baseline thyroid stimulating hormone level performed; it may also be worthwhile to repeat this test annually.

Whenever patients complain of side effects, clinicians should ask about other medications they are taking.

Whenever patients complain of side effects, clinicians should ask about other medications they are taking. Patients should be advised to share this list of medications with their primary care physician and specialists when new drugs are prescribed. There is always the chance that side effects may

occur due to other medications or to drug-drug interactions.

Conclusions

The introduction of DMTs has changed the course of MS therapy over the past 15 years. When initiating therapy with these agents, clinicians must be sure to communicate to patients what the drugs can and cannot do. Long-term data suggest that DMTs continue to reduce the incidence and severity of relapses and slow disease progression. However, patients must understand that these drugs are not cures.

Because patients are faced with a lifetime of self-injection, clinicians must be vigilant in ensuring that patients remain adherent to their treatment regimens. Regular assessment of injection technique and injection sites is essential, as is in-depth questioning of patients regarding any problems they may be experiencing.

The message that patients need to hear is one of hope. Before the introduction of DMTs, there was little that clinicians could offer their patients other than symptomatic management and ancillary therapy. Now, thanks to DMTs, patients can look forward to living full and active lives.

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MS COUNSELING POINTS™

Long-term Use of Disease-modifying Therapy

- Always emphasize the positive aspects of disease-modifying therapy (DMT).
- Remind patients that starting treatment with a DMT is a significant commitment that will continue until something better is developed.
- Stress that starting therapy sooner rather than later reduces the risk of relapses and disease progression.
- Inform patients that data from DMT trials and anecdotal experience suggest that patients taking these agents experience fewer and less severe relapses and less disability than patients who elect not to initiate therapy.
- Set realistic expectations about what DMTs can and cannot do.
- Instill a sense of competency—patients who feel confident and competent about self-injection are more likely to adhere to therapy in the long-term.
- In the first year following initiation of therapy, perform follow-ups at 3- and 6-month intervals, not only to check on patients' physical and psychological status, but also to reinforce the importance of correct injection technique, site rotation, and adherence.
- Have patients self-inject during an office visit at least once a year.
- Be specific in questioning patients about injection technique and problems, side effects, and concomitant medications.



In the Literature

RELAPSE RISK IN MS DUE TO SYSTEMIC INFECTIONS

In this prospective, uncontrolled study, 60 patients with relapsing-remitting multiple sclerosis (MS), most of whom were on immunomodulatory therapy, were prospectively monitored for changes in disease status in relationship to systemic infections.

Over an average follow-up of 20 months, 53 patients had 127 infections for an average of 1.2 infections per year. Of the 127 infections, the cause was documented in 73 (57%). Clinically, there was a marked spike in the number of clinical relapses that peaked 2 weeks after the onset of systemic infections. By week 5, the number of relapses had fallen back to baseline. An increase in cells producing such cytokines as interleukin-12 (IL-12), tissue necrosis factor alpha (TNF- α), and interferon gamma (IFN- γ) also peaked at about 2 weeks after the onset of infection. While these cytokines were nonspecific, additional experiments suggested that autoreactive T cells could be stimulated by these increases in the presence of a cognate antigen. In a subgroup being followed with magnetic resonance imaging, an increase in gadolinium-enhancing lesions at week 2 of the at-risk period after infection was also observed.

Overall, the study contributes to other evidence that systemic infections increase the risk of MS relapses. During the at-risk period in the weeks following a systemic infection, the relative risk of an acute exacerbation was increased by 3.2-fold relative to a period in which there was no episode of infection. The authors noted that there was no discernible difference in the risk of MS relapse for bacterial versus viral infections. Although the authors cautioned that this study may be criticized because of its lack of blinding, they indicated that this is an attractive area of research to pursue pathways of MS disease and to identify new opportunities to prevent relapses.

Correale J, Fiol M, Gilmore W. The risk of relapses in multiple sclerosis during systemic infections. *Neurology*. 2006;67:652-659.

ROLE OF DEMYELINATION IN CONTRIBUTING TO AXONAL LOSS IN MS

In this study, postmortem material was gathered from the cerebrum, brainstem, and spinal cord of 55 individuals with MS, ages 25 to 83 years. The major objective of the study was to place plaque as a total of white matter area into relationship with axonal density and total axon number. Both plaque load and axonal loss were quantified through software image analysis using standardized techniques.

When compared with control specimens taken from individuals without a diagnosis of MS, there was a significant reduction in axonal number and density. Plaque load was more variable, although average measures were similar for men and women. Total plaque load did not correlate with brain weight or with duration of disease.

The findings of this study are consistent with a series of recent evaluations that have demonstrated substantial loss of axons in areas not clearly affected by demyelination. These findings challenge the plaque-centered view of axonal damage. They support the possibility that neurodegeneration may take place independent of inflammatory demyelination related to plaque formation. However, the authors suggested that the findings do not rule out the potential for several pathogenic processes to be involved, with some being more prominent than others in individual patients.

The authors indicated that the best conclusion from these results is that the pathogenesis of MS encompasses both neurodegenerative and wallerian mechanisms of axonal loss. These concomitant pathophysiologic processes are compatible with the clinical variability of MS and deserve further evaluation in understanding MS etiology.

DeLuca GC, Williams K, Evangelou N, et al. The contribution of demyelination to axonal loss in multiple sclerosis. *Brain*. 2006;129 (Pt 6):1507-1516.

EXTENSIVE REMYELINATION SEEN IN SUBSET OF MS PATIENTS

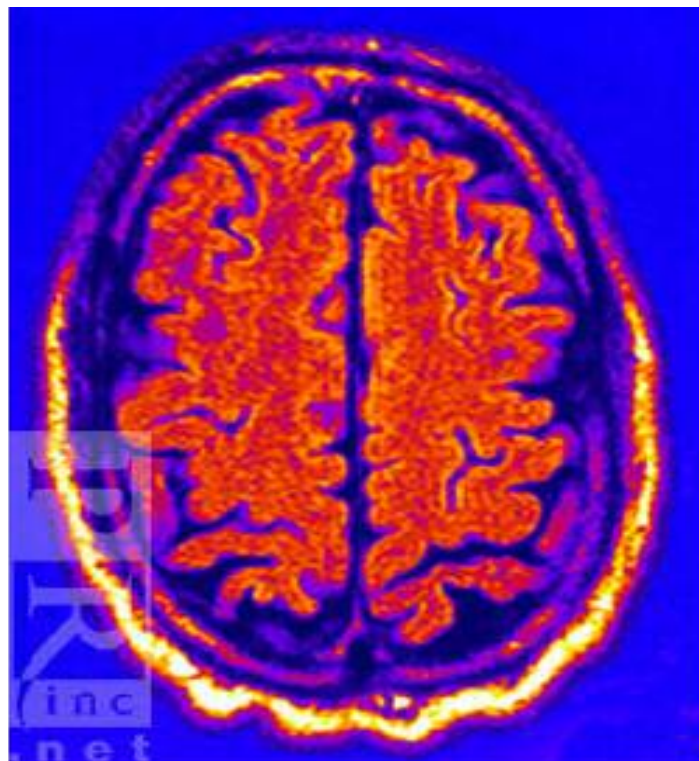
Remyelination of the focal white matter plaques that characterize MS has been reliably reported for 25 years, but the frequency of this repair has not been well documented and may be important to understanding the variability of clinical progression or the effects of therapies. This multicenter, prospective study evaluated the frequency of remyelination, including complete remyelination, in the context of clinical variables, such as duration of disease and gender.

Brain tissue from 51 deceased individuals with documented MS was assessed. A total of 1,026 lesions were evaluated.

In 10 (19%) of the cases, most of the focal plaques were remyelinated. In some cases, up to 96% of the total plaque area was remyelinated, leaving a lesion commonly referred to as a shadow plaque. In seven (14%) of the cases, there was substantial remyelination, affecting up to 60% of the plaque area. In the remaining 34 cases (67%), remyelination was characterized as sparse and confined to the edge of lesions, with remyelination never exceeding more than 25% of the plaque area.

One of the most important influences on the extent of remyelination was plaque location. Those lesions most likely to have substantial or complete remyelination were located in the deep white matter or were found subcortically. However, there were exceptions with some complete remyelination observed in periventricular areas. Remyelination also differed for type of clinical classification, with more remyelination in those with relapsing-remitting disease and primary progressive MS than those with acute or secondary progressive MS. Patients who died at an older age also had more completely remyelinated lesions than those who died younger.

Patrikios P, Stadelmann C, Kutzelnigg A, et al. Remyelination is extensive in a subset of multiple sclerosis patients. *Brain*. 2006;129(Pt 12):3165-3172.



NATURAL HISTORY OF MS

A recent study of the natural history of MS reported that in 80% of cases, a relapsing course is followed by chronic progression within two decades. The authors studied a cohort of patients with a mean follow-up of 25 years. Median times to reach Disability Status Scale (DSS) scores of 6, 8, and 10 were 12.7, 20.6, and 43.9 years, respectively. The majority of patients who presented with a relapse entered a progressive phase after a mean time of 10.4 years. The effects of relapses often cloud the clinical onset of progression. However, in some cases progression occurs early. The early progressive course is independent of relapses either preceding the onset of relapse-free progression or subsequent to it. Interestingly, the authors found that the site of the original attack was not usually where progression began within the central nervous system.

Kremenutzky M, Rice GP, Baskerville J, et al. The natural history of multiple sclerosis: a geographically based study 9: observations on the progressive phase of the disease. *Brain*. 2006 Mar;129(Pt 3):584-594.

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LONG-TERM USE OF DISEASE-MODIFYING THERAPY

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