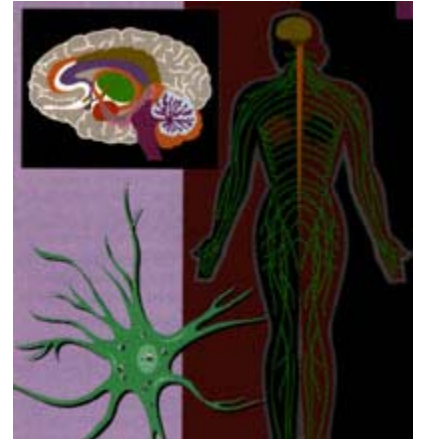


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Secondary Progressive Multiple Sclerosis: Clinical Challenges & Treatment Advances

Based on proceedings from the Annual Meeting of the Consortium of Multiple Sclerosis Centers, June 22, 2000, Halifax, Nova Scotia



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Introduction

While great strides have been made in the overall management of multiple sclerosis (MS) over the past decade, advances in pharmacologic treatment have focused primarily on the relapsing-remitting subtype. The lack of effective therapies for secondary progressive disease is disappointing, as natural history studies have shown that virtually all relapsing-remitting patients will eventually make the transition to progressive disease.

A variety of studies conducted in the past several years, however, have begun to demonstrate that secondary progressive MS is indeed a treatable disease. While trials of the immunomodulators have produced varying results, they are helping to identify subgroups of secondary progressive patients who may be more likely to respond to these injectable agents. Of the immunosuppressive agents, the seminal double-blind, European Mitoxantrone in Multiple Sclerosis study has demonstrated that mitoxantrone, administered every three months, can slow progression of disability in this patient group. Based on this research, mitoxantrone has recently been unanimously recommended for approval by the US Food and Drug Administration for secondary progressive MS treatment.

In addition to tough treatment choices, secondary progressive MS patients face unique psychosocial issues that accompany the disease transition. This supplement to the ***International Journal of MS Care***, sponsored by an unrestricted educational grant from Immunex Corporation, offers providers who manage MS patients an overview of the issues faced by patients with secondary progressive disease and the latest research on treatments in this area. We hope you find this supplement useful in identifying patients with secondary progressive disease and making the most informed management choices.

Therapeutic Approaches in Secondary Progressive MS Pathophysiologic Research Informs Treatment Choices

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While numerous treatment options have been examined in secondary progressive multiple sclerosis (MS) with varying degrees of success, the exact cause of the disease remains a mystery. "The current paradigm suggests that MS is an immune-mediated inflammatory disease of the central nervous system [CNS]," explained John R. Richert, MD, Professor and Chair of the Department of Microbiology and Immunology at Georgetown University Medical Center, Washington DC. "It may develop in genetically susceptible individuals who are exposed to as-yet undefined environmental triggers or multiple triggers."

Many investigators believe that MS is essentially a disease of "molecular mimicry," in which "tissue injury results from a misdirected immune response triggered by nonself antigens that have a similar antigenic structure to CNS myelin constituents"¹ (see Table 1). The receptors of myelin-reactive T cells are stimulated by combinations of these foreign antigen peptides and the host's human leukocyte antigen (HLA) molecules. "The T cell cannot distinguish between the foreign antigen and host antigens and will attack anything that looks like it," said Dr. Richert.

Table 1. *Nonsell Antigens Potentially Implicated in Multiple Sclerosis*

Herpesvirus
Adenovirus
Rubella virus
Retroviruses
Borrelia burgdorferi
Chlamydia

Activation of leukocytes also requires the presence of accessory molecules, including B7 on the antigen-presenting cell and CD28 on the T cell (if the helper T cell "sees" an antigen without these, it will undergo apoptosis or become anergic). The cells migrate through the vascular endothelium through use of adhesion molecules including VLA-4 and LFA-1, which bind the complementary adhesion molecules VCAM-1 and ICAM-1. After the T cells gain access into the CNS, it is believed that myelin destruction is mediated by processes including secretion of tumor necrosis factor-alpha and free oxygen radicals, and activation of complement that forms membrane-attack complexes in the myelin sheath.¹

Strategies for Treatment

Therapeutic strategies for MS have fallen into two basic categories based on our understanding of these autoimmune processes. The first strategy is to aim therapies at a particular target in the body's immune response (eg, helper T cells or inflammatory cytokines); the second involves nonselective immunosuppression of the entire system (see Table 2). Of the former category, all of the immunomodulators have been studied to some extent in secondary progressive disease. While none are currently approved specifically for secondary progressive disease in the US, interferon beta-1a has been approved for relapsing forms of MS, which may include relapsing progressive disease.

Table 2. Evidence for Efficacy in Secondary Progressive Disease

On-Label Use With Class I Evidence

Mitoxantrone

Interferon beta-1a

Interferon beta-1b (European trial)

Off-Label Use With Class II Evidence

Methotrexate

Glatiramer acetate

Methylprednisolone

Intravenous immunoglobulin G

Off-Label Use With Conflicting Data

Cyclophosphamide

The identification of any treatment for secondary progressive disease is made difficult by the inherent heterogeneity of MS. This difficulty in predicting which patients will respond to a particular therapy has been seen by clinical trials of the interferons in secondary progressive MS. "Technically, patients are stable between relapses in relapsing-remitting MS, whereas secondary progressive patients are slipping. On paper, this is a clear distinction," said Dr. Richert. "But in actuality, these two types of disease are sometimes very difficult to sort out." As a result, "we are beginning to realize that most clinical trials aimed at one form of the disease are probably contaminated with patients with the other form."

Immunomodulator Therapy

A more detailed discussion of the secondary progressive trials of the immunomodulators is found in the discussion by Hillel Panitch, MD, in the third section of this supplement. A brief overview of the results of the immunomodulators will be presented here. Glatiramer acetate (then known as copolymer 1) was one of the first agents studied for secondary progressive disease. In a two-center trial by Bornstein et al² involving 106 patients with "chronic progressive MS" (which appeared to include both primary and secondary progressive disease), glatiramer acetate showed a trend toward slowing of disability progression that failed to reach statistical significance. The study, however, was designed poorly, as it

included only two centers: One center showed a statistically significant benefit, while the other did not.

In a trial of the Rebif® preparation of interferon beta-1a in secondary progressive disease,³ secondary end points, including relapse rate and magnetic resonance imaging findings, did show improvement; however, findings in the primary end point, time to sustained progression of disability, were nonsignificant. The strongest results to date of any of the interferons in secondary progressive MS were found in the European study of interferon beta-1b,⁴ which showed a relative reduction of nearly 22% in confirmed progression of disability. Based on these findings, interferon beta-1b was approved for treatment of secondary progressive disease in Europe and Canada. A large-scale trial of this agent in North America, however, failed to duplicate these findings.⁵

"We have been trying to sort these findings out," said Dr. Richert. "In the European trial, there were more patients with superimposed relapses; while in the North American trial, there were fewer such patients. We have to think in therapeutic terms about who secondary progressive patients are. Will they or won't they have relapses, and does this play a role in treatment?"

Immunosuppressive Agents

Agents with general immunosuppressive activity include mitoxantrone, azathioprine, methotrexate, and cyclophosphamide. Of these, mitoxantrone has shown a statistically significant ability to delay progression of disability in secondary progressive disease, and it has been unanimously recommended for approval by the US Food and Drug Administration for this MS subtype. Its use is discussed below.

Cyclophosphamide is "one of the most controversial agents in MS therapy," according to Dr. Richert. Although it has been associated with modest benefit,⁶ it is an immunosuppressive chemotherapeutic agent and therefore is accompanied by toxicities that include hemorrhagic cystitis, nausea, vomiting, alopecia, and infertility. Its use "probably polarizes MS specialists more than any other drug. Some providers say it's terrific, others say you should never use it." There appears to be a narrow category of patients for whom this agent does appear to be effective. "It is one of the few drugs we have that may be able to reverse significant deficits, so we tend to use it for those who have rapidly progressed and are not responding to steroids, in whom we believe there is still room for remyelination." The agent is administered intravenously on a monthly or bimonthly basis.

The corticosteroid methylprednisolone is employed in monthly or bimonthly pulse administration. Using a composite measure of efficacy in a phase II study of 108 patients with secondary progressive MS, Goodkin et al⁷ showed a modest benefit for this agent at higher doses (500 mg vs 10 mg every eight weeks for two years) in time to onset of sustained progression of disability. However, no significant difference was seen in the primary end point, the proportion of patients in each treatment group who experienced sustained progression of disability. "This is one of the drugs that we consider adding on to the immunomodulators in persons whose disease is progressing," said Dr. Richert.

No formal safety data are yet available for methotrexate in combination with the inteferon betas, although data will probably be available within the next year. In a 1995 study of 60 patients, Goodkin et al⁸ demonstrated that low-dose (7.5 mg/week) oral methotrexate proved modestly beneficial in the absence of significant toxicity. "This drug showed some positive findings in a composite measure of disability" that included the Expanded Disability

Status Scale (EDSS), the Ambulation Index, the Box and Block Test, and the 9-Hole Peg Test, said Dr. Richert. However, considerable anecdotal experience indicates that most patients do not remain stable over the long term on 7.5 mg/week. "This agent can also be considered for add-on therapy," Dr. Richert observed. "We tend to start patients at 7.5 mg/week, and quickly increase the dose to 15 mg/week if they show signs of continued disease activity."

The newest agent used for MS treatment in this class, and the agent with the highest-quality efficacy data, is mitoxantrone. The Mitoxantrone in Multiple Sclerosis Study (MIMS),⁹ a European phase III trial in 194 patients over 17 centers, demonstrated a significant decrease in disability progression after two years as measured by EDSS scores, as well as a reduced relapse frequency and beneficial effects on various magnetic resonance imaging parameters. The doses employed were 5 mg/m² and 12 mg/m² via intravenous infusion every three months. "It had an effect on all three parameters that we like to measure for efficacy," pointed out Dr. Richert. By the end of the two-year study, the percentage of patients with gadolinium-enhancing lesions in the low-dose mitoxantrone group had dropped from 47.5% down to 10.8%, while the percentage in the high-dose group had dropped from 29.4% to 3.2%, compared with a drop from 22.2% to 15.6% in the placebo group—a highly significant difference.

Adverse effects were typical of those seen with a chemotherapeutic agent but were generally mild to moderate and manageable. Future study and clinical experience with this agent will direct whether it should be used as a first-line therapy or whether it should be added on or substituted for the immunomodulators for persons who fail these agents.

Challenges for the Future

Challenges for the future include how best to identify those secondary progressive cases that are likely to respond to therapy. "Our thinking has to be modified somewhat," said Dr. Richert. "Whereas a month ago neurologists were enthusiastically putting people on interferon beta-1b as a result of the European trial, now, with the North American study completed, we have begun to see that this agent is perhaps effective for those patients with relapses, but not for those without relapses." For mitoxantrone, "we do not have a similar breakdown yet, so it will be interesting to see if we can identify who is more likely to respond."

Key to determining efficacy in practice is first to define a threshold for nonresponse or suboptimal response. "The lowest threshold is any worsening at all. When disease progresses, we have to be very aggressive in altering our treatment regimens." It is uncertain, however, whether the most effective strategy is to switch to another immunomodulator, add another agent, switch to mitoxantrone, or use mitoxantrone as the first-line agent. "Over time, we are really going to have to look at these issues. What we do know is that secondary progressive MS is a treatable disease. We cannot cure it yet, but we can alter its course."

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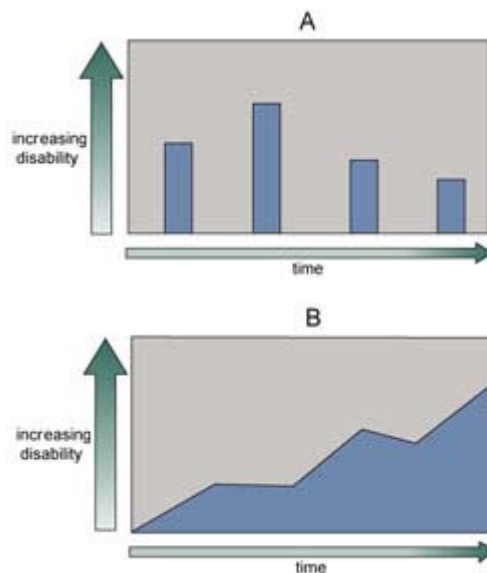
Diagnostic and Treatment Issues

Assessing Risks for Progression and Response to Treatment

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The clinical overlap among the various subtypes of MS and the inherent unpredictability of the disease can make a diagnosis of secondary progressive MS difficult. Certain factors, however, have proven useful in predicting the risk of progression and therapeutic response. Patricia K. Coyle, MD, Professor of Neurology at the State University of New York, Stony Brook, and Director of the Stony Brook MS Comprehensive Care Center, discussed findings that can be used to gauge the risk of MS progression and treatment response.

The current clinical model of MS includes four subtypes: primary progressive, relapsing-remitting, secondary progressive, and progressive relapsing (see Figure 1).¹ However, any attempt to establish discrete diagnostic criteria has limitations, because MS is an exceedingly heterogeneous disease and patients do not fall neatly into clinical categories. In addition, an estimated 25% of cases may be so mild as to be subclinical.² Nevertheless, "The use of clinical categories allows us to create meaningful subsets of patients for education and for clinical analysis," said Dr. Coyle.



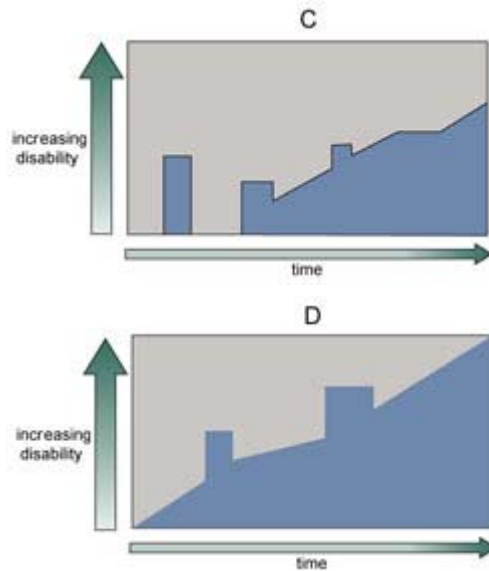


Figure 1. Graphic representations of the four clinical subtypes of MS. A: Relapsing-remitting; B: Primary progressive; C: Secondary progressive; D: progressive relapsing. Adapted from Lublin et al.¹

Of the clinical categories, approximately 85% of patients are initially diagnosed with relapsing-remitting MS; the disease is progressive from the outset in only 15% of cases.^{3,4} However, over the course of the disease, "ultimately a high proportion of relapsing patients move onto a progressive stage," said Dr. Coyle. "If you look at the overall distribution, approximately half of patients have relapsing-remitting disease" (see Figure 2).⁵ Within relapsing-remitting disease is a subset of patients with "benign MS." Although there is no uniformly accepted definition of benign MS, these persons can be characterized as individuals who "have a diagnosis of definite MS yet show minimal disability after many years. These patients do very well."

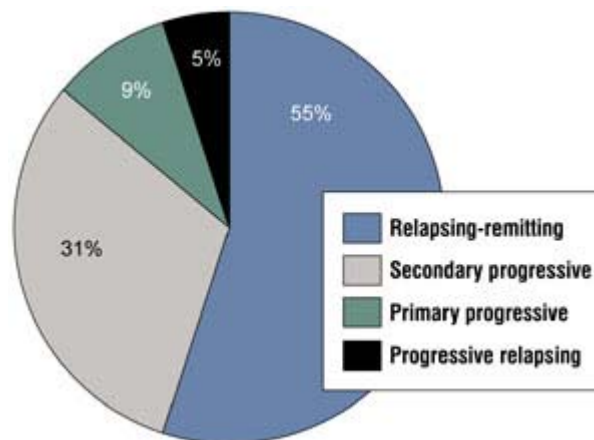


Figure 2. Distribution of MS clinical subtypes. While about 85% of initial diagnoses are relapsing-remitting, most of those patients eventually progress, meaning that only slightly more than half of total cases fall into this subtype.

Primary progressive MS is the most unusual subtype. By definition, these patients do not experience relapses. Accounting for about 10% of MS cases,⁴⁻⁶ this form of the disease exhibits different characteristics than the relapsing forms. Persons with primary progressive disease have an older age of onset, and primary progressive MS is the only clinical subtype that affects equal numbers of both sexes. Neurologically, these patients most often present with spinal cord disease (myelopathy), with comparatively little brain involvement. "Primary progressive patients tend to have very little magnetic resonance imaging [MRI] lesion burden and inflammation in the brain, with fewer gadolinium [Gd]-enhancing lesions," said Dr. Coyle.

The other initially progressive form, progressive relapsing, comprises 5% of cases. This subtype has a progressive onset, but unlike primary progressive disease, the patient experiences subsequent exacerbations.

The fourth MS category, secondary progressive, consists of relapsing-remitting patients who move on to the progressive form of the disease over time. "The natural history data show that after 25 years, about 90% of untreated relapsing-remitting patients will transition to secondary progressive disease," explained Dr. Coyle.^{4,7} Patients may continue to have relapses superimposed on their progressive course. Some data suggest that those whose relapsing-remitting disease began at a younger age tend to have a longer interval before they enter a progressive stage, compared with those whose MS began when they were older. "We do not know the significance of these data, but they are likely to teach us something important about the nature of the disease."

Predicting the Risk of Progression

The onset of secondary progressive MS represents an unfortunate milestone in the disease course, characterized by increasing limitations. "Secondary progressive disease assures eventual disability," reported Dr. Coyle. "The natural history studies show that within 17 years of entering the progressive stage, almost all patients will have limited ambulation."⁴ Some studies have suggested the existence of a "time lock" feature: "It appears that when relapsing-remitting disease has an earlier age of onset, secondary progressive disease may come later. Conversely, a patient who is older at the time of a relapsing-remitting diagnosis may progress sooner."

Several factors have proven useful in predicting the risk of progression to secondary progressive disease (see Table 1). Foremost among these is the Expanded Disability Status Scale (EDSS) score. "When you look at the EDSS, you see that most patients tend to cluster in the lower and higher ranges," said Dr. Coyle. "Very few patients are in the middle."^{3,8} Most relapsing-remitting patients are in the EDSS range of 1 to 3.5, and most with progressive disease are in the range of 6 to 8. "The shortest stay is at the 4 to 5.5 range. These are the patients who are at risk for secondary progression."

Table 1. Findings From New York State MS Consortium Database.		
Clinical Subtype	Mean No. Relapses/Year (n = 3,361)	Mean EDSS Score (n = 4,110)
Relapsing-remitting	1.3	2.7
Secondary progressive	0.3	5.9
Progressive relapsing	0.8	5.6

Primary progressive	N/A	5.8
EDSS, Expanded Disability Status Scale. Source: New York State MS Consortium database. ⁵		

An increase in the relapse rate is a second signal. "The clinical relapse rate normally falls over time as the disease progresses," said Dr. Coyle. "If you have a relapsing-remitting patient and her clinical attacks are increasing, it is a warning sign that her MS is worsening." Data from the New York State MS Consortium support these findings. In this database, which contains information on MS patients throughout the New York area, the mean EDSS scores were below 3 for relapsing-remitting disease and approximately 6 for all progressive forms of disease (see Table 2). The exacerbation rate in progressive disease was only one quarter that seen in relapsing-remitting disease.

Table 2. Predictors of Risk for Transitioning to Secondary Progressive Disease.

- EDSS score in 4-5.5 range
- Increase in relapse rate
- Polyregional relapses
- Decreased response to glucocorticoids
- Incomplete recovery between relapses
- Suboptimal response to immunomodulators
- Male sex
- Longer duration of relapsing-remitting disease
- Decrease in Gd-enhancing lesion activity
- Increase in total MRI burden of disease
- Increase in axonal pathology
- Decreased NAA levels on MR spectroscopy
- Periventricular/posterior fossa/spinal cord lesions
- Increase in T1 hypointensities ("black holes")
- Decrease in functional suppressor cell activity
- Increase in inflammatory cytokines/myelin-reactive T cells

Gd, gadolinium; MRI, magnetic resonance imaging; NAA, N-acetylaspartate.

The clinical characteristics of exacerbations also have prognostic significance for the risk for progression. Relapses in those at high risk tend to be polyregional, involving multiple neurologic systems (eg, a combination of sensory and motor symptoms). These patients also tend to show a decreasing response to treatments such as glucocorticoids, have incomplete recovery between relapses, and show a "suboptimal" response to immunomodulator therapy. Male sex is associated with an increased risk of progression, as is a longer duration of disease (the mean number of years from a relapsing-remitting diagnosis to progression is 9.3).⁴

Several investigations have reported differences in MRI findings in secondary progressive patients compared with their relapsing-remitting counterparts. With secondary progressive patients, the total burden of disease is continually increasing, but this progression is not reflected in Gd-enhancing activity, which actually decreases in secondary progressive MS. There is greater axonal pathology as shown by brain atrophy measures and decreased N-acetylaspartate (NAA) levels on magnetic resonance spectroscopy. Lesions in secondary

progressive patients are more likely to be periventricular and located in the posterior fossa; spinal cord lesions are more common, along with T1 hypointensities ("black holes").

Finally, "Some very preliminary data suggest different immunologic findings in the secondary progressive patient," said Dr. Coyle. These findings include a decrease in functional suppressor activity, an increase in inflammatory cytokine production, and a loss of ability to regulate myelin-reactive T cells.

Who Will Respond to Therapy?

Potential agents for the treatment of secondary progressive MS now include mitoxantrone, three interferon preparations, and glatiramer acetate. The trials to date and clinical experience, Dr. Coyle said, have shown that there are some "super-responders" to therapy and others who are poor responders. A number of factors can be helpful in assessing therapeutic success. The primary clinical parameters include the relapse response rate and the rate of progression (see Table 3).

Table 3. Indicators of Therapeutic Response in Secondary Progressive Disease.

Clinical Parameters
Decrease in relapse rate
Decrease in relapse severity
Improved recovery from relapses
Decrease in rate of accumulating disability
Decrease in Gd-enhancing lesion activity*
Decrease in total MRI burden of disease
Slowing of atrophy development
Neuroimaging Parameters
Decrease in Gd-enhancing lesion activity*
Decrease in total MRI burden of disease
Slowing of atrophy development

*The relapse rate and Gd-enhancing lesion activity decrease naturally as MS progresses; therefore, decreases in these factors do not necessarily indicate a therapeutic response.

Gd, gadolinium; MRI, magnetic resonance imaging.

Generally accepted signs of loss of response to therapy include the presence of three or more relapses per year. However, "you have to take into account the prior relapse severity," said Dr. Coyle. "If patients had been having devastating relapses with poor recovery before treatment but now their relapses are mild with full recovery, that is probably a positive response."

"We are also developing MRI parameters," she continued. "For example, we expect the number of contrast lesions to decrease with the use of disease-modifying therapies. In addition, the brain burden of disease should be stabilized, and brain and spinal cord atrophy should be brought down to what is expected in the normal aging process—not the accelerated rate in MS, which can be up to 10 times higher." Obvious Gd-enhancing lesions and increasing total T2-weighted burden of disease are MRI features that suggest loss of response. Development of other means to assess response, such as biologic markers that show therapies are working, are "the Holy Grail."

Choices to consider for loss of response include increasing the interferon dosage (for those who are on the interferons), choosing therapy with an immunosuppressive agent such as mitoxantrone, switching to glatiramer acetate or another agent, or adding a drug. (A study is in progress to assess the safety of combining an interferon beta and glatiramer.) Intravenous pulse corticosteroid therapy may also be tried.

Caution must be used in assessing a lack of response. "Secondary progressive patients start with more severe disease and may not have countable relapses," said Dr. Coyle. "The realistic treatment goal in these patients is to slow, rather than stop, progression and disability." In many of these patients, progression may be attributed to a "sublethal injury," so halting progression is unrealistic. Natural history studies show that relapses become less common with progression; therefore, "a decrease in relapse rate does not necessarily signal response."

Involving the Patient

Acknowledging the challenges in this area, Dr. Coyle emphasized that "We need to diagnose MS properly. . . . There is a 5% to 10% misdiagnosis rate. There are some diseases that mimic MS, so you must be aware of this." Examples include vitamin B12 deficiency, infections such as Lyme disease and HTLV-1 retrovirus infection, and the genetic cerebrovascular disease CADASIL.

Although a diagnosis of secondary progressive disease can be frightening, Dr. Coyle stressed the need to reassure patients that it need not mean immediate disability. "In up to 30% of patients, secondary progressive MS will stabilize for several years. It is important to discuss this with your patients." Above all, it is essential to make them part of the diagnostic and treatment process. "I depend very much on my patients. They know their bodies, and know what is happening to them. We have to discuss their symptoms and concerns with them."

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Clinical Trials in Secondary Progressive MS

Assessing Response to Therapy

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Although results from large clinical trials in secondary progressive MS have been encouraging, the data are raising significant questions on how best to identify those patients who are most likely to respond to therapy. Significant benefits were seen for each of the major end points in the trial of the immunosuppressive agent mitoxantrone; however, the same is not true for two of the three major studies involving the interferon betas. In these trials, delays in disability progression were seen only in those patients whose progressive disease course had superimposed relapses, suggesting that careful selection of patients is especially important to therapeutic success in this disease category.

Selection of patients is not an easy task given the heterogeneity of MS. "It is often very difficult to determine whether a patient who walks into your office in a worse condition than she was six months ago is having relapses with residual disability or is on a very slow course of progression," said Hillel Panitch, MD, Professor in the Department of Neurology at the University of Maryland, Baltimore. Dr. Panitch discussed the primary results of the four major clinical trials performed in this area. Three involved the interferon betas, and the fourth—the Mitoxantrone in Multiple Sclerosis Study (MIMS)—involved mitoxantrone, a chemotherapeutic agent that was recently unanimously recommended by the US Food and Drug Administration for approval for treatment of secondary progressive MS in the United States.

Trials of the Beta Interferons

European Study Group on Interferon Beta-1b

The European Study Group on Interferon beta-1b in Secondary Progressive MS was the first to publish results of a large-scale, randomized, placebo-controlled trial of interferon therapy in secondary progressive MS.¹ The researchers in this European multicenter trial enrolled 718 patients who were randomized to placebo or a standard course of interferon beta-1b (8 million IU every other day) over three years. The primary end point of the study was designed to examine time to confirmed progression of disability; patients met this end point if they experienced an increase of 1.0 point on the Expanded Disability Status Scale (EDSS) sustained over three months, or a 0.5 point increase if their baseline EDSS was 6.0 or 6.5. All patients had a baseline EDSS of 3.0 to 6.5.

Interferon treatment significantly delayed time to progression of disability in this trial. Overall, 38.9% of those on active treatment had confirmed progression over the course of the study, compared with 49.7% of placebo patients ($P = .0048$)—a relative reduction of 21.7%. Subanalyses of those patients with or without superimposed relapses on top of their progressive disease also revealed a relative risk reduction of about 20% for both groups.

Secondary outcome measures were also favorable. Consistent with its effect in studies of relapsing-remitting disease, interferon beta-1b reduced the mean annual relapse rate by 31.3% ($P = .002$). Those on placebo experienced an increase of 8% in total T2 lesion

volume on magnetic resonance imaging (MRI), while those on active therapy achieved a reduction of 5% (P = .0001). The number of new gadolinium (Gd)-enhancing lesions was also significantly decreased with treatment (P = .0014).

The trial was terminated early "because of the dramatic effect of treatment on progression of disability," explained Dr. Panitch. "In this study, interferon beta-1b delayed time to progression irrespective of superimposed relapses." The results provided the impetus for the approval of interferon beta-1b for secondary progressive MS in Europe and Canada.

NASP

Unfortunately, these positive results could not be replicated in a North American trial of interferon beta-1b. The North American Study of Interferon Beta-1b in Secondary Progressive Multiple Sclerosis (NASP) trial was conducted in an even larger group of patients (n = 939), in an attempt to build on the European study findings and provide data for approval of the agent in the United States.²

Unlike in the European trial, patients in the NASP study were randomized to one of three arms: placebo, an interferon beta-1b dose of 8 million IU, or a dose adjusted for body weight and size (5 million IU/m²). Each dose was administered every other day. The primary end point was also slightly different, with time to confirmed progression of disability defined as a 1.0-point EDSS increase (or 0.5 points if the baseline EDSS was 6.0 or 6.5) sustained for at least six months—"an even more stringent criterion."

The three groups were very well matched. Inclusion criteria were age 18 to 65 years, a relapsing-remitting course of disease followed by a progressive course for more than six months prior to study entry, and an increase of at least 1.0 point on the EDSS over the past two years. Secondary outcomes included change from baseline EDSS score and relapse rate. All patients were evaluated every three months for three years, and all received an annual nonenhanced MRI scan. A subgroup of 163 patients received monthly Gd-enhanced scans.

This study was also stopped early—after it was about 95% completed—but for the opposite reason: a lack of efficacy in the primary end point. Over the course of the study, the decrease in confirmed progression to disability was nonsignificant (P = .71), regardless of the baseline EDSS score (Table 1). However, in analyzing their data, the researchers discovered that efficacy was achieved in certain secondary measures. For example, the effect on relapse rate was highly significant for those individuals with relapses (–43% for the 8 million IU dose and –29% for the 5 million IU/m² dose, compared with placebo). In addition, the total T2 lesion volume increased by 11% in the placebo group, compared with only 0.4% for the 8 million IU group and 0.8% for the 5 million IU/m² group. The number of new Gd-enhancing lesions was reduced by 64% and 76% in these two groups, respectively (P = .0004).

Table 1. Progression of Disability in the North American Trial of Interferon Beta-1b in Secondary Progressive MS.

Baseline EDSS	% With Confirmed Progression of Disability*		
	Placebo	5 MIU/m ²	8 MIU
<4.0	27	38	41
4 – 5.5	39	28	39

>6.0	31	35	39
<p>*Defined as a 1.0-point EDSS increase sustained for at least six months, or a 0.5-point increase if the baseline EDSS was 6.0 to 6.5. EDSS, Expanded Disability Status Scale. Source: NASP Study Group.²</p>			

"There was a significant effect on disability in those patients who had relapses compared with placebo," observed Dr. Panitch. In comparison, the results were not significant in those who did not have relapses. "What can we conclude from these findings? If you compare patients with superimposed relapses in these two trials, there were more than twice as many in the European study. In addition, the increase in enhancing lesions was higher in the European study patients. Overall, it was a more active group in terms of their disease activity."

These distinctions may account for much of the difference in primary results in these two trials and suggest the presence "of a different pathophysiology between different types of secondary progressive MS," said Dr. Panitch. "There may be a change in immunologic characteristics as patients shift from an earlier relapsing type of secondary progressive MS into a more progressive course."

SPECTRIMS

Results of the third interferon beta trial appear to lend even more weight to this hypothesis. The Secondary Progressive Efficacy Trial of Rebif (Interferon beta-1a) in Multiple Sclerosis (SPECTRIMS) study examined the effect on disability of two doses of interferon beta-1a (22 and 44 µg) delivered subcutaneously three times per week.³ All participants had clinically definite secondary progressive MS, with baseline EDSS scores ranging from 3.0 to 6.5.

The primary outcome in this trial was time to progression by 1.0 EDSS point (or 0.5 point in those with an EDSS score >5.5) confirmed at two consecutive visits three months apart. (This was the same end point as for the European Secondary Progressive Study.) The outcome, unfortunately, "looked disturbingly like that in the North American trial," said Dr. Panitch: Interferon beta-1a failed to achieve a significant effect on progression of disability (P = .93). Again, however, subgroup analyses showed that those with superimposed relapses fared better than those who were relapse-free, with improvement in the former group almost reaching statistical significance. The MRI improvements were also similar to those seen in the NASP trial, with very little or no increase in T2 lesion burden with treatment compared with placebo.

"These results are beginning to fall into a consistent pattern," concluded Dr. Panitch. "We are beginning to realize that the beta interferons are effective in those secondary progressive patients who most resemble the relapsing-remitting groups." The findings call for development of studies to improve criteria for treatment so that optimal responders can be identified.

Mitoxantrone Shows Significant Overall Benefit

The immunosuppressant mitoxantrone provided significant benefits on all major outcomes in the fourth trial on secondary progressive MS. The agent delayed progression of disability and was well-tolerated overall. Results of this study had previously been reported at the 1999 meeting of the American Academy of Neurology in Toronto.^{4,5}

"If mitoxantrone is not familiar to you, it will be in the near future," said Dr. Panitch. "This study is really quite impressive and has been the impetus for an application to the US Food and Drug Administration for approval of this drug."

Mitoxantrone is an anthracenedione chemotherapeutic agent with broad immunosuppressive and cytotoxic activity. At higher doses, it has been used successfully in patients with certain malignancies, including leukemia and prostate and breast cancer. For the MIMS study, mitoxantrone was given in two lower doses (5 or 12 mg/m²) every three months via intravenous infusion over five to 15 minutes.

This double-blind, placebo-controlled, two-year study enrolled a total of 194 patients across 17 MS centers in four European countries. The participants were categorized as having secondary progressive or "remitting progressive" MS. This latter category consisted of patients whose course of disease resembled relapsing-remitting MS, but with increasing residual disability; such a classification, said Dr. Panitch, "acknowledges the difficulty in distinguishing between secondary progressive disease and relapsing-remitting disease with residual deficits."

The baseline EDSS scores in the MIMS trial ranged from 3.0 to 6.0, and all enrollees had experienced an increase of 1.0 point or more on the EDSS in the preceding 18 months. Patients and controls were well matched. The outcome measures in this study included EDSS change from baseline, number of relapses (which were treated with intravenous methylprednisolone, 500 mg/d for 5 days), and multiple MRI measures of disease activity.

Mitoxantrone showed a statistically significant benefit across all of these measures. Both mitoxantrone groups experienced a decrease in mean EDSS scores compared with baseline (-0.23 and -0.13 for the 5 mg/m² and 12 mg/m² groups, respectively, vs +0.23 for placebo; P = .0194; see Table 2 and Figure). Significant decreases were also seen in the percentage of patients who had sustained deterioration, defined as an increase of at least 1.0 EDSS points over six months (P < .05). In addition, the mitoxantrone groups had significantly fewer treated relapses, as well as a significantly longer time to first relapse (P < .0004).

Table 2. Clinical Results From the MIMS Study.

	Placebo	MX5	MX12
Baseline EDSS	4.7	4.6	4.5
Change in EDSS from baseline	+.23	-.23	-0.13
Mean no. of treatment relapses	1.2	0.7	0.4
Ambulation Index increase	0.8	0.4	0.2

MIMS, Mitoxantrone in Multiple Sclerosis; EDSS, Expanded Disability Status Scale; MX5, mitoxantrone 5 mg/m²; MX12, mitoxantrone 12 mg/m².
Source: MIMS-Study Group.⁴

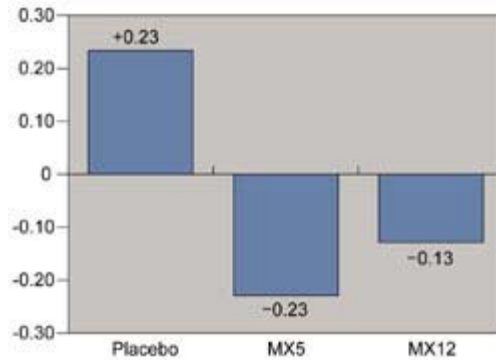


Figure. EDSS Change From Baseline in the MIMS Trial.

EDSS, Expanded Disability Status Scale; MIMS, Mitoxantrone in Multiple Sclerosis; MX5, mitoxantrone 5 mg/m²; MX12, mitoxantrone 12 mg/m².

Source: MIMS-Study Group.⁴

Similarly positive effects were seen on MRI. The percentage of patients with Gd-enhancing lesions was reduced (Table 3), and the mean number of Gd-enhancing lesions was "dramatically lower in the mitoxantrone group" (see Table 3).⁵ A significant reduction was also seen in the percentage of patients with new lesions.

	Placebo	MX5	MX12
% of patients with enhancing lesions:			
Baseline	22.2	47.5	29.4
24 months	15.6	10.8	3.2
Mean no. of enhancing lesions:			
Baseline	0.44	3.23	1.88
24 months	0.26*	0.11	0.03
Mean change in no. of T2 lesions from baseline	+1.94	+0.68*	+0.29
*Not significant ($P > .05$)			
MRI, magnetic resonance imaging; MIMS, Mitoxantrone in Multiple Sclerosis; MX5, mitoxantrone 5 mg/m ² ; MX12, mitoxantrone 12 mg/m ² .			
Source: MIMS-Study Group. ⁵			

Adverse effects are a potential concern with any chemotherapeutic agent. In the mitoxantrone group, typical chemotherapeutic side effects were seen, including nausea, vomiting, and alopecia. However, they were mild to moderate, and none required cessation of therapy. Of potentially greater concern is cardiotoxicity, which is an effect common to the anthracenediones. Mitoxantrone "is much less toxic," Dr. Panitch observed, "but it should not be used in patients who have heart disease to begin with." No evidence of significant cardiotoxicity was reported in the MIMS trial. The left ventricular ejection fraction decreased by at least 10% in 28 patients (22%) on active treatment in the MIMS study, but also in 11 patients (17.2%) on placebo. Dr. Panitch advised that, as with any agent, providers should

use mitoxantrone "with careful forethought" and not exceed a maximum cumulative dose of 140 mg/m², which amounts to about three years of treatment if the drug is given over three-month periods.

Moving Forward

Moving forward in the treatment of patients with secondary progressive MS, "we still have a lot of questions," said Dr. Panitch. Among these questions are the potential role of combination therapies in treatment and the proper role of mitoxantrone (ie, should it be used vigorously as first-line therapy or reserved for those who respond poorly to the immunomodulators?) Finally, he reminded providers not to neglect treatment of accompanying symptoms, such as fatigue and spasticity, emphasizing that "there are many ways to make our MS patients more comfortable."

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Psychosocial Issues in Secondary Progressive MS

A Unique Set of Challenges

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An initial diagnosis of relapsing-remitting multiple sclerosis (MS) can raise tremendous psychosocial issues for patients and caregivers. It is important for providers to realize, however, that the transition to secondary progressive MS presents its own unique psychosocial challenges, placing additional burdens on patients, families, and caregivers. This transition requires the health care team to be even more attentive to the needs of these individuals.

"The transition to secondary progressive MS forces people to redefine their illness," emphasized Rosalind C. Kalb, PhD, a Clinical Psychologist at the MS Care Center at St Agnes Hospital, White Plains, New York. "It shatters their denial. Any conviction that their disease was benign, or that they were going to be the one person who would beat it, is severely threatened."

Emotional and psychosocial issues are magnified in many cases by the fact that patients were not armed with the proper information about their disease from the beginning. "Unfortunately, many of these people were not told—or did not hear when they were told—that up to 50% of those with relapsing-remitting disease are likely to make the transition to secondary progressive MS within 10 years of diagnosis," observed Dr. Kalb. "Within 25 years, up to 90% can expect the transition.¹ They may not have known that the transition was actually expected as part of their disease. They may have believed that if they were determined enough, or careful enough, they would be relapsing-remitting forever."

A Variety of Meanings

Individuals with MS and their families attribute a variety of meanings to the transition to secondary progressive disease, reported Dr. Kalb, who is also Clinical Assistant Professor of Neurology at New York Medical College, in Valhalla, New York (Table 1). "At the very best, they see it as 'bad luck,' that they have been dealt 'crummy cards.' Whatever terms they use, they are conveying the belief that this could have happened to anyone, but that it is happening to them."

Table 1. Patient Reactions to Secondary Progressive Transition.

Meanings Attributed to Transition
A belief that it is "bad luck"
Personal failure
A sign of weakness ("not strong enough")
Treatment failure
Punishment for past failures/inadequacies
A belief that it is "God's will"

Emotional Reactions
Resistance to further treatment
Frustration
Despair
Fear
Guilt
Embarrassment
Grief
Anger
Anxiety

Many people, however, "take the diagnosis a lot more personally. They see it as a sign of personal failure, that they did not try hard enough." It is also common to view the transition as a sign of weakness. "Individuals believe that they weren't strong enough, that they couldn't handle all the stress, that they couldn't fight the disease," commented Dr. Kalb. Others see the transition as a treatment failure or the consequence of poor treatment choices. "These people think that they should have started on an immunomodulator sooner, that they should have picked a different drug, or that they should have chosen alternative therapies."

Yet another common belief is that the onset of secondary progressive MS is "a punishment for a past failure or some inadequacy, or even God's will." This last belief can be a particular obstacle for members of the health care team who are trying to encourage patients to be more proactive on their own behalf. In particular, said Dr. Kalb, "it poses a particular challenge to the medical team, who are trying to treat the disease early and aggressively."

Regardless of the meaning that patients attach to secondary progressive MS, Dr. Kalb warned that "This is also a time when we often see more resistance in our patients. They reason that their MS is getting worse, so they question whether they should keep treating." The financial burden of treating a chronic disease for many years may also contribute to this

resistance. "We need to be aware of the signs of fear and frustration and despair. This is a time when our patients need support and encouragement."

Emotional Reactions to Progression

The specific emotional reactions that are common to any diagnosis of MS may become even more pronounced during the transition to secondary progressive disease. One of the most common and powerful emotions felt during this period is grief.

"This is such an integral part of living with MS," said Dr. Kalb. "It is a very normal reaction to any kind of loss, and it is in full force during this transition period." Anything during this time, she said, can represent a "loss of self, of control, and of personal identity." Heightened anxiety is also to be expected, because "the future has suddenly become even more uncertain than it was before the transition, and no person is comfortable with that level of uncertainty."

During the transition period, patients can express a tremendous amount of anger, which they direct at themselves, their family, the management team, pharmaceutical companies, insurance companies, or even God. While patients are coping with this anger, it is crucial for providers not to give in to their own tendencies to avoid uncomfortable situations. "We may have a tendency to pull away from angry individuals just at the time when they need us the most," Dr. Kalb emphasized.

Guilt and embarrassment are two other powerful emotions that surface during the transition period. These feelings may have multiple origins. "For the most part, this guilt stems from the inability to carry out important functions at home or at work," said Dr. Kalb. "Patients worry that they are 'letting people down' and causing trouble, and that they are not 'holding up their part of the bargain.' They express embarrassment that they are getting worse, despite strong determination, good care, and immunomodulator therapy."

Like despair, feelings of embarrassment can also cause patients to avoid their providers, for fear of telling them that the disease is progressing despite the provider's best efforts. "These reactions show how much we must do to educate our patients about this disease," emphasized Dr. Kalb. "Embarrassment and guilt are unnecessary burdens that people should not have to bear."

Embarrassment also arises in a patient who does not want to appear disabled in public. "Many of our relapsing-remitting patients have told us that one of the most important things for them is not to look impaired," commented Dr. Kalb. "For these patients, the fact that their symptoms may have been invisible helped them cope with their situation. They could usually explain away any of the problems they were having to anyone who asked."

Cognitive Difficulties in the Secondary Progressive Patient

At least 50% of persons with MS will experience some change in cognitive function during the course of their disease.^{1,2} For most individuals, cognitive changes are mild to moderate; for 10% of those with MS, however, these changes will be severe enough to interfere with everyday functioning. Like depression, cognitive changes may appear at any point in MS, even as the initial symptom. Although the degree of cognitive impairment is related to the extent of MS lesions, this association is weak,²⁻⁴ meaning that a newly diagnosed person with few lesions can be severely cognitively impaired, while someone with advanced disease can remain cognitively intact.

It is important to enlist the patient's help in recognizing signs of cognitive difficulties. "We need to listen to what our patients are telling us about their own health," said Dr. Kalb. Cognitive symptoms in MS include problems with memory, attention, concentration, word finding, problem solving and judgment, and visuospatial abilities, as well as a general slowing of information processing. These changes can affect people's ability to take care of their daily activities and responsibilities, and to accomplish several tasks at one time.

Interference with the ability to communicate and to solve problems "can be a significant source of interpersonal and vocational difficulties and is a major factor in employment," said Dr. Kalb. For this reason, it is important for patients to be informed about cognitive changes so that they can alert the provider to any changes they are experiencing. While many MS providers are reluctant to broach the subject for fear of frightening or upsetting patients, "in my experience, those who are undergoing cognitive changes are relieved to have their experiences understood and validated."

Mild to moderate cognitive dysfunction can be managed with a variety of compensatory strategies. "Early assessment and intervention are the most effective tools we have to help individuals function at a maximum level," said Dr. Kalb. Early recognition of cognitive difficulties allows psychologists and occupational therapists to devise effective interventions.

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Psychosocial Challenges

The psychosocial issues surfacing during the transition to secondary progressive MS affect patients, families, and every member of the multidisciplinary health care team. For example, the need to focus on planning for the future is suddenly brought to the fore, requiring the expertise of everyone involved.

"For many persons with secondary progressive disease, the future seems even more uncertain—and planning for that uncertainty becomes increasingly important," said Dr. Kalb. Much of this planning involves setting strategies for adjusting to greater limitations. "It is important to help people plan and problem-solve more effectively," she emphasized. "People are forced to redefine themselves in terms of their activities, taking their limitations into account."

This process of "redefining themselves" can be especially difficult for those who think to themselves that "the old me is gone, and I can't figure out what's left." The search for a new definition of self occurs each time individuals lose the ability to do something the way they used to do it.

These ever-increasing limitations require those with progressive MS to "redraw their map of the world." According to Dr. Kalb, "Patients struggle with issues of how to get to places, and how to accomplish what they need to once they get there." In these situations, it is critical to involve the rehabilitation team. "If people cannot do the things they used to do in the way they used to do them, they run the risk of simply not doing them at all, until their world has shrunk to nothing."

For the secondary progressive MS patient who faces increasing limitations, the old goals and priorities may not be feasible anymore, forcing them to identify a new set of life goals. The changes impact patients, family, colleagues, and friends; therefore, "This goal-setting cannot occur in isolation," explained Dr. Kalb. "In addition to making adjustments within themselves, people must renegotiate these changes with everyone else. . . . Everyone must become involved for these changes to occur."

Ironically, those in the transitional phase may be called upon to make these difficult choices when they are least equipped to do so. "These persons are grieving over their losses and experiencing changes in their lives," Dr. Kalb said. In addition, "as many as half of them may be experiencing significant depression or cognitive dysfunction."

Managing Depression and Cognitive Dysfunction

Depression and cognitive dysfunction in secondary progressive MS can prevent patients from being active partners in their care (see Box, "Cognitive Difficulties in the Secondary Progressive Patient"). It is important to remember that depression can occur at any point in the course of MS. "It can occur in someone who has never seemed depressed, or who has never seemed like the type of person who might become depressed."

The nature of depression in MS remains unclear. "We know that clinical depression occurs more frequently in MS than in other chronic diseases," said Dr. Kalb. "As many as 50% of persons with MS will experience a major depressive episode at some point or other in the course of their disease."^{2,3} Although research findings are not conclusive, depression in MS may be caused by a reaction to the losses and challenges of MS, as well as to neuropathologic changes in the brain. "Whatever the cause, we have to identify these patients and we have to offer treatment. Those who are depressed are suffering an unnecessary extra burden, and depressive symptoms can prevent them from participating actively in their own care."

Depression differs from normal grieving and has specific diagnostic criteria (see Table 2).⁴ Making the diagnosis difficult is the fact that "Some of these symptoms, such as fatigue, inability to concentrate, or even guilt, can be confused with MS symptoms, drug reactions, or normal feelings about the illness," said Dr. Kalb. In addition, patients are often reluctant to discuss these feelings with their health care providers for fear of sounding "crazy" or weak. "Most people don't want to sound like they're complaining all the time. Education about depression can help people recognize depressive symptoms and be more understanding and accepting of painful feelings they may encounter."

Table 2. *Diagnostic Criteria for Major Depressive Disorder.*

- Depressed mood most of the day, every day
- Diminished interest or pleasure in activities
- Significant weight loss [or gain]
- Sleep disturbances (eg, difficulty falling asleep or staying asleep)
- Fatigue
- Agitation
- Feelings of guilt or worthlessness
- Inability to think or concentrate

Source: American Psychiatric Association.⁴

The adverse effects of many antidepressants make the choice of drug therapy difficult in the MS patient. "There are many medications out there. Some of them are sedating, some are stimulating, some may interact with other medications, and virtually all of them interfere with sexual function," said Dr. Kalb. Although most depressive episodes are best treated

with a combination of medication and psychotherapy, as with any other treatment, "the goal is not to treat the symptoms, but to treat the person living with the illness. It may take some time and work."

The Implications for Care

Overall, the patient's transition to secondary progressive MS has significant implications for the health care team. An important priority is to explain to the patient what he or she can expect. "In order for people to do any kind of effective planning and problem solving, they need to know what is in store for them," said Dr. Kalb. "Persons with MS tend to put off thinking about tomorrow, even to the point of resisting our efforts to talk about employment and other issues."

She reiterated that the provider must resist any tendency to avoid the subject of the transition. "We tend to collude with our patients, because we do not want them to lose hope or become severely depressed. Yet we are not helping them if they cannot make important decisions or create the safety net they need to avoid unnecessary crises."

The historical lack of treatment choices for secondary progressive disease has contributed to this reluctance to approach the subject of transitioning MS. "The fewer treatments we have, the harder it is to talk about it," said Dr. Kalb. However, the emergence of effective therapies has changed the way patients, caregivers, and the whole health care team tend to react. "Since the beginning of the clinical trials on secondary progressive MS, all of us, including researchers, clinicians, patients, and families, have been paying a lot more attention to the disease course. Before this, those who were diagnosed with relapsing-remitting MS were undergoing treatment, while those diagnosed with secondary progressive MS felt 'left out in the cold.' Medications have made a lot of difference."

Nevertheless, even potential treatment choices such as mitoxantrone can be daunting. "Chemotherapy of any type is difficult," said Dr. Kalb. "Patients know just enough about it to make it frightening." Providers must be aware that this is a time in which patients will seek even more aggressive experimental treatments.

"When people are making a lot of difficult choices with undetermined outcomes, they need a lot of support," Dr. Kalb concluded. "We need to give them sufficient time and education, and the necessary referrals." Fortunately, the transition to secondary progressive MS is also a time when persons who were previously unwilling to make use of available resources now seek the benefits of counseling and education. "We need to be ready to provide this. Through our collaborative efforts, we can help patients make this transition more comfortably."

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