

## Disease Management Consensus Statement – Treatment Recommendations for Physicians

a report by

**Medical Advisory Board of the  
National Multiple Sclerosis Society (NMSS)**

### Recommendations

While recognizing that factors entering into a decision to treat are complex and are best analyzed by the individual patient's neurologist, the Executive Committee of the Medical Advisory Board of the National Multiple Sclerosis Society (NMSS) has adopted the following recommendations regarding use of the current multiple sclerosis (MS) disease-modifying agents (DMAs).

#### Immunomodulators

- interferon-beta (IFN $\beta$ ) 1a-intramuscular (Avonex<sup>®</sup>);
- IFN $\beta$  1a-subcutaneous (Rebif<sup>®</sup>);
- IFN $\beta$  1b (Betaseron<sup>®</sup>); and
- glatiramer acetate (Copaxone<sup>®</sup>).

#### Immunosuppressant

Mitoxantrone (Novantrone<sup>®</sup>)

- Initiation of therapy with an immunomodulator should be considered as soon as possible following a definite diagnosis of MS with active disease, and may also be considered for selected patients with a first attack who are at high risk of MS.
- Patients' access to medication should not be limited by frequency of relapses, age, or level of disability.
- Treatment is not to be stopped while insurers evaluate for continuing coverage of treatment.
- Therapy is to be continued indefinitely, except if there is clear lack of benefit, there are intolerable side effects, or better therapy becomes available.
- All of these US Food and Drug Administration (FDA)-approved agents should be included in formularies and covered by third-party payers so that physicians and patients can determine the most appropriate agent on an individual basis – failure to do so is unethical and discriminatory.
- Movement from one immunomodulatory drug to

another should occur only for medically appropriate reasons.

- Immunosuppressant therapy with Novantrone<sup>®</sup> (mitoxantrone) may be considered for selected relapsing patients with worsening disease or patients with secondary-progressive MS.
- Most concurrent medical conditions do not contraindicate use of the immunomodulatory drugs.
- None of the therapies have been approved for use by women who are trying to become pregnant, are pregnant, or are nursing mothers.

### Introduction

MS has been substantially advanced by the availability of the DMAs IFN $\beta$  1a and 1b and glatiramer acetate, and the immunosuppressant agent, mitoxantrone. A number of positive outcomes have been demonstrated in people with relapsing disease – reduction in the frequency and severity of relapses<sup>1</sup> (Betaseron,<sup>2-5</sup> Avonex,<sup>6-9</sup> Copaxone,<sup>10-11</sup> Rebif,<sup>2-14</sup> and Novantrone<sup>15</sup>), reduction of brain lesion development, as evidenced by magnetic resonance imaging (MRI) (Betaseron,<sup>2,16-17</sup> Avonex,<sup>6-9</sup> Copaxone,<sup>18-20</sup> Rebif,<sup>12-14,21-22</sup> and Novantrone<sup>23</sup>), and the possibility of reduction of future disability<sup>24</sup> (Betaseron,<sup>2,16-17</sup> Avonex,<sup>6-9</sup> Copaxone,<sup>10-11</sup> Rebif,<sup>12-14</sup> and Novantrone<sup>15,23</sup>).

Based on several years of experience with IFN $\beta$ s and glatiramer acetate, it is the consensus of researchers and clinicians with expertise in MS that these agents can reduce future disease activity and improve quality of life (QOL) for many individuals with relapsing forms of MS, including those with secondary progressive disease who continue to have relapses. For those who are appropriate candidates for one of these drugs, treatment must be sustained for years. Cessation of treatment may result in a resumption of pre-treatment disease activity.<sup>25</sup>

Clinical trials are designed to evaluate the smallest number of people over the shortest period of time at the lowest cost. In order to accomplish this, inclusion criteria are necessarily narrow.



These restricted parameters of clinical trials are not intended to regulate subsequent clinical use of the agent. With demonstrated benefit to people with MS from continued use of Betaseron, Avonex, Rebif, or Copaxone, it is critical that these therapies be made available early in the disease process to appropriate candidates as indicated in the labeling of each of these medications, and that Novantrone be available for judicious use in aggressive relapsing disease and for those not responding to immunomodulators.

### Background

In August 1994, the Quality Standards Subcommittee of the American Academy of Neurology (AAN) published an advisory statement on the selection of patients with multiple sclerosis for treatment with Betaseron (IFN $\beta$  1b). Since then, four additional agents that modify the underlying disease process have been approved by the FDA – Avonex (IFN $\beta$  1a), Copaxone (glatiramer acetate), Novantrone (mitoxantrone), and Rebif (IFN $\beta$  1a). The benefits of these agents include direct evidence of disease modification,<sup>1-23</sup> with inferred advantage to function and quality of life. The NMSS has maintained the timeliness of its consensus statement as additional agents have been studied and approved, and new clinical trial data have become available. The current revision references all of the currently approved drugs.

Significant obstacles to obtaining these agents exist for appropriate candidates with MS. One is the lack of adequate information reaching primary care providers (PCPs) and general neurologists, who may each have only a few patients with MS, but collectively care for a large percentage of the MS population. Another is misunderstanding by some policy makers and insurers of the benefits of disease management therapy, leading to inadequate coverage, both initially and long-term.

This NMSS Disease Management Consensus Statement addresses these barriers, while acknowledging that the field is in flux, and frequent review of recommendations is essential. Other obstacles, such as non-adherence to protocols and ‘drop-out’ by those already on a drug, are not addressed in this statement. The controversial area of neutralizing antibodies is mentioned only to state that sufficient data do not yet exist to base clinical decisions exclusively on the results of neutralizing antibody assays.

### Discussion

The NMSS Consensus Statement is an education and advocacy tool. It is a component of the Society’s professional education programs, and is used to promote

increased access to the approved DMAs through legislative, judicial, and regulatory determinations.

This Consensus Statement serves as a communication device for interactions with insurers, both nationally and locally. The following points highlight the issues.

- Among patients who report that they have relapsing-remitting MS, 38% are not on immunomodulatory therapy.<sup>26</sup>
- This is of particular concern in light of numerous studies<sup>27-30</sup> confirming that axonal damage can coincide with destruction of the myelin sheath in the MS disease process, suggesting that even early relapses that appear benign may have permanent neurological consequences. Serial MRI studies<sup>31,32</sup> of individuals who are clinically in remission have demonstrated on-going brain lesion development and atrophy despite a seemingly benign clinical course. These findings strengthen the argument for early intervention with a DMA.
- Government advocacy is critical to address regulations regarding areas such as Medicare reimbursement for these injectable agents. Legislative measures are being debated regarding this and other issues, and some judicial decisions have broad implications for access to treatment. In one dispute, a patient was denied coverage for an MS disease-modifying drug based on her non-ambulatory status. This Consensus Statement supports efforts to expand governmental coverage to appropriate levels for this and similar cases.
- Variable and sometimes detrimental policies by insurers exist regarding the use of the immunomodulators, most likely resulting from insufficient information about the short- and long-term benefits of these drugs, or strict interpretation of the original trial criteria.

Insurance barriers include the following:

- selection and availability of only one or two of the agents for coverage, or a financial penalty to a patient for not being treated initially with the highest-tiered medication approved by his/her health plan;
- evaluation of the need for on-going treatment by cessation of treatment for a period of time;
- interpretation of absence of attacks as an indication for discontinuation of a drug;
- arbitrary restrictions, such as ambulatory status, full recovery from an attack, and age;

- requirement of two relapses within the preceding year in order to begin or continue on drug;
- placement of a ceiling on cost of treatment; and
- non-coverage of injectable agents.

The recommendations contained within this Consensus Statement address these issues.

### Process

The Executive Committee of the NMSS Medical Advisory Board identified the need for the NMSS to develop and periodically update a formal position on the topic of disease management with the DMAs. A Medline search was conducted to document major studies in this area. A task force was activated to develop the statement, and the NMSS Medical Advisory Board's Executive Committee provided final review of the document.

### Role of the NMSS

The mission of the NMSS is to end the devastating effects of MS. Various strategies are employed, including professional education and advocacy. As a representative body and advocate for both people with MS and the medical/health professionals who provide their care, the Society is positioned to provide structure and support for a consensus statement to facilitate access to therapies for disease management. The NMSS has a nationwide network of chapters, each with a Clinical Advisory Committee composed of community health professionals with expertise in MS. Over 330,000 Society members have self-identified as having MS, and are part of a mailing list of almost 600,000 people interested in MS-related issues. Regular communication is made with these various audiences through national and chapter publications. This extensive network and process for dissemination will ensure that the updated Consensus Statement is expeditiously communicated to care providers, insurers, and people with MS. ■

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**This statement was updated by the Executive Committee of the Medical Advisory Board of the NMSS.**

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