Treatment Optimization in Multiple Sclerosis*

Mark S. Freedman, David G. Patry, François Grand'Maison, Mary Lou Myles, Donald W. Paty, Daniel H. Selchen, on behalf of The Canadian MS Working Group

ABSTRACT: The treatment of multiple sclerosis has finally become possible with the advent of the current disease-modifying therapies (DMTs) that have had a significant impact on those living with this disease. Though demonstrating clear efficacy on a number of short-term outcome measures, unfortunately, these agents are not "cures" and many patients with multiple sclerosis continue to experience disease activity in spite of treatment. Clinicians are becoming more comfortable initiating therapy with DMTs, but it is now important to focus attention on monitoring the results of the chosen therapy and deciding whether or not a patient is responding well to treatment. At present, however, clinicians lack criteria for defining optimal versus suboptimal responses to DMTs as well as evidence-based guidelines on how to improve treatment outcomes. Using a recently published model as a framework, The Canadian Multiple Sclerosis Working Group developed practical recommendations on how neurologists can assess the status of patients on DMTs and decide when it may be necessary to modify treatment in order to optimize outcomes. The Canadian Multiple Sclerosis Working Group's recommendations are based on monitoring relapses, neurological progression and MRI activity. Other possible causes of suboptimal treatment responses or treatment failure are also considered.

RÉSUMÉ: Optimisation du traitement dans la sclérose en plaques. Le traitement de la sclérose en plaques (SEP) est enfin possible depuis l'arrivée des traitements modifiant l'évolution de la maladie. Bien que l'efficacité de ces agents ait été clairement démontrée à court terme, ils ne constituent malheureusement pas un traitement curatif et la maladie reste active malgré le traitement chez plusieurs patients atteints de SEP. Les cliniciens sont de plus en plus à l'aise de prescrire ces traitements. Cependant, il est important de porter une attention particulière aux résultats du traitement choisi afin d'évaluer la réponse thérapeutique. Actuellement, les cliniciens n'ont pas de critères pour distinguer une réponse optimale d'une réponse sous-optimale à ces traitements ou de lignes directrices basées sur les données actuelles de la science sur la façon d'améliorer son efficacité. Le Canadian Multiple Sclerosis Working Group a publié récemment des recommandations pratiques à l'intention des neurologues, comme modèle de référence pour l'évaluation de l'état des patients sous traitement et pour la conduite du traitement afin d'optimiser les résultats. Ces recommandations sont basées sur la surveillance des récidives, la progression neurologique et l'activité à l'IRM. D'autres causes possibles de réponses sous-optimales au traitement ou d'échec sont également abordées.

The introduction of the newer disease-modifying therapies (DMTs) for multiple sclerosis (MS) — interferon beta-1a (IFN -1a) (Rebif®, Avonex®), interferon beta-1b (IFN -1b) (Betaseron®) and glatiramer acetate (Copaxone®) — has had a significant impact on the management of those living with this disease.[1,2] These DMTs are the first agents that have been shown to alter the natural course of relapsing MS and, as such, Canadian and international guidelines emphasize the need to start treatment with these agents early in the disease course.[3,4]

Although there is evidence that the DMTs significantly reduce disease activity, these agents are not "cures" for MS. Thus, many patients with MS continue to experience disease

Table 1: Model for assessing treatment response based on patient outcomes (i.e., disease progression, relapses, and MRI findings).

Relapses

	Notable	Worrisome	Actionable
Frequency/severity	Single mild attack	Single, moderate attack in year, beginning 6 months after initiation of therapy	>1 moderate or severe attack in year, beginning 6 months after initiation of therapy
Recovery	Rapid following prompt steroid treatment	Slow following prompt steroid treatment	Incomplete

Progression

	Notable	Worrisome	Actionable
EDSS 3.5	<2 point change	2 point change	>2 point change
EDSS 4.0	<1 point change	1 point change	>1 point change
Clinically documented progression	No motor, minor sensory	Some motor, cognitive, or more pronounced sensory	Pronounced motor, cognitive, etc.

MRI

Change from previous MRI

	Notable	Worrisome	Actionable
New gadolinium-enhancing lesions New T2 lesions Enlarging T2 (burden of disease) New T1 hypointense lesions Enlarging T1 hypointense lesions Increased atrophy	Changes in 2 categories	Changes in 3 categories	Changes in >3 categories

Adapted with permission from Bashir K, Buchwald L, Coyle PK, et al. MS patient management: optimizing the benefits of immunomodulatory therapy. Int J MS Care 2002; (Suppl):1-7.

EDSS = Expanded Disability Status Scale

activity, in spite of treatment with DMTs, including continued relapses, progressive impairment, and ongoing accumulation of magnetic resonance imaging (MRI) disease burden. In controlled studies, the magnitude of a treatment effect can be viewed relative to a parallel group of patients on placebo treatment. Obviously, this is not possible when treating individual patients with DMTs in clinical practice. Therefore, if disease activity persists, it is difficult to measure whether a response to DMTs is better than that dictated by natural history. At present, clinicians lack criteria for defining optimal versus suboptimal responses to

DMTs as well as evidence-based guidelines on how to improve treatment outcomes. Recently, Bashir et al[5] made recommendations on how to determine suboptimal responses to immunomodulatory therapy based primarily on relapse-, progression-, and MRI-related outcomes (see Table 1) and proposed an analog model for when to reconsider treatment options (see Figure 1). The model ranks outcomes as "notable" (low level of concern), "worrisome" (moderate level of concern), or "actionable" (high level of concern) with regards to the need for considering modifications to the chosen treatment regimen. If

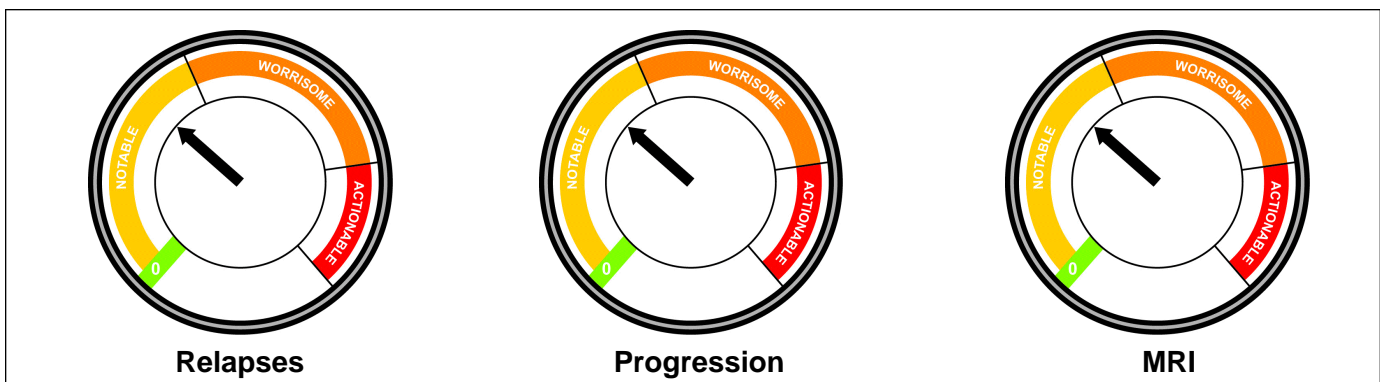**Figure 1:** *Analog model for assessing the effectiveness of therapeutic strategies.*
Each gauge represents a continuum from no concern (0 [zero]) to a high level of concern ("actionable"), and can be used to guide clinical decision-making. Reproduced with permission from Bashir K, Buchwald L, Coyle PK, et al. MS patient management: optimizing the benefits of immunomodulatory therapy. Int J MS Care 2002; (Suppl):1-7.

all three outcomes (i.e., relapses, progression, and MRI findings) are "notable", any two are "worrisome", or any one is "actionable", then it is likely that treatment response is suboptimal and that strategies to optimize treatment response need to be implemented.[5]

Using this model as a framework, The Canadian Multiple Sclerosis Working Group (CMSWG) developed practical recommendations on how neurologists can assess the status of patients on DMTs and decide when it may be necessary to modify treatment in order to optimize outcomes. Like those proposed by Bashir et al[5] the CMSWG's recommendations are based on relapses, disease progression as measured by the Expanded Disability Status Scale (EDSS) (or EDSS progression), and MRI outcomes. Other possible causes of suboptimal treatment responses or treatment failure are also considered.

RELAPSES

The CMSWG agreed with the following definition of a relapse proposed by the International Panel on the Diagnosis of Multiple Sclerosis:

"An attack (exacerbation, relapse) refers to an episode of neurologic disturbance of the kind seen in MS, when clinicopathologic studies have established that the causative lesions are inflammatory and demyelinating in nature."[6]

The Panel further states that *"for general diagnostic purposes, an attack…should last for at least 24 hours,"* and that *"in defining what constitutes separate attacks…it was agreed that 30 days should separate the onset of the first event from the onset of the second event."*[6]

The pivotal clinical trials of DMTs suggest that the relapse rate in patients with relapsing-remitting multiple sclerosis (RRMS) is approximately 1.0 per year (before treatment initiation),[7-12] while natural history data suggest a slightly lower relapse rate of 0.4 to 1.0 per year.[13] The correlation between relapse rates and long-term prognosis in MS is controversial. In a review of this subject, Weinshenker and Ebers[13] concluded that there is a weak correlation between early relapse rate and disease progression. Confavreux et al[14] found that once a clinical threshold of irreversible disability is reached (EDSS score=4.0), relapses have no effect on the progression of disability. However, a report on the collective experience with the placebo groups of several clinical trials suggests that relapses correlate directly with increasing disability.[15]

In addition to the uncertain predictive value of relapse rates on long-term disability, other factors may confound the use of relapse outcomes to determine treatment efficacy. First, evidence suggests that relapse rates decline over time[13] and that regression to the mean occurs (i.e., patients chosen for having high relapse rates at the start will invariably have lower rates with time due to a natural "falling back" to the mean population relapse rate), which makes it difficult to determine treatment efficacy based on relapses. Secondly, relapse rates are a direct function of how often patients are followed. For example, Thygesen[16] found that relapse rates decline with less frequent observation (e.g., annual relapse rate equal to 1.2 at three-week, 0.5 at three-month, 0.3 at six-month, and 0.2 at 12-month follow-up). Finally, the CMSWG noted that it may be difficult to translate relapse data from the clinical pivotal trials into a pathway for allocating treatment in routine clinical practice, since trial subjects tend to have higher relapse rates, a longer disease history and relatively low EDSS scores compared to typical patients seen in the clinical setting.

Despite these potential problems in interpreting relapse outcomes, the CMSWG agreed that relapses are significant to patients early in the course of MS (due to short-term disability, lifestyle, and psychosocial issues) and, therefore, warrant treatment. Although not yet supported by strong evidence, the cornerstone of the current rationale for early treatment is the possibility that suppression of early clinical and subclinical attacks may modify the course of MS.

RECOMMENDATIONS FOR DETERMINING THE LEVEL OF CONCERN WITH REGARDS TO CONSIDERING TREATMENT MODIFICATION BASED ON RELAPSE OUTCOMES

Currently, there is no consistent model for defining treatment success or failure based on relapse outcomes. Instead, "gestalt" seems to be the major determinant of treatment failure in clinical practice, plus the obvious negative factors such as clinical deterioration and unacceptable side effects. Therefore, the CMSWG agreed that the only clear measure of treatment efficacy (based on relapses) is to compare post-treatment relapse rates and severity to baseline rates and severity in each individual patient. At a minimum, the baseline reference time frame should be the two years prior to treatment initiation; ideally, objective and prospective relapse data should be collected during this reference period. If prospective data collection is not possible, the CMSWG suggested that, rather than having patients rely on memory to determine relapse outcomes, more accurate ways to collect historical relapse data are required. For example, regular telephone contact (e.g., every three months) with patients or a system of standardized patient diaries may be useful for obtaining more objective information.

Important factors to consider when judging treatment response based on relapse outcomes are relapse rate, severity, and extent of recovery. There is clear evidence that DMTs have an effect on relapse rate and severity: the pivotal clinical trials have shown a 29-33% reduction in the frequency of relapses after two years of treatment as well as a reduction in the number of hospitalizations and the need for steroids. It should be noted that in the pivotal trial of IFN -1a, 30 mcg, once weekly, the percent relapse reduction was derived from a *post-hoc* subgroup analysis. Intention-to-treat analysis of all patients treated with IFN -1a (Avonex®) for the entire study period found only an 18% reduction in relapse rate compared to placebo.[2,12] Some studies attempted to qualify the severity of attacks into mild, moderate, and severe based on changes noted in Scripps' Neurological Rating Scale scores. In these studies, DMT was found to significantly reduce the number of moderate and severe episodes.[9,10] Clinical trial evidence for an effect on recovery (i.e., either speed or degree) from relapses, however, has been more difficult to obtain.

An incidence cohort study of 308 MS patients followed for at least 25 years found that polysymptomatic (i.e. symptoms and signs reflecting multisystem involvement) attacks were predictive of poor long-term prognosis.[17] Furthermore, Bergamaschi et al[18] found that relapses involving motor and

Table 2: Recommendations for determining the level of concern with regards to considering treatment modification based on relapse outcomes.

	Low	Medium	High
Rate	Moderate reduction (>75%, <100%) vs baseline	Modest reduction (35-75%) vs baseline	Minimal reduction (<35%) vs baseline*
Severity	Mild • Steroids not required • Minimal effect on ADL • 1 functional domain affected • No or mild motor/cerebellar involvement	Moderate • Steroids required • Moderate effect on ADL • >1 functional domain affected • Moderate motor/cerebellar involvement	Severe • Steroids/hospitalization required • Severe effect on ADL • >1 functional domain affected • Severe motor/cerebellar involvement
Recovery	Prompt recovery	Incomplete recovery at 3 months	Incomplete recovery at 6 months

Note: Reference time frame 2 years prior to treatment initiation. Ideally, prospective and objective relapse data should be obtained during the reference period. ADL= activities of daily living
*Suggests treatment is no better than placebo.

sensory systems were predictive of suboptimal long-term outcomes. Therefore, the CMSWG recommended that the following should be taken into consideration when assessing relapse severity: the effect of the relapse on activities of daily living, the type and number of systems involved (i.e., relapses that are polysymptomatic or that affect the cerebellar/motor systems tend to be more severe), and whether or not a course of steroids was required. Relapses that require steroids or hospitalization, that have both a severe affect on activities of daily living and motor or cerebellar involvement, and that affect more than one functional domain should prompt a high level of concern and may warrant treatment modification (once other relapse factors, progression, and MRI findings are taken into consideration).

Runmarker[17] found that the degree of remission after the last relapse had prognostic significance at five years post MS onset: patients experiencing complete remission after the preceding relapse had a better prognosis than those experiencing incomplete remission. Lublin et al[15] also found that incomplete relapse recovery resulted in sustained neurological deterioration. Unexpectedly, Confavreux et al[19] showed that the rate of progression from an EDSS score of 4 to a score of 7, and progression from a score of 6 to a score of 7 took longer in cases with an incomplete versus complete recovery from the first relapse. The Kaplan-Meier analysis also showed that a longer time from onset of MS to the second episode of the disease did not influence time from assignment of a score of 4 to assignment of a score of 6. Thus, clinical relapse variables may only influence the course of early disease. The long-term outcome of patients in whom relapses have been suppressed by DMT is unknown.

Data from natural history studies suggest that the majority of relapses improve by three months in patients with early MS, while 22% improve between three and 12 months, and 10% improve between six and 12 months.[20] Therefore, the CMSWG recommended that treatment modification be considered in patients who have not recovered from relapses after six months from the time of onset (once other clinical outcomes are considered).

Recommendations for determining the level of concern with regards to considering treatment modification based on relapse outcomes are shown in Table 2.

The CMSWG acknowledged that the use of percent reductions in relapse rate compared to baseline could be confounding, particularly in patients with a low number of relapses at baseline (i.e. only one or two attacks in their entire history). Therefore, the meaning of a 75% reduction in relapse rate (based on Table 2) would be more relevant in a patient with a baseline rate of three events in the last two years. In patients with a low number of attacks, a longer baseline period of observation may be required and, to assist in making decisions regarding treatment modification, more weight may need to be placed on other factors, such as relapse severity and recovery, progression, or MRI outcomes.

Finally, the CMSWG agreed that relapse data from sources other than clinical trials need to be obtained and recommended that a government- or insurer-sponsored long-term registry of all consenting patients on DMTs be established in order to better understand the clinical importance of relapses as well as the long-term benefits of DMTs.

PROGRESSION

Currently, the Kurtzke EDSS,[21] that derives from a routine clinical examination, is the most commonly used standardized and validated measure of disease progression. Although the Multiple Sclerosis Functional Composite, which comprises quantitative functional measures of ambulation, arm and hand function, and cognition, represents a promising advance in the assessment of disease progression,[22] application of the Multiple Sclerosis Functional Composite in routine clinical practice still needs to be validated.

When using the EDSS to measure disease progression, the accurate assessment of ambulation is critical for EDSS scores between 4.0 and 5.5, since scores in this range are primarily based on the maximum unaided walking distance (i.e., 500 m=EDSS 4.0, 300 m=4.5, 200 m=5.0, and 100 m=5.5). A 1-point

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increase in EDSS scores within this range is considered significant deterioration in function.[23,24]

The CMSWG agreed that the ideal measurement of maximum unaided walking distance is to have the nurse walk with the patient (as is done in clinical trials). However, due to both space and resource limitations, this is difficult to do in clinical practice and, therefore, ambulation is often assessed by direct questioning of the patient about distance walked on a "good day". As a result, measurements of ambulation obtained in the clinical setting are less likely to be accurate than those obtained in clinical trials. The CMSWG agreed that more systematic, objective methods of direct patient questioning or self-assessments of distance walked are required in order to improve the accuracy of this measurement. Using a self-administered EDSS, Bowen et al[25] found a high correlation (r=0.89) between patient- and physician-ratings of ambulation. In this study, subjects were asked to estimate their ability to walk various distances with or without assistance. Other self-report questionnaires of disability and impairment (e.g., Minimal Record of Disability, The Symptom Inventory, Performance Scales) have been shown to have overall moderate correlations with physician ratings of disability[26-30] and should be considered when assessing disease progression. Recently, Hobart et al[31] developed the 12-item MS Walking Scale – a self-report measure of walking ability. The 12-item MS Walking Scale has been shown to be a reliable, valid and responsive measure of walking ability in MS, and may offer a more simple and flexible measurement of walking distance in clinical practice.

Providing a list of references for what constitutes 100 m, 200 m, 300 m and 500 m, may help improve patient estimates of distance walked (e.g. a standard football field or city block are nearly 100 m; the length of hallways the patient accessed to get from the elevator to the office, or the distance the patient walked from the parking lot to the building can be calculated and may aid in estimations of ambulation). Encouraging patients to consider unaided walking distance when estimating distance walked may also help ensure that more accurate EDSS measurements are obtained. For instance, many patients that utilize a cane do so for "security" or for comfort reasons, but do not actually require it. Using a cane dictates scoring a "6" on the EDSS scale. However, if the patient does not actually require the cane to walk distances of 100 m or 200 m, then the EDSS would drop to 5.5 or 5.0, respectively. Therefore, it is critical to properly assess changes in this EDSS range since even half-point increases indicate significant progression. If the EDSS is overestimated (e.g., score of 6.0 is assigned because the patient prefers to use a cane), the measure will become insensitive to change over the ensuing years. The timed 25-foot walk (T25-FW) has been suggested as a practical solution to patient estimations of distance walked;[32,33] to date, however, the results of the T25-FW are difficult to translate into EDSS scores. It is also hard to know what magnitude of change in the T25-FW is meaningful given the variability alone that is observed between successive measurements, even in the absence of any true disease progression (see discussion below).

In addition to the accuracy of distance measurement, it is important to note that day-to-day fluctuations in MS symptoms lead to significant measurement variability. Albrecht et al,[24] for example, found day-to-day variability in maximum walking distance that, in some cases, led to meaningful EDSS changes of up to 1.5 points; this variability could easily be misinterpreted as disease progression. A similar variability in measurements of maximum walking time was also noted.[24] Schwid et al[34] found that the T25-FW and nine-hole peg test varied by less than 20% of individual mean scores on repeated testing over five consecutive days. Therefore, in order to accurately interpret observed treatment effects, the CMSWG recommended that, in an individual patient, a 20% change on functional tests can be considered to be the threshold that reliably indicates a true change in function.

Other factors that may influence measures of progression include: depression, cognitive function, fatigue, and the presence or absence of infection. Although all CMSWG members agreed that it is important to assess cognition, they also acknowledged that there are currently no easy-to-use standardized scales to assess cognitive function and, furthermore, that it is often difficult to know what to do in cases where cognitive decline is noted. The CMSWG recommended that, in such situations, an MRI may assist in clinical decision-making; however, the question still remains as to whether treatment modification will impact cognitive function (due to the paucity of evidence in this area).

Depression is also common in MS, with a lifetime prevalence of 40-60% in clinic patients[35,36] and a cumulative risk for depression of 50%.[37] It is unclear to what degree depression is related to patients' emotional or psychological responses to having a chronic illness or to the disease process itself (i.e., MS may affect areas of the CNS that regulate mood). Evidence suggests that IFN treatment does not significantly predispose patients to develop depression,[38,39] nor does it appear to strongly influence pre-existing depression;[38] however, it should be noted that later studies in this area tended to exclude patients with a history of suicide attempts or uncontrolled depression.

Feinstein[40] found that depression is often undetected and untreated in MS patients. However, depression may significantly impact the measurement of disease progression and, therefore, should be assessed at regular intervals. Many formal screening tools for depression are available (e.g., Modified Beck Depression Inventory,[41] Hamilton Rating Scale for Depression,[42] Center for Epidemiological Studies Depression Scale[43] and the Zung Self-Assessment Depression Scale[42]). However, the US Preventive Services Task Force recommends that asking the following two simple questions may be as effective for assessing depression as these longer assessment scales:[44]

- "Over the past two weeks, have you felt down, depressed, or hopeless?"[45]
- "Over the past two weeks, have you felt little interest or pleasure in doing things?"[45]

Since mood disorders are dynamic and recurring, Caine et al[46] suggested slight modifications to these questions to ensure that depression that may have occurred during the interval between visits is detected (e.g., "Since I last saw you, have you felt down, depressed, or hopeless?"). Following a positive screening test, full diagnostic interviews that use standard diagnostic criteria (i.e., those from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) should be performed.[44] If the patient is diagnosed as depressed, referral for psychotherapy or antidepressant treatment should be initiated.

Finally, it is imperative that progression be confirmed over time in order to distinguish true, sustained progression from transient progression resulting from incomplete relapse recovery or other disease processes. Rio et al[47] found that a large proportion of IFN -treated patients with a confirmed EDSS increase of 1 or 1.5 points at three and six months had transient treatment failure and did as well as those patients with no periods of treatment failure. In the intramuscular IFN -1a trial, 47% of patients reaching the criteria for treatment failure in the first year of therapy subsequently improved; this transient failure was more common in patients with low EDSS scores.[48] A study examining the placebo cohorts of two large phase III trials (i.e., the United States glatiramer acetate trial and the multinational Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis study) found that almost 50% of untreated patients with progression defined as strictly as an EDSS increase of 2 points at six months, did not have sustained progression at two years (positive predictive accuracy of 55%).[49]

The time interval at which disease progression is reassessed varies considerably in clinical practice. The CMSWG agreed that, at a minimum, progression should be assessed annually in stable patients and every three months in patients who are not doing well.

RECOMMENDATIONS FOR DETERMINING THE LEVEL OF CONCERN WITH REGARDS TO CONSIDERING TREATMENT MODIFICATION BASED ON DISEASE PROGRESSION

Rio et al[47] assessed the clinical usefulness of different treatment failure criteria in a cohort of RRMS patients treated with IFN and found that the criterion of a confirmed 1-point EDSS increase at six months showed the best sensitivity (76.5%), with satisfactory specificity (89%) for predicting sustained progression at four years. Based on this finding, the CMSWG recommended that, prior to considering treatment modification on the basis of progression in disability, progression should be confirmed at six months. However, the CMSWG acknowledged that there may be exceptions to this recommendation, such as longer periods of observation in patients with low EDSS scores (to maximize specificity for true

versus transient progression). The CMSWG also noted that when documenting progression clinically, EDSS increases that are due to changes in multiple domains[17] (e.g. changes in motor and cerebellar subscores) are often more predictive of true, sustained disability progression and, therefore, are recognized as having a "high" level of concern (actionable)".

Table 3 summarizes the CMSWG's recommendations for determining the level of concern with regards to considering treatment modification based on disease progression.

The recommendations in Table 3 assume an observation period of at least one year. Throughout the observation period, it is important to consider when treatment was initiated. In the first year of therapy, for example, signs of progression may be reflective of disease activity that occurred prior to treatment initiation. Therefore, the CMSWG suggested that signs of progression noted during year two of therapy may provide a better reflection of the efficacy of DMT than those seen in year one. Furthermore, the CMSWG agreed that a second confirmed progression occurring within the period of observation, even if less than a "high" level of concern, warrants considering treatment modification.

Finally, when assessing progression, it is important to document the functional subscales that are having the most impact on the EDSS score. Lublin et al,[15] for example, found that 46% of EDSS changes noted at one point in time compared to a different time point were due to different functional subscores. In these cases, it is more likely that the incomplete recovery from a relapse is responsible for EDSS changes than is true progression in disability. Determining true, sustained progression requires that changes seen in one or more particular subscores are maintained over time. Furthermore, EDSS increases that are due primarily to ocular changes are probably of less concern than those resulting from changes in cerebellar or motor function.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging measures of disease activity include new gadolinium (Gd)-enhancing lesions, new or enlarging T2 hyperintense and T1 hypointense lesions, and atrophy. These MRI measures have had a major impact on understanding the pathology of MS. Liest et al,[50] for example,

Table 3: Recommendations for determining the level of concern with regards to considering treatment modification based on disease progression.

	Low	Medium	High
EDSS 3.5	< 2 points	2 points confirmed at 6 months	>2 points confirmed at 6 months 2 points confirmed at 12 months
EDSS 4 to 5	<1 point	1 point confirmed at 6 months	>1 point confirmed at 6 months 1 point confirmed at 12 months
EDSS 5.5		0.5 point confirmed at 6 months	>0.5 point confirmed at 6 months
Clinically documented progression	No motor, minor sensory	Some motor, cerebellar or cognitive; multiple domains affected	Pronounced motor, cerebellar, or cognitive; multiple domains affected

Table 4: Recommendations for determining the level of concern with regards to considering treatment modification based on MRI outcomes.*

Change in MRI categories	Low	Medium
New Gd-enhancing lesions		
New T2 lesions		
Enlarging T2 (burden of disease)	Any new lesion	Increase in >2 MRI categories
New T1 hypointense lesions		
Enlarging T1 hypointense lesions		
Atrophy		

*Note: Routine follow-up MRI is not recommended in established MS; MRI must have been performed according to a standardized protocol; treatment modification should not be considered based on MRI outcomes alone. Gd = gadolinium

found that RRMS patients with a high proportion of enhancing lesions in the early stages of the disease are at higher risk for the development of cerebral atrophy. Using T1- and T2- weighted images, Kalkers et al[51] found that significant brain atrophy occurs in MS and that the rate of atrophy development is largely independent of the course of the disease and other clinical characteristics. Other studies using MRI measures to assess axonal injury have shown that cerebral axonal damage occurs in the early stages of MS and continues throughout the course of the disease.[52,53]

O'Riordan et al[54] found that baseline T2-weighted MRI findings in patients with a clinically isolated syndrome were highly predictive of the risk of developing clinically definite MS as well as the type of disease and the extent of disability. A serial MRI study found that in patients with a clinically isolated syndrome suggestive of MS, increases in the volume of MRI lesions noted in the first five years correlated moderately with the degree of long-term disability from MS.[55] However, unlike the studies of clinically isolated syndrome patients which have examined the predictive value of MRI over a five- to ten-year period, studies of patients with RRMS have generally been limited to cross sectional investigations or studies that examined the relationship between various MRI abnormalities and clinical disease over two years or less. In general, the relationship between MRI findings and clinical disease noted in these studies has been weak, albeit statistically significant.[55-58] The weak predictive value of MRI on future disability may be due to the relatively short follow-up period; regardless, these findings likely indicate that progression in persistent disability is related to changes other than acute disease activity measured by MRI. In fact, an international group of investigators recently stated that although MRI provides a reflection of the underlying pathology of the disease, it is not a valid surrogate in any clinical form of MS and no single MRI measurement in isolation is sufficient to monitor the disease.[56]

RECOMMENDATIONS FOR DETERMINING THE LEVEL OF CONCERN BASED ON MRI OUTCOMES

Based on the weak predictive value of MRI on future disability, the CMSWG concluded that decisions to modify DMT

should not be based on MRI findings alone. Therefore, the "high" level of concern section has been removed from the recommendations made in Table 4.

In accordance with the new Vancouver Consortium of MS Centres MRI Guidelines,[59] the CMSWG agreed that an MRI that meets a standardized protocol should be done as part of the initial evaluation and diagnosis of suspected MS, and follow-up MRI should be performed to confirm the diagnosis of MS. The guidelines also recommend that the baseline evaluation of a patient with established MS include an MRI that meets a standardized protocol, in addition to a comprehensive neurological history and examination.[59] However, routine, follow-up MRI is currently not validated in the absence of clinical indications.[59] Indications for follow-up MRI include:
- Unexpected clinical worsening;
- Re-assessment for treatment initiation or modification;
- Suspicion of a secondary diagnosis (other than MS).

If a follow-up MRI is required for established MS, the Vancouver Guidelines recommend that it be performed according to a standardized protocol and compared to previous studies.[59] The CMSWG noted that MRI evaluations performed every two years may provide valuable information in the future if they are performed according to this proposed standardized protocol and the results are collected and correlated with clinical outcomes.

Recommendations for determining the level of concern based on MRI outcomes are shown in Table 4.

OTHER POSSIBLE FACTORS RELATED TO TREATMENT RESPONSE

The CMSWG also addressed other possible factors for suboptimal responses to DMT or treatment failure. Possible causes of suboptimal responses to therapy include: the heterogeneity of MS immunopathology; genetic disease load; interferon response genes; or overall poor healing mechanisms (i.e., "poor healers"). Lucchinetti et al[60] have described the pathologic findings from a database of patients with MS, including acute lesions studied by biopsy or autopsy. Four patterns of lesion morphology were found, based on the distribution of myelin-protein loss, the geography and extension of the plaques, the extent and pattern of oligodendrocyte destruction, and whether or not there was evidence of immunoglobulin or complement activation. They found that one of these patterns usually predominates in a particular patient, suggesting that the mechanisms and targets of demyelination in MS may be fundamentally different in distinct subgroups and/or stages of the disease.[60] These findings may explain the heterogeneity in treatment responses to DMTs. However, further studies are required to determine how different pathologic features can be used to distinguish treatment responders from nonresponders.

Numerous studies have demonstrated a strong genetic component to MS. Therefore, susceptibility genes may be of value in predicting response to DMT. It has also been suggested that polymorphisms in interferon receptor genes may play a role in determining treatment response; to date, however, no significant relationship between these receptor genes and therapeutic outcomes has been identified.[61]

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The CMSWG also discussed the concept of "poor healers" – those patients with overall poor response mechanisms. Some patients do not appear to remyelinate very well, while others may not secrete sufficient brain-derived neurotrophic factor[62] or other trophic factors within an inflammatory focus that may lead to more effective repair processes and, hence, recovery. Future studies should investigate ways to identify these poor healers, to identify factors that might be responsible for this phenomenon, and to possibly develop criteria for determining potential poor responders prior to treatment initiation.

Treatment failure or a suboptimal response to the DMTs may also be related to a number of other factors. First, disease activity may be too excessive for DMT from the outset (e.g., progression to nonrelapsing secondary progressive MS or primary progressive MS). However, it is currently not possible to know exactly at what stage DMTs are no longer effective. Other reasons include poor adherence to therapy, misdiagnosis, "pseudo" failure (e.g., spasticity), or loss of drug effect. For example, patients may self-adjust treatment to manage side effects, and this may be responsible for a poor response to therapy. The assessment of treatment adherence at each clinic visit should be considered mandatory in the management of MS patients that use DMTs.[63] When simply asked if they continue to use their medications as instructed, many patients will answer affirmatively. However, responses tend to be more varied when patients are questioned more specifically about the number of injections used in a given month.[63] Therefore, patients should be counseled regularly on the importance of treatment adherence. In this sense, a friendly patient diary can help note discrepancies in adherence. A "pseudo" failure resulting from treatment-induced spasticity, depression, or loss of conditioning should also be considered. Distinguishing a "pseudo" failure from a true treatment failure requires close patient examination and questioning by the neurologist.

Loss of drug effect may also be responsible for treatment failure, particularly in patients who were initially treatment responders. Epitope spreading, changes in the underlying immunology, tachyphylaxis, or neutralizing antibodies (NAbs) may all play a role in the loss of treatment efficacy.

ROLE OF NEUTRALIZING ANTIBODIES

Neutralizing antibodies occur in up to one-third of patients treated with IFN .[64] The rate of NAb production, however, appears to be less with IFN -1a than with IFN -1b treatment, depending on the dose, frequency and mode of injection.[65] Although evidence suggests that NAbs may reduce the bioavailability and clinical efficacy of IFN treatment,[66] one study found no definitive relationship between NAb formation and the loss of clinical or MRI response.[67] Furthermore, the effects of NAbs appear to be transitory, occurring primarily in the first few years of therapy, with the majority of NAbs disappearing over time.[64] In the Prevention of Relapses and Disability by Interferon- -1a Subcutaneously in Multiple Sclerosis-4 study,[11] NAbs demonstrated their greatest effect on reducing biological markers and clinical outcomes after they were present for one year or more, with significant clinical effects occurring only in the third year of the study. By the end of this study, however, there was no significant difference in the

reduction of relapses between patients with or without NAbs.

Although the European Study Group in IFN -1b in Secondary Progressive MS found that the presence of NAbs was associated with a negative effect on relapse rate, there was considerable variation depending on how the data were handled statistically and what titres were found. In NAb positive patients, MRI T2 burden of disease was higher, however, there was no attenuating effect of NAbs on EDSS disability progression.[68] Similar data regarding the lack of progression despite NAb positivity have recently been demonstrated in a large group of Danish patients followed for almost five years.[69] There also looms a most curious and unexplained phenomenon: in virtually all of the studies that collected NAb data prospectively in IFN-treated patients, there was a seemingly enhanced relapse rate reduction in the first year of treatment in patients that went on to eventually become NAb positive.

Although glatiramer acetate is not considered a product to which NAbs can develop, one study found that all glatiramer acetate-treated patients developed binding antibodies and that there was a tendency toward fewer relapses in patients who developed the highest titres.[70] More recently, a small, preliminary study found that less than 50% of glatiramer acetate-treated patients were found to have binding antibodies, and those patients with higher titres were reported not to fare as well clinically.[71] Thus the role of binding antibodies to glatiramer acetate is still unclear.

There are many unanswered questions with regard to the use of NAbs for determining treatment response. Clinically relevant cut-off points for "low" and "high" NAb titres have not been established. Measurements in clinical trials were taken using different assays and, therefore, titres cannot be compared across studies. Furthermore, due to the high inter-laboratory variability in methods used to obtain titres, it is likely not possible to designate minimal antibody positivity. In addition, the assay that best assesses "meaningful" NAbs, how and when to monitor for the appearance of NAbs, the predictive value of a single positive test, and the long-term clinical significance of transient versus persistent NAb positivity are still unknown. Clearly, there are patients who respond either very well or very poorly in studies regardless of NAb positivity. Therefore, the CMSWG concluded that although NAb positivity may be associated, in some cases, with a suboptimal response to IFN therapy, it is not possible to make conclusions about the magnitude of this effect and, hence, it is currently not possible to make recommendations for treatment modification based on NAb findings. Instead, treatment decisions should be based primarily on clinical grounds, as was concluded recently by others.[68]

ANALOG MODEL FOR DETERMINING TREATMENT RESPONSE

Based on the progression, relapse, and MRI recommendations (Tables 2, 3, and 4), the CMSWG proposed a revised analog model for determining the level of concern with regards to consideration for modifying a treatment regimen (see Figure 2). Like the model proposed by Bashir et al[5] each gauge represents a continuum from a "low" (0 [zero]) to a "high" level of concern (consider treatment modification). Sub-gauges within each gauge can help provide a cumulative assessment of the patient's response to treatment. In the relapse gauge, for
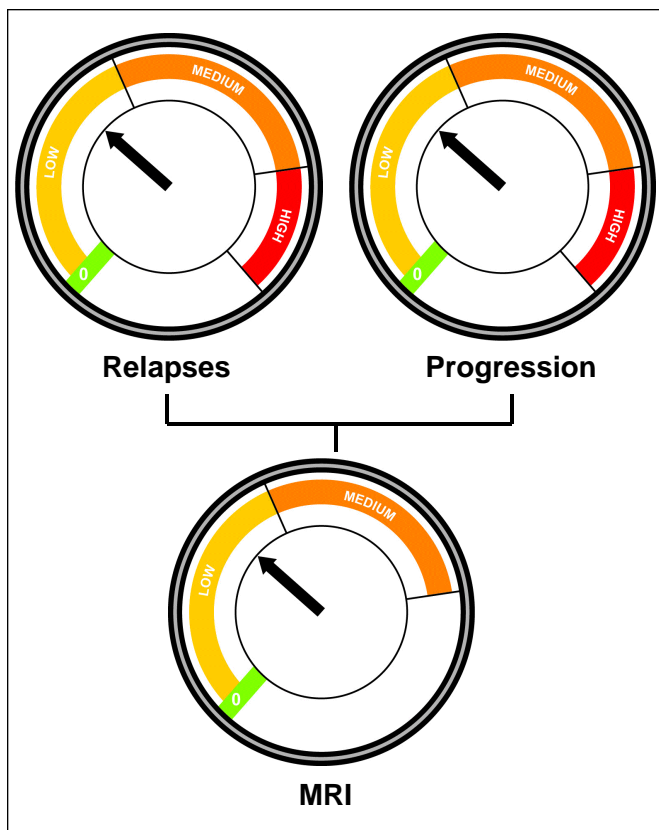
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Figure 2: *Revised analog model for assessing the level of concern with regards to considering treatment modification.*

example, sub-gauges would include relapse rate, severity, and recovery.[5]

The revised model differs from that proposed by Bashir et al[5] with regards to the use of MRI findings: in the revised model, MRI outcomes can be used to support relapse or progression outcomes, but cannot be used in isolation to determine the level of concern with regards to considering treatment modification.

SUMMARY

This review helps to define levels of concern regarding the various outcomes physicians look for when judging treatment response in MS patients with active disease. At this time, it is not possible to define a set formula for indicating when to alter treatment, but this should be done by each physician, weighing all the evidence for a suboptimal response for an individual patient.

The recommendations proposed by the CMSWG and Bashir et al[5] represent an important first step in the development of criteria for defining optimal versus suboptimal responses to DMT and recommendations for determining when treatment modification is warranted in order to optimize outcomes. Implicit in these recommendations is the importance of regular and standardized clinical assessments to document relapses and evaluate disease progression.

The next step is to test and validate these recommendations and, if possible, design comprehensive guidelines for treatment optimization based on the results of this validation process. Currently, the CMSWG is developing a standardized patient diary that can be used to obtain more objective information regarding patient outcomes as well as a quantifiable scale that will make decisions regarding treatment modification easier in the future.

Jean-Pierre Bouchard, MD, FRCPC

Laval University
MS Clinic of Quebec ARGA
Quebec City, Quebec

Carol A. J. Boyle, MD, FRCPC

Division of Neurology
University of Saskatchewan
Saskatoon, Saskatchewan

Jean-Pierre H. Coté, MD, FRCPC

University of Montreal
Cité de la Santé de Laval
Montreal, Quebec

Mark S. Freedman, MSc, MD, FRCPC

MS Research Clinic
University of Ottawa
Ottawa Hospital General Campus
Ottawa, Ontario

Warren C. Goldstein, MD, FRCPC

University of Toronto
Toronto, Ontario

Andrew J. Gomori, BSc, MD, FRCPC

Section of Neurology
Department of Medicine
University of Manitoba
Winnipeg, Manitoba

François Grand᾿Maison, MD, FRCPC

Division of Neurology
University of Sherbrooke
Hôpital Charles LeMoyne
Longueuil, Quebec

Stanley Atsumu Hashimoto, MD, FRCPC

Department of Medicine
Division of Neurology
University of British Columbia
Vancouver, British Columbia

Samir Jarjoura, MD, FRCPC
MS Clinic
Faculty of Medicine
University of Sherbrooke
Fleurimont, Quebec

Yves Lapierre, BA, MD, FRCPC
MS Clinic
Montreal Neurological Institute
McGill University
Montreal, Quebec

Michael H. MacEachern, MD, FRCPC
Dr. Georges-L. Dumont Regional Hospital
Moncton, New Brunswick

Debbie Mason, MBChB, FRACP
MS Clinic
London Health Sciences Centre
London, Ontario

David R. Morgenthau, MD, FRCPC
Humber River Regional Hospital
St. Michael's Hospital
Toronto, Ontario

Mary Lou Myles, M.Cl.Sc, MD, FRCPC
University of Alberta
Edmonton, Alberta

David G. Patry, MD, FRCPC
MS Clinic
Department of Clinical Neurosciences
University of Calgary
Foothills Medical Centre
Calgary, Alberta

Donald W. Paty, MD, FRCPC
Division of Neurology
Department of Medicine
University of British Columbia
Vancouver, British Columbia

John Erik Paulseth, MD, FRCPC
McMaster University
Hamilton, Ontario

Daniel H. Selchen, MD, FRCPC
University of Toronto
Trillium Health Centre-Mississauga
St. Michael's Hospital
Toronto, Ontario

Norbert J. Witt, MD, FRCPC
University of Alberta Hospital
University of Alberta
Edmonton, Alberta

Michael M. C. Yeung, MD, FRCPC
MS Clinic
Department of Clinical Neurosciences
University of Calgary
Foothills Medical Centre
Calgary, Alberta

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