Changing Therapy in Relapsing Multiple Sclerosis: Considerations and Recommendations of a Task Force of the National Multiple Sclerosis Society

INTRODUCTION

The last decade has witnessed the introduction of a series of disease-modifying agents as rational therapies to alter the near term course of multiple sclerosis (MS). Their general acceptance in relapsing forms of MS is based on adequate Class I evidence from controlled clinical trials used to gain approval from the Food and Drug Administration (FDA). These include several different formulations of interferon beta (interferon beta-1a; Avonex® and Rebif®, and interferon beta-1b; Betaseron®), glatiramer acetate (Copaxone®) and mitoxantrone (Novantrone®). The evidence supporting the use of the immunomodulatory drugs interferon beta and glatiramer acetate has been reviewed in a practice guideline issued by the American Academy of Neurology.[1] The data supporting approval of the chemotherapeutic immunosuppressant mitoxantrone were published in 2002.[2]

Unfortunately, while all of these drugs represent advances for MS management, none is fully effective. The pivotal trials of all of these agents show that only limited numbers of patients were free of disease activity over each study's duration, that this proportion was only modestly larger than that found in the trial's placebo arm, and that for most subjects, treatment was only partially effective in controlling the clinical and magnetic resonance imaging (MRI)-monitored expressions of their disease. Whatever the relative merits of these drugs, all can only be considered partially effective agents. This reality raises the difficult problem of the identification of a suboptimal response or treatment failure in an individual case and, once identified, leads to consideration of the appropriate avenues for alternative treatments. Regrettably, primary data for evidence-based recommendations on these important concerns do not exist. Given the pressing nature of these issues, the Medical Advisory Board believed that some expert advice would be useful to help guide decision-making for the general physician confronted with this problem.

BACKGROUND

Treatment failure is readily recognized when the expected effect is the rapid reversal of an obvious abnormality. Failure to reduce symptoms of bladder infection and sterilize the urine within several days of initiating antibiotic therapy is one example. Prevention of the development of a late and variable complication of a disease can be more difficult, such as when stroke occurs as a complication of hypertension. However, anticipation of future drug failure might be recognized by such treatment's inability to reduce hypertension. The goal of current disease-modifying treatments in MS is to prevent further disability, not to reverse existing deficits. When the clinical state that the drug is expected to prevent is delayed and not precisely defined, substitute targets for treatment efficacy are often used. In relapsing MS, these include clinical attacks, which in and of themselves are of concern and importance for patients, and acute subclinical activity as monitored by MRI. While both likely contribute to disability over time, neither is highly correlated with either disability or even accumulated, persisting neurological deficits within most clinical trials of only a few years' duration. Nevertheless, the effects of current therapies on attack rates and MRI measures of newly accumulated lesion burdens are the outcome measures that are best described by modern treatment trials, and are the events that are most readily available to the clinician when considering treatment failure or suboptimal response in an individual patient. In relapsing MS, clinical events occur relatively infrequently, making it unlikely that treatment failure can be declared with any assurance within six months of compliant drug exposure.

The concept of "rescue therapy" is deceptive as applied to MS. It implies that treatment failure or suboptimal response can be defined and consistently identified in the individual patient, even though these concepts derive from the results of grouped data reported in relevant clinical trials.[3] It also assumes that the rescue treatment is either too toxic to be considered for all patients with relapsing MS, or is itself only partially effective for the majority of patients so treated. Were rescue treatment safe, universally effective, and its protection sustained, that treatment should be the definitive first line therapy. Even if toxic, risk-benefit considerations might also favor the "rescue" treatment as a primary therapy were it highly effective in preventing disability for the vast majority of patients in a sustained manner. Rescue therapy also implies a sense of urgency, a step that if not taken expeditiously will result in irreparable harm. For MS, this suggests that the level of recent disease activity observed despite therapy predicts a high likelihood of impending disability if not aggressively managed. Such strong outcome predictors remain to be defined for MS.

Currently, it is unclear to what extent the effectiveness of approved MS treatments reflects a partial responsiveness of all treated patients, or a complex mix of complete, partial, and unresponsive patients within the study cohorts.[4] Nor is it fully appreciated whether unresponsiveness or partial responsiveness to a treatment may develop over time.[5] Thus, in failing to show a response to an initially-selected immunomodulatory therapy, the perceived need to switch within interferon beta formulations, or to change therapy from an interferon to glatiramer acetate or vice versa, is appropriately considered selection of an alternative therapy rather than rescue therapy. Similarly, the patient's inability to cope with local or systemic drug side effects or be adequately compliant with treatment, while a treatment failure in the strict sense, is not a failure of drug efficacy. In some cases, it may reflect a failure of the patient's physician to adequately prepare the patient for the commitment to chronic treatment with injectable drugs, or to provide adequate management of side effects.

POSSIBLE MARKERS OF TREATMENT FAILURE

Attacks (Relapses). Although not always the primary outcome measure in pivotal trials of relapsing MS, acute attacks with concomitant neurologic disability are measured and reported in all modern, controlled MS studies. Across all studies immunomodulators reduce relapses by about 30% compared to placebo treatment. While in all studies, the decrease in relapses found during the study compared to the number reported in the 2–3 years prior to enrollment is proportionately greater on active treatment, it is also substantial in controls. There are a number of possible explanations; undoubtedly one is that relapses counted on trial are defined more rigorously and objectively than those recalled or recorded before trial. Certainly, continued attacks at a rate similar to that found before starting a patient on an immunomodulator is therefore a concern. In practice, however, this is likely to be more difficult to discern than in trials. Often there is pressure to determine if a single attack reflects treatment failure, regardless of the duration of treatment or number of attacks prior to initiating therapy. Moreover, pressures to initiate treatment early in the disease course will mean that increased numbers of treated patients may have a single or very few attacks before initiation of treatment. Nevertheless, declaring treatment failure based on a single attack on therapy is not justified by the known efficacy of these agents. Nor is it reasonable to declare treatment failure within a few months of initiating treatment.

Acquired Neurologic Deficits (Disability). All modern MS trials have reluctantly embraced the Expanded Disability Status Scale (EDSS)[6] as the best available measure of neurologic disability. Despite its complexity and shortcomings, the EDSS is easier to apply in everyday practice than more quantitatively-derived composite measures of disability,[7] and its general use might help practitioners better understand possible treatment failures based on evidence from clinical trials. Change in the EDSS linked to an acute attack only measures the severity of the relapse, may spontaneously recover over 3–6 months with or without corticosteroid therapy, and should not be used in isolation to determine a suboptimal response or treatment failure. However, an annual increase in the EDSS of 1 point from a previous score of 3.0 to 5.5, or a 0.5 point increase from a previous score of 6.0 or greater in the absence of clinical attacks, should raise concern. This may indicate that the previously relapsing-remitting patient has transitioned to secondary-progressive disease, or that the secondary-progressive patient has only a partial response to therapy. Measurement of change in the very low EDSS ranges (<3.0) is too variable to be used in isolation to define treatment failure.

MRI Activity. Findings on random MRI, or on MRI performed at arbitrary, predefined intervals in the absence of clinical activity, are difficult to interpret. MRI activity at the time of an acute clinical attack provides little additional data for the assessment of treatment failure. However, patients on treatment that exhibit high enhancing activity or substantial new lesion formation after an attack has subsided, particularly in the presence of attack-independent EDSS worsening, are likely to be treatment failures. Precise benchmarks for excessive MRI activity are difficult to define, but might include three or more enhancements or two or more new T2 lesions on each repeated scan separated by at least quarterly intervals. While quantitative measures of lesion activity on periodic MRI may eventually prove useful indicators of the risk of future clinical treatment failure, providing timely indicators for the need for alternative therapy, the use of MRI as a sole surrogate indicator of treatment failure for any of the available approved treatments is not adequately developed at this

time. If and when available, it will require a standardized MS imaging protocol that currently does not exist in general practice.

SUMMARY

◆ There are no direct comparative data to allow a fully informed choice of the best immunomodulatory drug class (interferon beta or glatiramer acetate) with which to initiate therapy in relapsing forms of MS.

◆ Higher-dosed, more frequently administered formulations of interferon beta may provide better short-term clinical efficacy than lower, less frequently dosed formulations of interferon beta in relapsing MS.[8,9]

◆ The presence of neutralizing antibodies to interferon beta may be associated with incomplete response to therapy in patients taking one of the interferon products. The presence of neutralizing antibodies to interferon in the face of continued frequent relapses or excessive MRI activity may justify the use of non-interferon disease-modifying drugs. Presently, in the absence of clinical or MRI activity, finding high titer interferon beta neutralizing antibodies in the serum does not warrant a change in therapy. This conclusion may need to be revised as additional evidence accrues.

◆ Mitoxantrone (or other chemotherapeutic agents not specifically approved for use in MS) is not advised as a first choice for most relapsing MS patients due to its relative toxicity profile.

◆ Continued, frequent relapses, or non-relapse associated excessive MRI activity, may justify selection of an alternative immunomodulating strategy—increased dose frequency of an interferon beta or switch to glatiramer acetate, switch from glatiramer acetate to an interferon beta, or consideration of mitoxantrone. While this is a widely accepted practice, it is re-emphasized that there are unfortunately no Class I data to support the underlying assumption that switching therapy improves clinical outcome. Ideally, this could be evaluated in the setting of well-conceived trials that could lead to data substantiating the use of these drugs in such a manner.

◆ Continued frequent relapses, or non-relapse associated excessive MRI activity, may justify combination therapy using different classes of FDA-approved drugs, or an FDA-approved drug with a currently available drug without an FDA approved indication for MS. The Task Force recognizes that clinicians familiar with treating MS and the toxicities of these drugs may use combination therapy for suboptimal responders and treatment failures as an alternative to changing immunomodulator therapy under these circumstances. While this may be a widely accepted practice, it is re-emphasized that there are unfortunately no Class I data to support the underlying assumption that adding therapy improves clinical outcome. This is preferably done in the setting of well-conceived trials that could lead to data substantiating the use of these drugs in such a manner.

◆ Treatment failure due to continued, frequent, severe relapses, particularly those with incomplete recovery, justifies consideration of mitoxantrone or an alternative chemotherapeutic agent.

◆ Patients failing approved therapies as defined above should be considered for well-designed, institutional review board (IRB)-approved therapeutic trials of drugs deemed promising for treatment of MS.

In the development of these guidelines, the Task Force recognized a number of areas where additional clinical research would translate into better-informed use of these drugs. **First**, we encourage the re-analysis of data from existent trials to determine early clinical and MRI measures that best predict a favorable and unfavorable course on active treatment. **Second**, we encourage a national registry of treated patients to better understand the importance of early therapy and early recognition of treatment failure and their longer-term consequences. **Third**, we encourage the development of regional networks between centers highly experienced in the use of these drugs and primary treating physicians in more isolated settings.

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