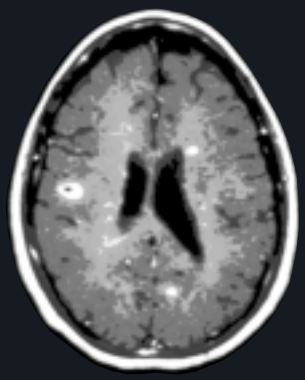
CLINICAL PRACTICE GUIDELINES



Disease Modifying Therapies in MULTIPLE SCLEROSIS

Evidence-Based Management Strategies for Disease Modifying Therapies in Multiple Sclerosis

DISEASE MODIFYING THERAPIES

Multiple Sclerosis Council
for Clinical Practice Guidelines

Administrative and financial support provided by Paralyzed Veterans of America

Multiple Sclerosis Council
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American Congress of Rehabilitation Medicine

American Neurological Association

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Canadian Neurological Association

Consortium of Multiple Sclerosis Centers

Eastern Paralyzed Veterans Association

International Organization of Multiple Sclerosis Nurses

Kaiser-Permanente Health Maintenance Organization

National Multiple Sclerosis Society

Paralyzed Veterans of America

Rehabilitation in Multiple Sclerosis

U.S. Department of Veterans Affairs

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Other Publications

Fatigue and Multiple Sclerosis

Urinary Dysfunction and Multiple Sclerosis

Immunizations and Multiple Sclerosis

October 2001

This guide has been prepared based on scientific and professional information available in 2001. Users of this guide should periodically review this material to ensure that the advice herein is consistent with current reasonable clinical practice.

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FOREWORD

Professional organizations from all sectors of the health-care community have embraced the development, use, and evaluation of practice guidelines through which they collate and evaluate empirical evidence and expert opinion. Generally, the goals of these practice guidelines are to reduce inappropriate care and improve patient outcomes, reduce health-care costs, enhance quality assurance, and improve medical education. Their benefit is in documenting the advice of clinical experts, documenting the clinical research, and assessing the clinical significance of conflicting research findings.

Many public and private health-care organizations are involved in developing practice guidelines, and the scope of topics researched and methodologies used is quite diverse. The choices of topics and methods reflect each organization's major practice concerns, the empirical evidence available on those topics, and, just as importantly, the resources available to the organization for developing the guidelines. Whenever possible, clinical practice guidelines are based on empirical evidence and in those cases the recommendations are graded on the quality of evidence. Nonetheless, expert opinion remains an integral part of guideline development because "reliable scientific evidence is lacking for most clinical practices" (S.H. Woolf, 1992. Practice guidelines: a new reality in medicine. II Methods of developing guidelines. *Archives of Internal Medicine* 152:946-52).

I am pleased to present these clinical practice guidelines on disease modifying therapies in multiple sclerosis (MS) patients to the health-care community. This topic synthesizes the currently available literature and identifies many key questions that remain to be investigated. This guideline will need to be updated as evidence from on-going studies becomes available. An important aspect of these investigations is the development and use of new and increasingly meaningful outcomes assessment tools. It is important to be aware of these new measures when considering emerging evidence.

These guidelines and the others developed by the Multiple Sclerosis Council for Clinical Practice Guidelines reflect both the published research on this topic as well as the expert opinion of the panel members. That expert opinion has been supported in turn by the expert consensus of a broad range of clinicians who are MS specialists.

Thse guidelines are written for health-care professionals to assist them in clinical decision making. We anticipate that the document will be useful to clinicians in discussing MS with their patients and in making treatment decisions. We also expect the publication will be useful to individuals and organizations responsible for allocating health-care resources.

People with MS come from all walks of life and live with a broad range of disability. Their care is provided by many types of health-care professionals in varied settings. For this reason, the guidelines have been developed for a range of patients, clinicians, and treatment settings. Adaptability has been a guiding principle of the Multiple Sclerosis Council for Clinical Practice Guide-

lines, whose members represent the major professional and consumer MS groups, and of the members of the Guidelines Development Panel, who also reflect this provider and consumer diversity.

These guidelines will be of benefit only if they are studied, used, evaluated, and updated. The council welcomes the responsibility of ensuring the current and future value of these guidelines as part of its ongoing activities. However, we will be successful in this effort only with the participation of you, the health-care providers who use this document. We look forward to your comments on these guidelines and encourage you to undertake the investigations for future research recommended in this publication.

We are grateful to the Paralyzed Veterans of America for convening and providing ongoing support to the representatives of the 21 organizations that constitute the Multiple Sclerosis Council for Clinical Practice Guidelines. PVA's concern for the well-being of people with MS and its commitment to ensuring that appropriate care is available to every person with MS are an example to us all.

Deborah M. Miller, Ph.D.
Chair, MS Council for Clinical Practice Guidelines

ACKNOWLEDGEMENTS

The chairs and members of the Disease Modifying Therapies Guidelines Development Panel wish to express special appreciation for the leadership and encouragement shown by the 21 organizations that make up the Multiple Sclerosis Council for Clinical Practice Guidelines and their representatives. We especially appreciate the contributions of the 23 professionals who provided expert review of the final draft. The efforts of all of these groups have been crucial in establishing the expert consensus that underpins these recommendations.

Assistance in conducting the literature review was provided by the staff of the Center for Clinical Health Policy Research at Duke University, especially David B. Matchar, MD, Douglas C. McCrory, MD, MHSc, Olivier Rutschmann, MD, MPH, and Jane Kolimaga, MA. Their assistance was essential to the successful completion of these guidelines.

The Guidelines Development Panel is indebted to the leaders and staff of the Paralyzed Veterans of America, who provided organizational, administrative, and financial support to the Guidelines Development Panel. In particular, the panel recognizes Lara Chisa, project administrator of the MS Council, who demonstrated her organizational and management skills throughout this project; John Carswell, associate executive director of the Health Policy department, who championed the cause of PVA members who have MS; Fred Cowell, staff director of that department, who made sure that the project was appropriately staffed; James A. Angelo, Patricia E. Scully, Christine Campbell, and Susan England of the Communication Department who provided editing, formatting, and design; and legal reviewer William H. Archambault of Goodman, West & Filetti, PLLC, Charlottesville, VA. Finally, we are grateful for the steadfast commitment and advocacy of PVA's senior officers, including Immediate Past President Homer S. Townsend, Jr., National President Joseph L. Fox, Sr., Executive Director Keith Wingfield, Deputy Executive Director John C. Bollinger, and the entire PVA board of directors.

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THE MULTIPLE SCLEROSIS COUNCIL

Two separate organizational efforts stimulated the 1997 formation of the Multiple Sclerosis Council for Clinical Practice Guidelines. The first of these efforts was formalized in 1995 when the American Academy of Neurology, the Consortium of Multiple Sclerosis Centers, and the National Multiple Sclerosis Society established the interorganizational Collaborative Group for Multiple Sclerosis Management Strategies (CGMSMS). The term "management strategies" was used in this collaboration because of concern that although the recommendations would be based on all available empirical evidence, development of the recommendations would be largely dependent on expert consensus. In that same year, CGMSMS formed a steering committee, which established criteria for topic selection and management strategy development, and convened management strategies development panels on two topics-fatigue and bladder dysfunction.

The second organizational effort was initiated by the Paralyzed Veterans of America. To better serve the approximately 30 percent of PVA members who experience multiple sclerosis, the organization made a board-level decision in 1997 to commit resources for developing practice guidelines for MS. This commitment paralleled the guidelines support PVA had been providing to the spinal cord injury community since 1995, through the Consortium of Spinal Cord Medicine. In making these resources available, PVA also ensured that its only influence on the recommendations generated through the MS guidelines effort would be through its one voting member on the council. In 1997, the two organizational efforts were integrated, and the Multiple Sclerosis Council for Clinical Practice Guidelines was established. This merger allowed a greater number of organizations to participate and a more ambitious schedule for producing the guidelines to be set.

The Multiple Sclerosis Council for Clinical Practice Guidelines is made up of 21 representatives from key MS professional and consumer organizations. A multidisciplinary group, it includes civilian and military representatives who have experience in fee-for-service and managed care payment systems, as well as in academic, group, and individual practice settings. These representatives and their organizations are listed on page ix. Each member organization is responsible for providing the following:

- Appointment to the council of one member with expertise in the topic area.
- High-level professional and technical peer review of the guidelines materials.
- Dissemination and application of the guidelines through the organization's educational offerings.
- Organizational endorsement of the completed practice guidelines and related products.

In addition, each member of the council participates in one of three advisory subcommittees: the Methodological and Scientific Review Advisory Subcommittee; the Topic Selection and Panel Recruitment Advisory Subcommittee; or the Peer Review, Dissemination, and Outcomes Evaluation Advisory Subcommittee.

The preparation of individual guidelines is completed by a guidelines development panel that includes multidisciplinary experts in the field. The Disease Modifying Therapies guidelines development panel followed a process that integrates the methodologies of the Collaborative Group for MS Management Strategies and the Consortium for Spinal Cord Medicine. The first phase of the work process was setting the parameters of the guidelines. The literature review strategy was subsequently developed and documented by the Disease Modifying Therapies guidelines development panel and by process methodologists who have expertise in medical literature review, data extraction, and data synthesis. Potentially relevant original research articles

were collected through electronic search procedures, reviews of research and survey article bibliographies, and recommendations from experts in the field. Relevant original research articles were identified, and levels of evidence were assigned. The levels of evidence and strength of recommendations used in this process are listed in table 1. All members of the Disease Modifying Therapies guidelines development panel read all relevant articles.

The guidelines writing process occurred as the Disease Modifying Therapies guidelines development panel wrote the supporting annotations, based on the available literature. This process took several iterations between the Disease Modifying Therapies guidelines development panel and the process methodologist.

The final step in the consensus process consisted of a review of the document by the 21

Table 1. Rating of Evidence Classification Scheme

Rating of recommendation	Translation of evidence to recommendations	Rating of therapeutic article
A = Established as effective, ineffective, or harmful for the given condition in the specified population	**Level A** rating requires at least one convincing class I study or at least two consistent, convincing class II studies	**Class I:** Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: a) primary outcome(s) is/are clearly defined b) exclusion/inclusion criteria are clearly defined c) adequate accounting for drop-outs and crossovers with numbers sufficiently low to have minimal potential for bias d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
B = Probably effective, ineffective, or harmful for the given condition in the specified population	**Level B** rating requires at least one convincing class II study or at least three consistent class III studies	**Class II:** Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-d above OR a RCT in a representative population that lacks one criteria a-d.
C = Possibly effective, ineffective, or harmful for the given condition in the specified population	**Level C** rating requires at least two convincing and consistent class III studies	**Class III:** All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.
U = Data inadequate or conflicting. Given current knowledge, treatment is unproven		**Class IV:** Evidence from uncontrolled studies, case series, case reports, or expert opinion.

members of the Multiple Sclerosis Council for Clinical Practice Guidelines and by as many as 3 additional reviewers from each member organization. Endorsement of the guidelines was made by each organization of the Multiple Sclerosis Council for Clinical Practice Guidelines according to their own rules of governance.

Dissemination of the guidelines is through the member organizations and other key societies, including publication in *Neurology*, the journal of the American Academy of Neurology. Evaluation of the guidelines is the responsibility of the Multiple Sclerosis Council for Clinical Practice Guidelines, which will consider the guidelines' utility, their impact on clinical outcomes, and the need for revision as new information becomes available.

OVERVIEW

Epidemiology and Diagnosis of Multiple Sclerosis

Multiple sclerosis (MS) is a chronic recurrent inflammatory disorder of the central nervous system (CNS). The disease results in injury to the myelin sheaths, the oligodendrocytes, and, to a lesser extent, the axons and nerve cells themselves (1–5). Women are affected more often than men. The disease typically becomes clinically apparent between the ages of 20 and 40 years, although it can begin either earlier or later in life. In Canada, Europe, and the United States (US) the prevalence ranges from 100 to 200 cases per 100,000 population.

The cause of MS is unknown, although immune-mediated mechanisms are almost certainly involved, either primarily or secondarily, and many authors favor a primary autoimmune basis for MS (5).

MS is characterized pathologically by patches of demyelination that are found multifocally within the CNS white matter. Grey matter is relatively spared, as are the nerve axons, although recent reports have highlighted the importance of axonal injury (4, 6). There is considerable evidence indicating that autoreactive T-cells proliferate, cross the blood-brain barrier, and enter the CNS under the influence of cellular adhesion molecules and pro-inflammatory cytokines (7, 8). In addition to T-cells, other mononuclear cells (macrophages and, to a lesser extent, B-cells) are also present in acute MS lesions. In chronic MS lesions, by contrast, the histological evidence of active inflammation is less conspicuous and lesions are characterized by gliosis as well as by a variable degree of axonal loss.

The symptoms of MS vary, depending, in part, upon the location of plaques within the CNS. Common symptoms include sensory disturbances in the limbs, optic nerve dysfunction, pyramidal tract dysfunction, bladder or bowel dysfunction, sexual dysfunction, ataxia, and diplopia (5).

Four different clinical courses of MS have been defined (9). The first, relapsing/remitting MS (RRMS), accounts for approximately 85-90% of MS cases at onset (1–3). It is characterized by self-limited attacks of neurological dysfunction. These attacks develop acutely, evolving over days to weeks. Over the next several weeks to months, the majority of patients experience a recovery of function that is often (but not always) complete. In between attacks the patient is neurologically and symptomatically stable.

The second clinical course, secondary progressive MS (SPMS), begins as RRMS but, at some point, changes such that the attack rate is reduced and the course becomes characterized by a steady deterioration in function, unrelated to acute attacks. This type of MS, which ultimately develops in approximately 80% of RRMS patients, causes the greatest amount of neurological disability. Longitudinal population-based studies have found that 50% of patients require some assistance with ambulation after 15 years and that over 80% of MS patients reach this level of disability after 30 years. Even among patients who have experienced little disability in the first 10 years of their illness, significant disability often develops subsequently (10). The clinical course for an individual patient is difficult to predict. Men, patients with early motor or cerebellar symptoms, patients with frequent attacks, patients with residual deficits after early attacks, patients with greater disease burden seen on magnetic resonance imaging (MRI), and patients with moderate disability after 5 years of illness, seem to have a greater likelihood of becoming disabled than patients without these risk factors.

The third clinical type, primary progressive MS (PPMS), represents only about 10% of cases at onset. In PPMS, patients experience a steady decline in function from the beginning and never have acute attacks. These patients have a more even sex distribution, tend to have a later age of

onset, and may have a worse prognosis for ultimate disability compared to patients with RRMS.

The fourth type, progressive/relapsing MS (PRMS), also begins with a progressive course although these patients experience occasional attacks, which are superimposed upon their steadily progressive disease course.

Some patients with RRMS have a benign illness and never develop marked disability. This fact needs to be considered when treatment options are contemplated for individual patients. Moreover, it is possible that the poor long-term prognosis for MS may be considerably overestimated. For example, in patients with attacks of optic neuritis (a condition closely linked to MS with similar genetic determinants), the conversion rate to clinically definite MS in one report was as low as 64% at 40 years (11). If this observation is correct, it may be that benign forms of MS are much more prevalent than is currently believed.

Nevertheless, in patients with clinically isolated syndromes, certain laboratory features, such as abnormalities on brain MRI, the presence of oligoclonal bands in the cerebrospinal fluid (CSF), or abnormalities on evoked potential testing, significantly increase the likelihood of developing MS in the future (12–14), and it may be possible to use the results of these investigations to select those patients who are most suitable for therapeutic intervention. For example, over 50% of patients with monosymptomatic disease will have MRI abnormalities consistent with MS and, of these, 80% will develop clinically definite MS (CDMS) within the next 10 years (12). By contrast, in the absence of such MRI abnormalities the 10-year risk of developing CDMS is less than 20%.

In 1982, an international Workshop on the Diagnosis of Multiple Sclerosis developed the currently used diagnostic criteria for MS (15). These criteria incorporate clinical information together with evoked potential results, MRI findings, and CSF analysis into the diagnostic algorithm. For example, utilizing such paraclinical evidence of a second lesion (e.g., from MRI or evoked potential studies), these criteria allow a diagnosis of CDMS to be made in a patient with a relapsing course but in whom there is only clinical evidence of a single lesion (15).

The diagnosis of CDMS, however, can still be made without any additional studies in a patient who has a relapsing/remitting course and who has evidence of disease at more than one CNS location on neurological examination. CSF evaluation can demonstrate the local CNS production of gamma globulin (IgG) and, during an acute attack, may also show a pleocytosis. This local IgG production is reflected by an increased percentage of IgG in the spinal fluid compared to the serum (expressed as either an IgG index or an IgG synthesis rate), or by the presence of oligoclonal IgG bands specific to the CSF on protein electrophoresis. Evoked potential testing may demonstrate functional disturbances in afferent pathways that are not evident on clinical examination and, thus, establish the presence of multifocal disease (13).

MRI is capable of identifying areas of demyelination or inflammation within the CNS that are clinically silent. Recently, an international consensus conference was convened in London to revise the current diagnostic classification scheme so that advances in our understanding of the MRI in MS could be better incorporated into the diagnostic algorithm (16). The new diagnostic classification scheme, however, makes the MRI criteria for diagnosis much more stringent than previously and it is unclear how widely they will be accepted.

Outcome Measures in MS Clinical Trials

Evaluation of the relative effectiveness of different therapies requires consideration of which outcome measure, or measures, are relevant to the goals of therapy. Clearly, the most important therapeutic aim of any disease modifying treatment of MS is to prevent or postpone long-term disability. However, long-term disability in MS often evolves slowly over many years (1–3). Clinical trials, by contrast, study patients for only short periods of time (two or three years) and, therefore, use only short-term outcome measures to assess efficacy. As a result, it is important to validate any short-

term measure by its correlation with the actual patient outcome many years later. Regrettably, data of this kind are largely unavailable.

As a result, most clinical trials have tended to use a combination of short-term measures to establish that treatment at least reduces the biological activity of MS. In such a circumstance it is probably best to use a combination of measures including both clinical and MRI outcomes.

Clinical measures are clearly the most important to the patient but they are also subject to errors arising from observer unblinding and bias. MRI measures, by contrast, are objective measures of some aspects of the pathology of MS. These measures, however, although objective, are not perfect and can be influenced by differences in technique. Nevertheless, these measures are not susceptible to the same kinds of errors as clinical measures and they can be used to provide objective support for a clinical outcome that is of primary interest.

For example, several recent trials have used MRI measures of disease activity (e.g., new lesions, enhancing lesions, or combined unique active lesions) to support therapeutic claims relating to clinical attack rate (17–28). Similarly, MRI measures of disease severity such as changes in the total volume of T2-disease burden seen on MRI (and, in the future, measures such as cerebral atrophy, total brain N-acetylaspartate, or T1-black holes) have been used to support claims of therapeutic benefit with respect to clinical measures of disease severity such as confirmed disability progression (17–28).

The assessment of disability is clearly a critical part of clinical trial design. The expanded disability status scale (EDSS) has been the most widely employed scale for this purpose (29) and this scale has been used in almost all recently published studies (17–28). Unfortunately, the EDSS is quite complicated to score and, at lower degrees of disability, the scale is quite subjective and has poor inter-rater and test-retest reliability (30–32). Moreover, it is very non-linear over its range in comparison with the actual level of function (33). For example, a one-point EDSS change at the low end of the scale reflects only a trivial change in function, compared to a similar change at the mid-point, which reflects a substantial increase in disability.

Some recent clinical studies (17, 26, 27) have tried to make the scale more reliable by measuring the so-called confirmed 1-point EDSS change (i.e., a change of one or more EDSS point sustained on two consecutive assessments performed 3 or 6 months apart). Others, excluding determinations made during acute relapses, have used an unconfirmed EDSS change of 1.5-point (23) to define treatment failure as analyzed by survival methods. Still others have used an EDSS change of 1-point or more from baseline (unconfirmed) at the end of the trial to represent a categorical failure of therapy (17, 22, 23).

All of these methods, however, fail to account for the deficiencies of the EDSS. For example, using any fixed EDSS change (whether confirmed or not) fails to account adequately for the non-linearity of the EDSS scale. It is also of note that survival analysis methods presuppose that any patient who fails treatment cannot recover. Importantly, however, when the outcome in the placebo arms of two recent clinical trials were analyzed (20, 22), the authors found that, of patients with a confirmed EDSS progression of either 1 or 2 points sustained for as long as 6 months, approximately 50% improved toward their baseline level of function and reverted to a non-progressive status (34). Clearly, such findings undermine the validity of confirmed progression as a measure of fixed disability.

Such a finding, however, also undermines the validity of the other clinical disability measures, particularly those outcomes that are measured at one point in time (i.e., measures that are unconfirmed), which will be substantially contaminated by both short-term and long-term fluctuations in function that are characteristic of this disease.

One method of including more of the data that has been proposed is to calculate the so-called area under the curve (AUC) or the integrated (I) DSS (34). In fact, however, when the EDSS determinations are evenly spaced, the IDSS

method reduces to a simple arithmetic average of the recorded EDSS scores. As such, it gives equal weight to scores measured soon after the beginning of treatment (when few group differences are expected) and to scores at the end of the trial period (when, hopefully, the group differences would be maximal). As a result of all of these considerations, more valid measures of fixed clinical disability progression are clearly needed.

Alternative scales, such as the Scripps neurologic rating scale (SNRS) or the ambulatory index (AI), have been proposed as possible substitutes for the EDSS (35, 36). However, scores on these other scales are highly cross-correlated with the EDSS (37) and, thus, they provide little theoretical advantage. Another difficulty with each of these scales is that they mainly assess patients' physical disability and not their mental function, even though cognitive dysfunction is known to be common in MS patients (38, 39).

In response to some of these concerns, a task force of the National MS Society developed the multiple sclerosis functional composite (MSFC) score with the notion of ultimately replacing the EDSS (40, 41). This score is an impairment measure derived from the so-called z-scores on the 25-foot timed-ambulation test, the paced auditory serial addition test (PASAT), and the 9-hole peg test (9HPT). Thus, the MSFC score puts a greater weight on mental function than other measures and it may be that this scale will prove to be an important tool in clinical trials.

Nevertheless, the high correlation of the MSFC with EDSS (40, 41), the marked variability in the standard deviation of the component scores (i.e., the timed ambulation, the PASAT, and the 9HPT) over the range of EDSS scores (40, 41), and the difficulty of defining a confirmed change on this measure, raise at least some questions about how much of an improvement this scale actually represents. In addition, it would be disconcerting if, in a particular clinical trial, the treatment effect found using the MSFC (or any composite scale) were due entirely to the findings on only a single component score such as the 9HPT (42). In this circumstance, the validity of the composite measure would be uncertain unless a change on that component score, by itself, proved to be correlated with long-term functional outcome. Nevertheless, the MSFC is relatively untested at the moment and its clinical utility remains to be established.

As a result of difficulties in the measurement of disability, many authors have preferred to use attack rate as the primary outcome of clinical trials (17–25). Such an approach is attractive for several reasons. First, attack rate seems to measure a relevant clinical aspect of the disease. Moreover, when used together with MRI measures of lesion activity, it provides an estimate of the biological activity of the illness. Second, it is a reasonably objective clinical measure, especially in circumstances where minor fluctuations in function are eliminated from the definition of an attack. Third, patients typically experience several attacks during the course of a clinical trial so that the statistical power to detect group differences with this measure is generally adequate. Fourth, and perhaps most importantly, clinical attack rate can be confirmed by related (and objective) MRI measures (e.g., new lesions, enhancing lesions, or combined unique active lesions), which reveal considerably more disease activity when compared to their clinical counterpart. Thus, these MRI measures provide even better statistical power to detect group differences.

The main disadvantage to the use of attack rate measures, however, is the uncertain relationship between the attack rate and long-term disability (3, 43, 44). Indeed, one recent report (45) suggested that reducing short-term attack-rate measures may not be associated with a delay in the accrual of disability in MS. Unfortunately, however, this study failed even to evaluate the relationship between early attack-rate and subsequent disability in RRMS. The reported data, therefore, cannot be used to address this question. Moreover, as discussed earlier, other population-based studies (1-3), as well as an analysis of a large database from a combination of recent clinical trials (46), have shown a relationship between the early clinical attack rate and the development of subsequent disability.

Scope of This Guideline

There are at least three potential kinds of therapy for patients with MS. The first is treatment aimed at reducing the biological activity of MS in order to prevent or postpone future neurological injury; the second is symptomatic treatment for specific clinical complaints (e.g., bladder dysfunction, spasticity, fatigue); and the third is treatment to repair the neural damage caused by MS.

Recently there has been a considerable increase in the number of agents available for the treatment of multiple sclerosis, particularly agents in the first of these categories. It is the purpose of this assessment, therefore, to consider the clinical use of these disease-modifying agents including the anti-inflammatory, immunomodulatory, and immunosuppressive treatments that are currently available. Symptomatic and reparative therapies are not considered.

Before considering the evidence from individual trials, however, a few statistical and interpretational points are worth bearing in mind. First, although a p-value of 0.05 is commonly taken as evidence of a therapeutic benefit to treatment, there is concern that this may be too liberal a standard. For example, the Type I error rate (i.e., the so-called α-error) reflects the likelihood of concluding incorrectly that a useless treatment is of value. Surprisingly, however, for an experimental observation with a p-value of 0.05, the calculated (i.e., theoretically expected) minimum Type I error rate, for a two-tailed comparison, is actually 13% (47–50). For a one-tailed comparison this minimum Type I error rate is actually 21% (47-50). Thus, if the aim is to reduce the Type I error rate to the nominal value of 5% for statistical significance (for a single comparison), using this type of analysis, the observed p-value would need to be 0.01 or less (47–50).

Consequently, when evaluating the results from a particular trial, statistical observations between $p = 0.01$ and $p = 0.05$ should be regarded as marginal. This is especially true when the study under consideration reports multiple between-group statistical comparisons, because multiple comparisons markedly inflate the actual Type I error rate and require a much more stringent statistical adjustment (51–55).

There is also concern about the Type II error rate of clinical trials (i.e., the so-called β error), which reflects the likelihood of concluding incorrectly that a useful treatment is of no value (56). For example, one recent trial (22) found that, after two years of treatment, sustained disability progression was non-significantly reduced by 12%. Clearly, such a result cannot be used to reject a true 12% reduction in this measure and, in fact, this non-significant observation is still compatible with an even more robust treatment effect (56). The issue is the statistical power (i.e., $1-\beta$) of the clinical trial to detect group differences and this, in turn, is related to the number of subjects studied (56). In this particular trial (22), the number of subjects studied (i.e., 251) provided insufficient power to detect a 12% change on this outcome. If a much larger number of subjects had been entered into the trial, and if the same magnitude and variability of the treatment effect had been obtained, this change would have been statistically significant. As a consequence of such difficulties, it is important to recognize that negative results from small clinical trials generally provide little assurance that a true treatment effect has not been missed.

Second, because it is uncertain which outcome measures correlate best with future function, clinical trials that use a combination of outcome measures (including both clinical and confirmatory MRI measures) should be judged as stronger evidence than those that rely on only a single measure, especially when that measure is a subjective clinical score.

Third, it is important to recognize that both the statistical significance of a finding and the magnitude of the treatment effect (i.e., the effect size) provide important complementary information about the quality of the evidence. The statistical significance relates to the believability of a result whereas the effect size relates to its clinical importance. Trials with large effects of marginal significance and trials with significant effects of

marginal importance should both be judged as providing equivocal evidence.

Fourth, it should be noted that treatments aimed at limiting future CNS injury would not be expected to cause an already disabled patient to improve dramatically, even though some patients may experience some clinical improvement based on intrinsic self-repair mechanisms. As a consequence, reports of substantial improvement following the use of such agents should be viewed with caution.

Lastly, there are concerns regarding the cost-benefit ratio of any therapy that is widely recommended to patients with MS. These concerns are relevant to circumstances, such as with the currently available immunomodulatory agents, where the cost is high and the expected short-term benefit is modest. Indeed, differences (both between individual physicians and between countries) in how this cost-benefit ratio is assessed will inevitably influence how these agents are actually prescribed. However, cost-benefit calculations are complex. They generally require many assumptions of debatable validity and often result in a ratio of uncertain value, both to the patient and to society. Nevertheless, if early treatment is demonstrated to preserve employment, intellect, and self-care for years or decades, both societal costs and family welfare will benefit. Although of unquestioned import, these concerns are more a matter of public policy than of patient care. As a result, a consideration of these issues is beyond the scope of the present manuscript, which is focused instead on the evidence in favor of clinical efficacy for the different therapeutic strategies.

The literature search was conducted by the Center for Clinical Health Policy Research at Duke University under a contract with the Paralyzed Veterans of America. Articles were initially searched in the database MEDLINE and subsequently in the databases of HealthSTAR and CINAHL. The latter two databases, however, did not contribute additional articles to the search. Additional articles were identified by review of citation lists of articles reviewed for inclusion. There were seven topic-specific searches including ACTH, glatiramer acetate, interferon, intravenous gamma globulin, plasmapheresis, steroids, and a combined search on mitoxantrone, methotrexate, azathioprine, cladribine, cyclophosphamide, and cylcosporine. The basic search strategy incorporated terms for study design and MS.

Studies that were included involved predominantly adults (>17 years), were randomized prospective trials of 20 or more subjects, and included outcome measures related to either disease activity or disability. In all, 683 abstracts and 207 full-text articles were reviewed, of which 81 were summarized as evidence tables. Three additional articles were identified by panel members and summarized in evidence tables. The original searches were conducted in August 1998 and were updated for the last time in November 1999. More recent articles included in this document were identified by panel members using both a MEDLINE search and a review of recent issues of key journals. Individual panel members also reviewed all of these articles (so identified) with respect to the Duke classification and evidence tables.

SUMMARY

GLUCOCORTICOIDS:

1. On the basis of several and generally consistent Class I and Class II studies, glucocorticoid treatment has been demonstrated to have a short-term benefit on the speed of functional recovery in patients with acute attacks of MS. It is appropriate, therefore, to consider for treatment with glucocorticoids any patient with an acute attack of MS (Type A recommendation).

2. There does not appear, however, to be any long-term functional benefit following the brief use of glucocorticoids in this clinical setting (Type B recommendation).

3. At present, there is not compelling evidence to indicate that these clinical benefits are influenced by the route of glucocorticoid administration, the particular glucocorticoid prescribed, or the dosage of glucocorticoid, at least at the doses that have been studied to date (Type C recommendation).

4. On the basis of a single Class II study it is considered possible that regular pulse glucocorticoids may be useful in the long-term management of patients with RRMS (Type C recommendation).

INTERFERON BETA:

1. On the basis of several consistent Class I studies, IFNβ has been demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with MS or with clinically isolated syndromes who are at high-risk to develop MS (Type A recommendation). Treatment of MS with IFNβ produces a beneficial effect on MRI measures of disease severity such as T2 disease burden and probably also slows sustained disability progression (Type B recommendation).

2. As a result, it is appropriate to consider IFNβ for treatment in any patient who is at high-risk to develop CDMS, or who already has either RRMS or SPMS and is still experiencing relapses (Type A recommendation). The effectiveness of IFNβ in patients with SPMS but without relapses is uncertain (Type U recommendation).

3. It is possible that certain populations of MS patients (e.g., those with more attacks or at earlier disease stages) may be better candidates for therapy than others although, at the moment, there is insufficient evidence regarding these issues (Type U Recommendation).

4. On the basis of Class I and II studies and several pieces of consistent Class III evidence, it is considered probable that there is a dose-response curve associated with the use of IFNβ for the treatment of MS (Type B recommendation). It is possible, however, that a portion of this apparent dose-effect may be due, instead, to differences in the frequency of IFNβ administration (rather than dose) between studies.

5. On the basis of several Class II studies, the route of administration of IFNβ is probably not of clinical importance, at least with regard to efficacy (Type B recommendation). The side-effect profile, however, does differ between routes of administration. There is no known clinical difference between the different types of IFNβ although this has not been thoroughly studied (Type U recommendation).

6. On the basis of several Class I studies, treatment of MS patients with IFNβ is associated with the production of neutralizing antibodies (NAbs) (Type A recommendation). The rate of NAb production, however, is probably less with IFNβ-1a treatment than with IFNβ-1b treatment (Type B recommendation). The biological effect of NAbs is uncertain, although their presence may be associated with a reduction in clinical effectiveness of IFNβ treatment (Type C recommendation). Whether there is a difference in immunogenicity

between subcutaneous and intramuscular routes of administration is unknown (Type U recommendation). The clinical utility of measuring NAbs in an individual on IFNβ therapy is uncertain (Type U recommendation).

GLATIRAMER ACETATE:

1. On the basis of Class I evidence, glatiramer acetate has been demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with RRMS (Type A recommendation). Treatment with glatiramer acetate produces a beneficial effect on MRI measures of disease severity such as T2 disease burden and possibly also slows sustained disability progression in patients with RRMS (Type C recommendation).

2. As a result, it is appropriate to consider glatiramer acetate for treatment in any patient who has RRMS (Type A recommendation). While it may be that glatiramer acetate is also helpful in patients with progressive disease, there is no convincing evidence to support this hypothesis (Type U Recommendation).

CYCLOPHOSPHAMIDE:

1. Based on consistent Class I evidence, pulse cyclophosphamide treatment does not seem to alter the course of progressive MS (Type B recommendation).

2. Based on a single Class III study, it is possible that younger patients with progressive MS might derive some benefit from pulse plus booster cyclophosphamide treatment (Type U recommendation).

METHOTREXATE:

1. Based on limited and somewhat ambiguous Class I evidence from a single trial, it is considered possible that methotrexate favorably alters the disease course in patients with progressive MS (Type C recommendation).

AZATHIOPRINE:

1. On the basis of several, but somewhat conflicting, Class I and II studies, it is considered possible that azathioprine reduces the relapse rate in patients with MS (Type C recommendation).

2. Its effect on disability progression has not been demonstrated (Type U recommendation).

CLADRIBINE:

1. On the basis of consistent Class I evidence, it is concluded that cladribine reduces Gd-enhancement in patients with both relapsing and progressive forms of MS (Type A recommendation).

2. Cladribine treatment does not, however, appear to alter favorably the course of the disease, either in terms of attack-rate or disease progression (Type C recommendation).

CYCLOSPORINE:

1. Based on this Class I study, it is considered possible that cyclosporine provides some therapeutic benefit in progressive MS (Type C recommendation).

2. However, the frequent occurrence of adverse reactions to treatment, especially nephrotoxicity, together with the small magnitude of the potential benefit, makes the risk/benefit of this therapeutic approach unacceptable (Type B recommendation).

MITOXANTRONE:

1. On the basis of generally consistent Class II and III studies, it is concluded that mitoxantrone probably reduces the attack rate in patients with relapsing forms of MS (Type B recommendation). The potential toxicity of mitoxantrone, however, may outweigh the clinical benefits early in the course of disease.

2. On the basis of several Class II and III observations, it is considered possible that mitoxantrone has a beneficial effect on disease progression in MS although, at the moment, this clinical benefit has not been established (Type C recommendation).

INTRAVENOUS IMMUNE GLOBULIN:

1. The studies of IVIg, to date, have generally involved small numbers of patients, have lacked complete data on clinical and MRI outcomes, or have used methods that have been questioned. It is, therefore, only possible that IVIg reduces the attack rate in RRMS (Type C recommendation).

2. The current evidence suggests that IVIg is of little benefit with regard to slowing disease progression (Type C recommendation).

PLASMA EXCHANGE:

1. On the basis of consistent Class I, II, and III studies, plasma exchange is of little or no value in the treatment of progressive MS (Type A recommendation).

2. On the basis of a single small Class I study, it is considered possible that plasma exchange may be helpful in the treatment of severe, acute episodes of demyelination in previously nondisabled individuals (Type C recommendation).

SULFASALAZINE:

1. Based on a single Class I study, it is concluded that treatment of MS with sulfasalazine provides no therapeutic benefit in MS (Type B recommendation).

ANALYSIS OF THE EVIDENCE

Glucocorticoids

Adrenocorticotropic hormone (ACTH) stimulates both glucocorticoid and mineralocorticoid production. Following early reports regarding the potential benefit of ACTH on MS exacerbations, Rose and colleagues undertook a large multicenter trial of ACTH in patients with MS (57). This trial involved 197 patients with acute MS attacks treated with either placebo or intramuscular (i.m.) ACTH (40 units twice daily for 4 days followed by a tapering course over 7 days). Patients were evaluated prior to therapy and weekly thereafter for 4 weeks.

It was found that ACTH accelerated clinical improvement compared to the placebo treated group, although there was no significant difference in outcome between groups at the end of the study. Moreover, the blinding of this study may not have been adequate because side-effects were significantly more common in the treated arm compared to the placebo arm ($p < 0.0001$), and because the evaluating physicians were able to guess correctly the treatment assignments of the patients in 68.5% of cases ($p < 0.0001$ compared to chance). As a result, the authors themselves concluded that these findings were quite marginal, noting that "at no time was the improvement particularly obvious or outstanding." In summary, this study provides Class II evidence (see Table 1 for Ratings of Evidence Classification) that ACTH speeds clinical recovery following an acute attack of MS. No long-term benefit to ACTH treatment is suggested by these data.

In a comparison study (58), 61 MS patients with an acute relapse were randomized to receive either 1 g of intravenous (i.v.) methylprednisolone treatment (IVMP) daily for three days or i.m. ACTH for 14 days (80 units per day for a week followed by a one week taper). Masking was accomplished by administration of i.v. placebo to the ACTH group for 3 days and i.m. placebo to the IVMP group for 14 days. Although both groups improved clinically, there was no significant difference (ns) in outcome between the two treatment groups. In another small study of MS exacerbations, oral dexamethasone and ACTH treated groups experienced shorter duration relapses compared to a group treated with oral methylprednisolone, although these effects were not statistically significant (59).

These studies provide only weak support of a treatment benefit for any of the glucocorticoid regimens investigated because no placebo groups were included. They also provide some Class II evidence that there is little therapeutic difference between the different glucocorticoid regimens used. The data, however, are inadequate to draw strong conclusions in this regard.

There were 27 articles identified in which the use of glucocorticoids in MS was studied. However, six of these trials involved the use of additional medications, either given together with steroids or compared with steroids. These agents included azathioprine, cyclosporine, mitoxantrone, and beta interferon. As a result it is not possible to separate any potential contributory effect of steroids in these trials. Of the remaining 21 papers, 9 were Class I, 6 were Class II, and the remainder were either Class III or IV.

Of the 15 articles identified with Class I or II evidence, 5 related to the optic neuritis treatment trial (ONTT) begun in 1988 (60–66). This multicenter trial evaluated the effectiveness of glucocorticoids in the treatment of acute optic neuritis in 457 patients. The two active treatment arms received either 1 g of IVMP daily for 3 days followed by 11 days of oral prednisone (1 mg/kg/day), or a 14-day course of oral prednisone alone. Each group was compared to a third group that received placebo. IVMP-treated patients were only single-blinded and the blinded outcome assessment was compromised.

The primary endpoints of the trial were visual field and contrast sensitivity. Visual acuity and color vision were secondary endpoints. With

regard to the primary and secondary endpoints, these authors reported that the IVMP group had a faster recovery of visual function than the placebo group in the first month. By 6 months, the two groups were not statistically different with respect to visual recovery. The rate of recovery of visual function in the oral prednisone group was intermediate between the other two groups and was not statistically different from either. This trial also reported that there was an increase in the number of episodes of recurrent optic neuritis following oral prednisone treatment alone (60). This unexpected finding was only marginally significant ($p = 0.02$) and it was not one of the preplanned primary outcomes of the ONTT. This trial also reported that treatment with IVMP slows the time to development of CDMS over 2 years (64).

The methodology used by the ONTT and the validity of both of these observations, however, have been challenged (50, 67-69). Moreover, an earlier study of patients with optic neuritis (70) reported exactly opposite findings. In this small retrospective study (Class III), patients treated with IVMP for three days at 1g/day experienced more recurrent episodes of optic neuritis and a faster progression to CDMS than did patients treated with oral prednisone alone (70).

In summary, this study provides Class II evidence that the use of IVMP increases the rate of recovery of visual function in optic neuritis. There were no significant differences in visual outcome between the IVMP and prednisone treated groups, so that the relative value of oral and intravenous glucocorticoids in the treatment of optic neuritis cannot be easily judged. Moreover, this study provides no evidence of any benefit from short-term glucocorticoid treatment with regard to visual outcome. Because methodological flaws affect certain aspects of the ONTT (50, 67-69), its results regarding recurrent optic neuritis and the development of MS should be regarded as unproven.

In a 1987 study (71), 22 patients with acute relapses were randomized to receive IVMP at 500mg/day for five days or i.v. placebo. A benefit on EDSS and functional scores was observed at 1 and 4 weeks in the treatment group compared to the placebo group ($p = 0.04$). Another study with 23 patients (72) showed that patients experiencing an acute relapse experienced short-term benefit from IVMP and an oral prednisone taper compared to placebo. Both of these studies, although small, provide some Class II data to support a short-term benefit to treatment of acute MS attacks with IVMP.

The total dose of glucocorticoid administered and the need for a taper following treatment may be important. For example, the use of high dose steroid treatment is known to accelerate resolution of gadolinium enhancement on MRI scanning (73-76). In one study, Oliveri et al. (76) investigated two doses of IVMP in patients with RRMS; 0.5g/day compared to 2g/day, each administered for five days. The higher dose regimen was associated with a greater reduction in both the number of MRI enhancing lesions and the number of new enhancing lesions at 30 and 60 days following onset of therapy (77). Following the cessation of steroid treatment, however, a second burst of gadolinium enhancement has been reported to occur, which may relate to the rate of steroid discontinuation (78-80). Reder has suggested that the abrupt withdrawal of glucocorticoids may produce a temporary adrenalectomy-like hypoglucocorticoid state until adrenal function and glucocorticoid receptor levels rebound (81). In the animal model of inflammatory demyelination, experimental allergic encephalomyelitis, a 1994 study found that abrupt withdrawal of dexamethasone led to severe clinical and histological relapses whereas a slow taper of steroids was associated with a prevention of relapses (81).

Unfortunately, the clinical data regarding these points have been limited. There have not been any well-designed placebo-controlled trials that compare high dose oral steroids to high dose IV preparations. These drugs are off-patent and the costs of randomized double-blind studies of sufficient size are often prohibitive.

In a small study of 35 MS patients with acute relapse who were randomized to receive either IVMP (500 mg for five days plus an oral placebo) or oral methylprednisolone (500 mg for five days plus an i.v. placebo) (82). Both groups demon-

strated significant improvement following therapy without any differences between the groups with respect to EDSS. In 79 relapsing MS patients, a comparative study of low dose oral methylprednisolone taper (starting at 48 mg) versus IVMP at 1g/day for three days failed to show any differences in EDSS or AI following therapy (83). It is possible, however, that the wait before beginning treatment in this study was too long to show a benefit to more aggressive treatment.

Additionally, a 1998 study reported the results of two placebo controlled high-dose oral methylprednisolone studies in patients with RRMS or with those with monosymptomatic optic neuritis (84, 85). Oral methylprednisolone at 500 mg for five days followed by a ten-day taper was compared to placebo and a significant short-term benefit to treatment was noted in both studies (84, 85). A 1998 study evaluated IVMP at 500 mg versus 10 mg given bimonthly for two years in 108 patients with secondary progressive MS with relapses (86). Assessed outcomes included EDSS, AI, 9HPT, Box and Block test, and the number of patients with three or more exacerbations. Log rank comparisons favored the higher dose group although the primary outcome measure for this trial (sustained failure on a composite outcome) was not significantly different between groups ($p = 0.18$).

In sum, these studies, although small, are, in general, well-designed (Class I and II) and provide consistent evidence that glucocorticoids have a short-term benefit in the management of acute MS attacks. They do not, however, provide convincing guidance with regard to the optimal total glucocorticoid dose or route of administration.

The preliminary results of a trial of pulse high-dose methylprednisolone in the treatment of MS were recently presented (87). This trial involved 10 patients using a single crossover design. Patients were observed for six months and those patients with active disease (three new lesions in six monthly scans) were subsequently treated with monthly IVMP (500 mg followed by a three day oral taper). The number of Gd-enhancing lesions during treatment was reduced by 47% compared to the baseline activity during the six months prior to treatment ($p < 0.05$). The concerns regarding this study include the small number of patients studied. Of greater concern, however, is the fact that the patients were selected for this study because of a high baseline level of MRI activity during the first six months of observation. In this circumstance, regression to the mean would be expected to result in a reduction in MRI activity in the second six months of the trial regardless of therapy. As a result, this trial only provides Class III evidence of efficacy for this therapeutic approach.

Another trial of glucocorticoids in the treatment of RRMS was recently presented (88). This trial was a single-blind, randomized controlled phase II trial comparing regular use of pulse IVMP with IVMP given only during times of acute relapse in 88 patients treated over 5 years (Class II evidence). This trial reported that, after 5 years of treatment, the group receiving regular IVMP had a smaller T1-weighted black hole volume on MRI ($p < 0.0001$), less brain atrophy ($p = 0.003$), and a longer time to EDSS worsening ($p < 0.0001$), compared to patients who received IVMP only for acute attacks. There was no difference between groups with respect to T2-lesion volume or annual relapse rate. Although this trial is small and the results preliminary, the reported findings suggest that this therapeutic approach deserves further investigation.

- In summary, on the basis of several and generally consistent Class I and Class II studies, glucocorticoid treatment has been demonstrated to have a short-term benefit on the speed of functional recovery in patients with acute attacks of MS (Type A recommendation). There does not appear, however, to be any long-term improvement in the degree of functional recovery from an attack following the use of glucocorticoids (Type B recommendation). Neither is there, at present, compelling evidence to suggest that these modest clinical benefits are influenced by the route of glucocorticoid administration,

the particular glucocorticoid prescribed, or the dosage of glucocorticoid, at least at the doses that have been studied to date (Type C recommendation).

* On the basis of a single Class II study, it is considered possible that regular pulse glucocorticoids may be useful in the long-term management of patients with RRMS (Type C recommendation).

Immunomodulatory Treatments

In 1993, the Food and Drug Administration (FDA), on the basis of a large multicenter placebo-controlled trial, approved interferon beta-1b (IFNβ-1b or Betaseron) for the treatment of RRMS in the United States. Subsequently, two additional immunomodulatory agents (IFNβ-1a [Avonex] and glatiramer acetate [Copaxone]) have also been approved by the FDA for use in the United States and, in addition, a third (IFNa or Rebif) has been approved in Canada, Europe, and other parts of the world.

INTERFERON BETA

Clinical Trial Results. The multicenter study of IFNβ-1b (Betaseron) in RRMS (17–19) was randomized, double-blind, and placebo-controlled (Class I evidence). It included 372 RRMS patients who had scores on the EDSS of 5.5 or below and who had experienced at least 2 attacks in the prior 2 years. Patients were randomized to receive placebo, low-dose (1.6 MIU; 50 μg), or high-dose (8 MIU; 250 μg) IFNβ-1b, subcutaneously (s.c.), every other day for 2 years. After 2 years, compared to placebo, treatment with high-dose IFNβ-1b reduced the clinical relapse rate (-34%; $p < 0.0001$), which was the primary end-point of the study. In addition, the MRI attack rate as measured by median number of T2 active lesions (-83%; $p < 0.009$) and the median volume of MRI T2 disease burden (-17.3%; $p = 0.001$) were reduced in the IFNβ-1b arm compared to placebo-treated patients. The high dose also resulted in a reduction in the confirmed 1-point EDSS progression rate but this was not statistically significant (-29%; $p = 0.16$). This trial, however, did report a reduction in the unconfirmed 1-point EDSS worsening over three years of study (-31%; $p = 0.043$).

In summary, this trial provides Class I evidence that IFNβ reduces the relapse rate (measured either clinically or by MRI) in patients with RRMS. The effect of treatment on measures of disease severity (i.e., MRI disease burden and disability progression) is less consistent. There was a robust effect of treatment on the MRI disease burden but no statistically significant effect on the measure of confirmed 1-point EDSS progression.

The IFNβ-1a (Avonex) trial (26, 89, 90) was also multicenter, randomized, and placebo-controlled (Class I evidence). It included 301 RRMS patients who had an EDSS score of 1.0-3.5 and who had experienced at least 2 attacks in the 3 years prior to study entry. Patients were treated either with placebo or IFNβ-1a, 6 MIU/wk (30 μg/wk), i.m. for two years. This trial was stopped earlier than originally designed, so that only 57% (172 patients) completed the full two years on study medication.

Compared to placebo, treatment with Avonex for two years produced a reduction in the confirmed 1-point EDSS progression rate (-37%; $p = 0.02$), which was the primary end-point of the trial. In addition, the clinical attack rate (-18%; $p = 0.04$) and the MRI attack rate as measured by the median number of gadolinium enhancing lesions (-33%; $p = 0.05$) were reduced in the IFNβ-1a arm compared to placebo-treated patients. The total volume of T2 disease burden seen on MRI was also reduced compared to placebo but this was not statistically significant (-6.7 %; $p = 0.36$).

This trial also found that the reduction in attack rate in the first year of therapy (-9.6%; ns) was less than the reduction in patients who had completed two years of therapy (-32%; $p = 0.002$), suggesting that the full clinical benefits of IFNβ-1a therapy might be delayed for a year or more after the initiation of treatment (21, 26, 91). Nevertheless, the authors provide no statistical evidence of a difference between the one-year and two-year data and, in addition, the other IFNβ trials in RRMS did not observe such a delay in therapeutic benefit (17-19, 21, 24, 92). Most importantly, however, this subgroup of patients (who

had a 32% reduction in attack-rate over 2 years) had a similar reduction in attack-rate (-29%) at the 1-year mark (91). Such an observation indicates that this particular subgroup of patients (i.e., the 2-year completers) is unrepresentative of the study cohort as a whole. As a result of this anticipated bias, therefore, the validity of any separate analysis on this subgroup of patients is questionable.

A re-analysis of the trial data (done on only the subgroup of 2-year completers) using the "brain parenchymal fraction" (BPF) to measure brain atrophy (93) showed no statistically significant reduction in brain atrophy following two years of treatment ($p = 0.30$). A sub-group analysis did show a reduction of accumulated atrophy in the second year of treatment ($p = 0.03$). This latter observation, however, was only marginally significant and was the result of a post hoc analysis on a biased subset of the study population, and the reported p-value was not adjusted for the three between-group statistical comparisons of BPF presented in the figure of the paper (93). The validity of this observation is therefore uncertain.

In summary, this trial provides Class I evidence that IFNβ-1a reduces the biological activity of RRMS. Importantly, the results of this trial replicate, in general, the earlier IFNβ-1b trial for both clinical and MRI outcomes although, again, the effect of treatment on attack rate measures was more consistent than for measures of disease severity. Thus, both clinical and MRI measures of attack rate were similarly improved at two years. Additionally, there was a reduction in the confirmed 1-point EDSS progression rate, although there was no statistically significant concomitant benefit on either MRI disease burden or brain atrophy over the two years of study.

The IFNβ-1a (Rebif) trial (24, 92) was similarly a randomized, multicenter, double-blind, and placebo-controlled study (Class I evidence). A total of 560 RRMS patients with an EDSS score of 5.0 or less were entered. Only patients who had experienced 2 or more relapses in the prior 2 years were included. Patients were treated for 2 years with placebo or IFNβ-1a at doses of either 22 μg (6 MIU) or 44 μg (12 MIU) s.c. three times weekly. After two years there was a significant beneficial effect of treatment with either dose on both clinical and MRI outcome measures. Thus, compared to placebo, treatment with IFNβ-1a, 132 μg /wk (36 MIU/wk) reduced the clinical attack rate (-32%; $p < 0.005$), which was the primary end-point of the trial. In addition, the MRI attack rate as measured by median number of T2 active lesions (-78%; $p < 0.0001$), the volume of white matter disease seen on T2-weighted MRI (-14.7%; $p < 0.0001$), and the confirmed 1-point EDSS progression rate (-30%; $p < 0.05$) were also reduced in the IFNβ-1a arm compared to placebo.

In summary, this trial provides Class I evidence that IFNβ-1a reduces the biological activity of RRMS. As in other IFNβ trials, this trial demonstrated a benefit to treatment on both clinical and MRI measures of attack rate. Also, this was the first trial of IFNβ in RRMS to show both a reduction in the confirmed 1-point EDSS progression and a highly significant reduction in the T2 disease burden.

The IFNβ-1b (Betaferon) trial in SPMS (27) was a randomized, placebo-controlled, double-blinded study conducted amongst 32 European centers (Class I evidence) that included 718 patients with an EDSS of 3.0-6.5. Patients had to have either two relapses or more than 1.0 point increase in EDSS in the prior two years. Those included were randomized to receive either placebo or IFNβ-1b, 250 μg (8 MIU) s.c. every other day for up to three years.

Compared to treatment with placebo, treatment with 28 MIU/wk of Betaferon reduced the confirmed 1-point EDSS progression rate (-22%; $p = 0.0008$), the primary end-point of the study. In addition, the clinical attack rate (-31%; $p = 0.0002$), the MRI attack rate (-78%; $p = 0.0008$), and the volume of white matter disease seen on MRI (-13%; $p = 0.0001$) were all significantly reduced in the IFNβ-1b arm compared to placebo. This study also demonstrated that treatment with IFNβ-1b reduced the likelihood of becoming wheelchair bound during the study (-33%; $p = 0.01$).

After dividing patients into those who had experienced clinical attacks in the two years prior to study entry and those who only experienced steady clinical deterioration, the benefit of treatment was comparable in both subgroups. After dividing patients into those who did and those who did not experience attacks during the trial, the benefit of treatment was again found to be similar in the two subgroups. After dividing patients into three groups based on their baseline EDSS scores (Group 1 = 3.0-3.5; Group 2 = 4.0-5.5; and Group 3 = 6.0-6.5), IFNβ-1b was found to be similarly beneficial in all three groups. However, when the full three-year data are analyzed, the benefit of treatment in patients with an EDSS ≥ 6.0 is not apparent.

In summary, this trial provides Class I evidence that treatment with IFNβ-1b favorably impacts both clinical and MRI outcomes for attack rate and disease severity in patients with SPMS.

The results of another recently completed Class I trial of IFNβ-1b (Betaseron) in SPMS have also been reported in preliminary form (94). This trial failed to find a statistically significant reduction in the confirmed 1-point EDSS progression rate (the primary end point of the trial), although it did report significant reductions in the clinical attack rate, the MRI attack rate, and the volume of white matter disease seen on T2 weighted MRI. Publication of the final results from this trial is pending. The reason for the apparently discrepant findings between these two trials of IFNβ-1b is not clear. Some observers have noted that the North American cohort of patients had significantly fewer attacks than their European counterparts and that, perhaps, IFNβ is most effective in the relapsing phase of the illness. At the moment, however, such a notion is speculative.

The recently published trial of IFNβ-1a (Rebif) in SPMS (95, 96) also failed to find a statistically significant reduction in the confirmed 1-point EDSS progression rate (the primary end point of the trial). Like the IFNβ-1b (Betaseron) trial, however, this trial also found significant reductions in the clinical attack rate, the MRI attack rate, and the volume of white matter disease seen on T2 weighted MRI. Also, when the results of this trial were re-analyzed by separating patients into those with and those without attacks, a benefit to treatment on the confirmed 1-point EDSS progression rate was noted ($p = 0.027$) in patients with relapses. The validity of such a re-analysis of the data is clearly open to question but, nevertheless, might be taken as weak support for the speculation (noted above) that IFNβ is more effective in SPMS patients who continue to experience relapses.

Another recent Class I study of IFNβ-1a (Avonex) in the treatment of SPMS has been reported in preliminary form (97). Using the MSFC as the primary outcome, this trial found that, compared to placebo, treatment with IFNβ-1a, 60 μg/wk, i.m., was beneficial over a two-year period ($p = 0.03$). This study, however, did not find any concomitant benefit on the outcome of confirmed 1-point EDSS progression. Moreover, the benefit seen on the MSFC outcome was based primarily on the results from the 9HPT portion of the composite score. The reported benefit of therapy in this trial, therefore, is of uncertain reliability.

Two recently completed trials of IFNβ-1a (Avonex and Rebif) in patients at high risk of developing MS have shown that early treatment significantly slows the subsequent rate of conversion to CDMS (98, 99). The IFNβ-1a (Avonex) trial (98) was a multicenter, randomized, placebo-controlled trial involving 383 patients who were followed for up to 3 years (Class I evidence). Patients needed to have just experienced their first clinically isolated (monosymptomatic) CNS event consisting of an optic neuritis, a spinal cord syndrome, or a brainstem/cerebellar syndrome. Patients also had to have an abnormal brain MRI defined as two or more clinically silent lesions (≥ 3mm) on T2 weighted MRI scans, at least one of which needed to be ovoid in appearance or periventricular in location. Patients were initially treated with IVMP, 1 g/d for 3 days followed by a course of oral prednisone, 1 mg/kg/d for 15 days. Patients subsequently received either IFNβ-1a (30 μg/wk, i.m.) or placebo throughout the study.

Using a Cox proportional hazards model, the relative risk of developing CDMS in the treated group was 0.56 ($p = 0.002$), indicating a 44% decrease in the rate of conversion to MS following administration of IFNβ-1a, which was the primary endpoint of the trial. MRI measures also demonstrated a robust treatment effect. Thus, at 18 months, the number of new lesions (-57%; $p < 0.0001$), the percentage change in the T2 lesion volume (-14%; $p = 0.0004$), and number of enhancing lesions (-67%; $p < 0.0001$) were all reduced using IFNβ-1a when compared to placebo.

The IFNβ-1a (Rebif) trial (99) was also a multicenter randomized trial (Class I evidence) involving 309 patients who had experienced their first clinical episode suggestive of demyelinating disease (either mono- or polysymptomatic) and who were followed for 2 years thereafter. Patients received either IFNβ-1a (22 μg/wk, s.c.) or placebo throughout the study. The proportion of patients converting to CDMS was less in the treated group compared to placebo (-24%; $p = 0.047$). In addition, the median number of T2 active lesions seen on MRI was also reduced in the treated compared to placebo patients ($p < 0.001$). Also the T2 disease burden was also reduced in the treated arm compared to placebo in both year 1 and year 2 of the trial ($p = 0.006$ and $p = 0.002$ respectively).

These trials, therefore, provide Class I evidence that treatment with IFNβ-1a delays the development of CDMS in patients at high risk for this outcome. Such a result is hardly surprising. Indeed, any treatment for RRMS that can delay the time between attacks 2 and 3 or between attacks 3 and 4 (i.e., any treatment that reduces the attack rate) would also be expected to delay the time between attacks 1 and 2. These studies do not, however, provide evidence that the ultimate development of CDMS is prevented by such treatment. Neither do they provide any evidence that early treatment affects long-term disability outcome.

Side effects to IFNβ therapy include flu-like symptoms (including fevers, chills, and myalgias) as well as mild abnormalities on routine laboratory evaluation such as mild elevation in liver function tests or a mild lymphopenia (17, 20, 26). Rarely, more severe hepatotoxicity may occur. When IFNβ was injected intramuscularly, muscle abscesses have been rarely reported. When injected subcutaneously, IFNβ also often causes reactions at the site of injection including pain, redness, induration, or, rarely, skin necrosis (17, 20). These side effects are generally more severe with higher doses of IFNβ, but they can usually be managed effectively with instructions on proper injection technique and with the use of concomitant non- steroidal, anti-inflammatory medications at the time of injection. Depression, increased spasticity, and mental abnormalities have been reported, although these symptoms also occur as part of the underlying disease and their relationship to medication is unclear. In any event, the side effects to IFNβ typically subside with continued therapy (17, 20, 26).

- In conclusion, on the basis of several consistent Class I studies, IFNβ has been convincingly demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with MS or with clinically isolated syndromes who are at high-risk to develop MS (Type A recommendation). In individual trials the benefits of treatment on measures of disease severity (e.g., the 1-point EDSS progression rate, the T2 disease burden seen on MRI, or measures of brain atrophy), have been less consistent. Nevertheless, even in trials where the changes on these measures were either nonsignificant or statistically marginal, the trends were always in favor of treatment, and the best results from individual trials show convincing treatment effects. It is therefore concluded that treatment of MS with IFNβ produces a beneficial effect on MRI measures of disease severity such as T2 disease burden and probably also slows sustained disability progression (Type B recommendation).
- As a result, and on the basis of the same Class I evidence, it is appropriate to consider for IFNβ treatment any patient who is at high-risk to develop CDMS or who already has either RRMS or SPMS and is still experiencing relapses (Type A recommen-

dation). The effectiveness of IFNβ in patients with SPMS but without relapses is uncertain (Type U recommendation). The actual decision to begin treatment in an individual patient, however, must be tempered by an understanding of the facts that the magnitude of the reported treatment benefit is modest, that the attack rate and disease severity measures used as outcomes in clinical trials have an uncertain relationship with long-term disability outcome, that some patients will experience notable side effects to therapy, and that some patients with MS, even without specific therapy, will have a relatively benign disease course.

- It is possible that certain populations of MS patients (e.g., those with more attacks or at earlier disease stages) may be better candidates for therapy than others, and that such differences may, in part, explain apparently discrepant observations such as those reported in the North American and European trials of IFNβ-1b in SPMS. At the moment, however, there is insufficient evidence regarding these issues (Type U Recommendation)

The Effects of IFNβ Type, Route of Administration, and Dose on Clinical Outcome. The total dosage of IFNβ used in the different clinical trials of both RRMS and SPMS has varied considerably between studies and it is important to consider the evidence that there may be a dose-response curve in the use of IFNβ for the management of patients with MS. Because the pharmaceutical companies that manufacture Avonex, Betaseron, and Rebif use slightly different assays to measure IFNβ activity, the millions of international units (MIU) scales reported in the different papers are not directly comparable between publications. Nevertheless, because Avonex and Rebif are both forms of IFNβ-1a, they can be compared on a μg for μg basis. Also, the conversion IFNβ-1a to IFNβ-1b doses can be calculated using published data (100), with the result that 6 MIU of Avonex (30 μg) is equivalent to approximately 9 MIU of Betaseron (280 μg).

IFNβ induces the expression of many gene products and interferon-specific markers, including 2',5'-oligoadenylate synthetase (2',5'-OAS), neopterin, tryptophan, β2-microglobulin and human Mx protein (101). These markers reflect a range of biological activities of IFNβ, including MHC Class-I gene expression, antiviral and anti-proliferative actions, and monocyte activation. These markers have been used as indicators of the biological activity of IFNβ. The relative dose of the different preparations can also be assessed from another recent publication (102) in which antiviral protein (MxA) stimulation was studied in the untreated blood from 10 healthy volunteers. In this study, in vitro stimulation of peripheral blood with all three agents (Avonex, Betaseron, and Rebif) resulted in a dose-dependant increase in MxA levels that was roughly equivalent for each agent on a MIU for MIU basis using the published MIU values.

One study (103) initially suggested that i.m. administration of IFNβ-1a caused a substantially greater area under the concentration-time curve for IFNβ activity in the serum compared to s.c. administration. By contrast, a different study (100) compared the effects of IFNβ-1a given s.c. and i.m. and IFNβ-1b given s.c. on neopterin, human Mx protein, and 2',5'-OAS in 75 healthy volunteers. IFNβ-1a was administered at doses of 1, 3, 6, 9, and 12 MIU and IFNβ-1b at doses of 2, 4, 8, 12, and 16 MIU; each patient in the study received a single dose. The results showed that the production of all three markers was induced in a dose-dependent manner for both IFNβ-1a and IFNβ-1b. Moreover, this study found no differences in any of these biological effects between the two types of IFNβ or between the different routes of administration. Similar results have been found by other investigators (104, 105). Thus, the balance of the evidence favors the view that the route of IFNβ administration is not of clinical importance.

The previously cited study (102) also examined the levels of MxA in the peripheral blood in 237 patients with CDMS following administration of IFNβ. There were 78 patients receiving IFNβ-1b (Betaseron) at a dose of 8 MIU (250 μg) every other day; 71 patients receiving IFNβ-1a (Rebif) at a dose of 6 MIU (22 μg) s.c. either weekly or

three times weekly; and 21 patients receiving IFNβ-1a (Avonex) at a dose of 6 MIU (30 μg) intramuscularly once weekly. The level of MxA was 2.29 ng/105 peripheral blood lymphocytes (PBLs) in the Betaseron-treated patients, 1.00 ng/105 PBLs in the Rebif-treated patients, and 0.57 ng/105 PBLs in the Avonex-treated patients. In summary, the results of this trial suggest that increasing the total weekly IFNβ dose is associated with an increasing biological effect (Class II evidence). However, whether the measured biological effect (on MxA levels) is relevant to the effect of IFNβ on disease activity cannot be assessed from this trial.

The results of the pivotal clinical trials of IFNβ in RRMS also suggest a dose-response curve (17-19, 24, 26, 89, 90, 92). Thus, in general, when comparing the different findings of these trials, both the magnitude of the reported effects on clinical and MRI outcomes, as well as their statistical significance, seems to be greater with increasing dosages of IFNβ. Nevertheless, because of differences in trial design, differences in the MS populations studied, and the fact that the results were obtained in independent clinical trials, this observation can only be considered as Class III evidence of a dose-response.

The findings from the two placebo-controlled Class I IFNβ studies that investigated different doses of IFNβ provide mixed results (17-19, 24, 92). Thus, in the Betaseron trial (16-18), treatment with low-dose IFNβ-1b (5.6 MIU/wk) was significantly better than placebo ($p < 0.01$) on the measure of clinical attack rate over the first two years, although it was significantly less effective on this measure ($p < 0.0086$) than the higher dose of 28 MIU/wk. Trends in favor of higher dose were also seen on other outcome measures, although no other statistically significant dose-effects were noted. In the Rebif trial (24, 92), both doses were highly effective, although the high-dose arm did better on each clinical and MRI outcome measure than the low-dose (18 MIU/wk) arm. With the exception of the outcome of T2 active lesions ($p = 0.0003$ comparing low-dose to high dose), however, there were no statistical differences between the two doses at the 2-year time-point. Thus, although based on Class I studies, the evidence in favor of a dose-response provided by these trials is only equivocal.

The Rebif trial was continued for an additional 2 years (106). Placebo-treated patients during the first two years were re-randomized in a double-blind fashion to receive IFNβ-1a, either 66 μg or 132 μg weekly, in divided doses. After four years, a dose-response relationship was seen for some clinical and MRI outcomes but not for others. Thus, the high dose was more effective than the lower dose ($p < 0.05$) at reducing the relapse rate during years 3 and 4, prolonging the time to second relapse, and increasing the percentage of relapse-free patients. Similarly, treatment with high dose IFNβ-1a reduced the MRI disease burden and T2 lesion activity ($p < 0.001$) compared to low dose (Class I evidence). By contrast, the high-dose group was not statistically better than low-dose group on the outcomes of attack rate measured over years 1-4 (-12%; $p = 0.069$) or the time to confirmed 1-point EDSS progression (+17%; $p = 0.33$). Additionally, an analysis (Class III evidence) of the combined results of the Avonex and Rebif trials suggested that IFNβ-1a has increasing clinical efficacy (as measured by the clinical attack rate at one year) between the doses of 22 and 132 μg weekly (21). By contrast, the results of the SPECTRIMS trial of IFNβ-1a in SPMS demonstrated no difference between 66 and 132 μg weekly with respect to any clinical outcome measure relating to relapse rate (95).

The results of a multi-center, double-blind, dose comparison trial of IFNβ-1a (Avonex) have recently been reported (107). This trial included 678 patients with RRMS who received IFNβ-1a, either 30 μg/wk or 60 μg/wk, i.m., once weekly for a period of at least 3 years (Class I evidence). There was no difference in outcome between the two dosage groups with respect to EDSS progression, relapse rate, Gd-enhancing lesions, T2 lesion burden, or brain atrophy over the course of the trial (105). This trial, thus, provides Class I evidence that 60 μg of IFNβ-1a, i.m., once weekly

provides no additional benefit over 3 years of therapy compared to 30 μg, i.m., once weekly over the same period.

Recently, the preliminary results of two head-to-head comparison trials of different IFNβ preparations have been reported (108, 109). The first (108) was a two-year open-label, randomized trial of IFNβ-1b (Betaseron; 28 MIU/wk, s.c.) compared to IFNβ-1a (Avonex; 30 μg/wk, i.m.) in 188 patients with RRMS. Only the data after 1 year of therapy have been presented. This trial found a greater clinical benefit in the higher dose (more frequently administered) IFNβ-1b group, both on clinical outcomes (i.e., relapse-free status and sustained progression) and on MRI outcomes (i.e., new T2 lesions or Gd-enhancing lesions), compared to the IFNβ-1a group. The evaluating physician, however, was unblinded for clinical outcomes so that the clinical observations from this trial represent only Class III evidence. MRI, by contrast, was assessed blindly so that these observations represent Class I evidence.

The second was a randomized, one-year open-label trial (109) comparing high-dose, more frequently administered IFNβ-1a (Rebif; 132 μg/wk, s.c.) to low-dose, once weekly IFNβ-1a (Avonex; 30 μg/wk, i.m.) in 677 patients with RRMS. Both clinical and MRI outcome measures were assessed in a blinded fashion (Class I evidence). Only data after six months of therapy, and only outcome measures relating to relapse rate, have been presented. At six months, the higher dose (more frequently administered) IFNβ-treated group was statistically superior to the low-dose group on both clinical and MRI outcome measures related to attack rate. These clinical outcomes included the odds of being attack-free, the attack rate, the time to 1st exacerbation, and steroid use. The MRI outcomes included the odds of not having new T1 or T2 lesions, the total number of new lesions, and the cumulative number of new active lesions.

The design of these trials confounds the effect of IFNβ dose with the effect of the frequency of IFNβ administration because, in each, both parameters differed between the two treatment arms. Nevertheless, these trials provide Class I evidence that either the dose or the frequency of IFNβ administration (or both) significantly influences the short-term outcome in patients with RRMS. The final results from both trials are not currently available. Nevertheless, these final results are critically important and it will be necessary to assess whether these apparent short-term advantages to high-dose (more frequent) IFNβ therapy are sustained over time.

- On the basis of individual Class I and II studies and several pieces of consistent Class III evidence, it is considered probable that there is a dose-response curve associated with the use of IFNβ for the treatment of MS (Type B recommendation). It is possible, however, that a portion of this apparent dose-effect may be due, instead, to differences in the frequency of IFNβ administration (rather than dose) between studies. Moreover, the optimal dose in current use, and the potential value of even higher doses, cannot be determined from the evidence.
- On the basis of several Class II studies, the route of administration of IFNβ is probably not of clinical importance, at least with regard to efficacy (Type B recommendation). The side-effect profile, however, does differ between routes of administration.
- Important clinical differences between the different types of IFNβ have not been reported although it is unknown, at present, whether such differences might exist (Type U recommendation).

***Neutralizing Antibodies to IFN*β**. Most patients treated with IFNβ will develop antibodies to the molecule (110). Two different kinds of antibodies are produced. The first, the so-called binding antibodies, are the most prevalent and, in many cases, do not interfere with the receptor-mediated functions of IFNβ. It is possible, however, that these antibodies might increase the clearance of IFNβ through the reticuloendothelial system and, thereby, lower serum IFNβ levels. The second, the so-called neutralizing antibodies (NAbs), do interfere with receptor-mediated func-

tions and can be associated with loss of biological activity. For example, a recent report found NAbs were associated with a loss of detectable serum IFNβ activity (111).

Several different techniques can be used to detect the presence of antibodies to IFNβ in the serum of patients (112). Enzyme-linked immunosorbent assays (ELISAs) measure antibodies to all of the expressed epitopes on IFNβ , including both binding antibodies and NAbs. The MxA assay measures a serum protein that is induced by IFNβ and that is reduced in the presence of NAbs to IFNβ . Cytopathic effect (CPE) assays detect NAbs by demonstrating the neutralization of IFNβ -induced inhibition of viral-mediated cell lysis. Currently, most diagnostic laboratories utilize the CPE assay.

In the phase III Betaseron trial (17), 38% of patients in the high dose arm became NAb positive (defined as two consecutive positive titers three months apart) after two years. When NAb positive and negative patients were analyzed separately, NAb positive patients seemed to behave more like the placebo-treated patients (110). Nevertheless, many of the patients analyzed in this fashion didn't become NAb positive until late in the trial and it is not clear that clinical attacks during a patient's antibody-negative period should be attributed to the antibody-positive group. In addition, many of the antibody-positive patients (defined in this way) ultimately became NAb-negative over time.

Similarly, in the recently published four year PRISMS trial of IFNβ -1a (106), although NAbs were more common in the high-dose compared to the low-dose arm (14.3% and 23.7% respectively), the NAbs appeared to have a significantly negative impact only in the high-dose patients ($p < 0.002$). In the recently published SPECTRIMS study of IFNβ -1a (95, 96) the percent of patients with NAbs in the high-dose arm (14.7%) was again smaller than in the low-dose arm (20.6%). In addition, in this study, the median time to progression was actually longer, the attack-rate in the low-dose arm was reduced, and the attack-rate in the high-dose arm was increased in the NAb positive compared to NAb negative patients. Such findings are very difficult to rationalize and, as a consequence, the possibility that the results are spurious cannot be excluded. As a result, it is uncertain how to interpret these apparent reductions of biological activity in the NAb-positive patients. Moreover, it is not certain that the biologic activities neutralized by NAbs are even relevant to the effect of IFNβ on MS. Also, the long-term consequences of NAbs are unknown. Despite these uncertainties, however, it is difficult to imagine that persistently high NAb titers, at least in some circumstances, would not have some deleterious effect on the clinical efficacy of IFNβ .

In the phase III Avonex trial, only 22% of patients developed NAbs after two years of therapy (26). Moreover, a separate study (113), using a two-step assay, reported that 39% of IFNβ -1b-treated patients and only 6% of IFNβ-1a-treated patients developed NAbs. In this two-step method, patient sera are first analyzed by ELISA for the presence of IFNβ binding antibodies, and positive sera are then screened using a CPE assay. Part of the difference in NAb-positivity between the Betaseron and Avonex trials might relate to the dose of IFNβ administered to patients. Nevertheless, as mentioned above, in both the PRISMS and SPECTRIMS trials the prevalence of such antibodies was actually greater in the low-dose group (20, 95, 106). It was suggested that so-called high zone tolerance might explain the lower rate of NAb in the high-dose group. This notion, however, is speculative and a similar effect was not seen in the IFNβ -1b trial when comparing the two dosage arms (110).

A prospective study of 754 patients treated with different IFNβ preparations (114) found neutralizing antibodies in a larger percentage of patients treated with IFNβ-1b, s.c. (on alternate days), compared to patients treated with IFNβ-1a, i.m. (weekly). This difference, however, was most conspicuous early after treatment was initiated and, after 25 months of therapy, the two groups were essentially equivalent with regard to this measure. This study also examined "neutralizing capacity" in patients treated with other IFNβ regi-

mens, but how this measure relates to the percentage of NAb positive patients in each group is unclear. Also, although mentioned in the paper, it is unclear from the actual text why the authors were unable to compute the percentage of NAb positive patients in these other treatment groups.

The apparently lower immunogenicity of IFNβ -1a in comparison with IFNβ -1b may relate to a number of factors. IFNβ -1a is glycosylated (the naturally occurring state for human IFNβ), and it may be that this form is less immunogenic compared to the non-glycosylated IFNβ -1b (115–117). In addition, the non-glycosylated IFNβ -1b has a tendency to form aggregates (115–117). These aggregate forms probably have lower biological activity, are less able to interact with the IFNβ receptor, and might potentially lead to an increased immunogenicity in comparison with non-aggregated forms. Another factor that may produce a higher rate of NAb formation is a subcutaneous route of administration of IFNβ . The skin, in contrast to muscle, is quite active immunologically, with resident antigen presenting cells to mediate both humeral and cellular immune responses. Such a circumstance might predispose to the formation of NAbs, although the results of the Avonex and Rebif trials (see above) provide mixed evidence in this regard.

- On the basis of several Class I studies, treatment of MS patients with Avonex, Betaseron, or Rebif is associated with the production of NAbs to IFNβ (Type A recommendation). It is likely, however, that the rate of NAb production is less with IFNβ-1a treatment in comparison to IFNβ-1b treatment (Type B recommendation). The biological effect of NAbs is uncertain, although it is possible that their presence may be associated with a reduction in clinical effectiveness of IFNβ treatment (Type C recommendation). Whether there is a difference in immunogenicity between subcutaneous and intramuscular routes of administration is unknown (Type U recommendation). The clinical utility of measuring NAbs in an individual on IFNβ therapy is uncertain (Type U recommendation)

GLATIRAMER ACETATE

Glatiramer acetate (Copaxone) is a random polypeptide made up of four amino acids (L-glutamic acid, L-lysine, L-alanine, and L-tyrosine) in a specific molar ratio (1.4, 3.4, 4.2, and 1.0 respectively). The mechanism of action is not known, but may relate to a number of immunological effects such as the induction of antigen-specific suppressor T cells, inhibition of antigen presentation, displacing bound MBP, or causing an immune deviation in CD4+ T cells from a Th_1 to a Th_2 phenotype (118-120).

The results of a large multicenter, randomized, double-blind, placebo-controlled trial of glatiramer acetate (22, 23) were reported initially in 1995. This trial involved 251 RRMS patients who had an EDSS score of 5.0 or less and who had experienced two or more relapses in the 2 years prior to study entry. Patients received either placebo or 20 mg of glatiramer acetate s.c. daily for up to three years. This trial found that treatment with glatiramer acetate significantly reduced the clinical attack rate over a two-year period (-29%; $p = 0.007$), which was the primary end-point of the study. It also reduced the confirmed 1-point EDSS progression rate, although this change was not statistically significant (-12%; ns). This trial also reported a reduction in the unconfirmed 1-point EDSS worsening over the first two years of the study (-28%; $p = 0.037$).

Also, in a secondary analysis of data from the extension phase of this trial (21), after excluding determinations made during acute attacks, these authors reported a significant reduction in the unconfirmed 1.5 point EDSS progression rate over three years in the treated patients compared to controls (-48%; $p = 0.004$) using survival analysis methods. This last analysis, however, is of uncertain reliability. This outcome has not been used by other investigators and, moreover, this particular outcome was arrived at through post-hoc exploration of the data and the observation is, thus, of uncertain validity.

No MRI outcomes were determined as part of this trial. A second short-duration European/Canadian trial was undertaken to look specifically

at MRI measures (121). This was a placebo-controlled trial and involved 249 RRMS patients who were randomized to receive either placebo or 20 mg of glatiramer acetate s.c. daily for 9 months (Class I evidence). Patients, at entry, had to have an EDSS score of 0-5.0, they had to have experienced at least one clinical attack in the previous 2 years, and they had to have a Gd-enhancing lesion on their screening brain MRI. This trial reported that, compared to placebo, the treated group had a reduction in the total number of enhancing lesions (-35%; $p = 0.001$), which was the primary end-point of the trial. This treatment effect, however, was delayed until 6 months after initiation of treatment. Treated patients also had a reduction in the clinical attack rate (-33%; $p = 0.012$) and a reduction in the median change in T2 burden of disease (-8.3%; $p = 0.0011$) compared to placebo. EDSS change over the course of the trial was minimal and not different between the treatment and placebo groups (121).

An earlier pilot trial (Class I) of glatiramer acetate at comparable dosages (122) also reported a reduction in both the clinical attack rate (-76%; $p < 0.001$) and the confirmed 1-point EDSS progression rate (-60%; $p = 0.05$). MRI outcomes were also not assessed in this pilot trial. Another early pilot trial (Class I) of glatiramer acetate in the treatment of chronic progressive MS (including both PPMS and SPMS), reported that treatment with glatiramer acetate (30 mg/day s.c.) reduced the confirmed 1-point EDSS progression rate compared to placebo (-31%; ns) although this difference was not statistically significant (123).

Recently, experience with the extended use of glatiramer acetate over a six-year period has been reported (124). This trial reports on the experience following 152 RRMS patients who were initially enrolled in the placebo-controlled randomized trial (22, 23) and who continued to be followed after the breaking of the blind. All patients were on active drug during the follow-up interval and were compared to previously published natural history controls (Class III evidence). The authors reported stabilization of the EDSS score and a marked reduction in the clinical attack rate during follow-up.

However, with a 40% dropout rate (compared to the number who were initially enrolled in the randomized trial), there are concerns that the cohort might be self-selected and, therefore, that the study may be biased in favor of a treatment effect. For example, the annual attack rate during the double-blind phase in patients who elected to continue on treatment was significantly less ($p < 0.001$) than in patients who decided not to continue (0.78 and 1.23 attacks/yr respectively). Similarly, there was a significant difference ($p = 0.003$) in the percentage of patients who had deteriorated by 1.5 EDSS points during the double-blind phase between those who elected to continue treatment (40%) and those who didn't (62%). This cohort represents the longest continuous follow-up of a group of treated MS patients for any of the currently available therapies, although, without a concurrent control group for comparison and given the limitations discussed above, it is difficult to know how best to use these data.

Although MRI was not part of the original Phase III clinical trial of glatiramer acetate (22, 23), the authors recently reported the results of follow-up MRI in 135 of the 147 patients who remained in the long-term open-label follow-up cohort as of January 1999 (125). In those patients who were initially on placebo, MRIs were obtained an average of 4 years after being switched to active drug. By contrast, in those patients on active treatment from the beginning of the trial, MRIs were obtained an average of 6.7 years after initiation of glatiramer acetate. Outcome was assessed by comparing different MRI parameters (including a composite MRI measure) between the two groups.

The most significant difference reported between groups was a reduction in the percentage of MRIs showing Gd-enhancement in the patients on glatiramer acetate from the beginning compared to patients originally on placebo (18.8% and 36.4% respectively; $p = 0.02$). Taken at face value, this observation would suggest that the full benefit of glatiramer acetate therapy in reducing Gd-enhancement (a phenomenon that only lasts about 3 months) is delayed for four or

more years following the initiation of treatment. However, there are several reasons to doubt such an explanation. First, no comparable delay is suggested by the clinical data, where the two groups had very similar attack rates within a year of when placebo-treated patients had been switched over to active therapy (124,125). Second, no similar delay in the onset of efficacy is suggested by the results of the 9-month MRI trial (121). And third, it is very difficult to rationalize how the effect of glatiramer acetate on Gd-enhancement could be so markedly delayed. As a result of considerations such as these, it may be more plausible to ascribe this unexpected result to a Type I error; a circumstance that raises similar concerns with respect to the other outcomes reported in this paper (125).

Recently the results of a prospective, one-year, open-label, nonrandomized trial of once weekly IFNβ-1a (Avonex; 30 μg/wk), IFNβ-1b (Betaseron; 28 MIU/wk), glatiramer acetate (Copaxone; 20 mg/day), or no treatment in the management of 156 patients with RRMS were reported (126). These authors found that, compared to no treatment, clinical relapse rate was reduced in all three active-treatment groups, although this reduction was statistically significant only for the IFNβ-1b and glatiramer acetate treated groups ($p \leq 0.003$), suggesting that these two preparations were more clinically effective than IFNβ-1a, at least at the dose and route of administration used in this study. This trial, however, utilized a nonrandomized design and a nonblinded assessment of outcome and, therefore, these data represent only Class III evidence in support of this conclusion.

Side effects to glatiramer acetate are typically minimal. They include injection site reactions (e.g., pain, redness, and induration) although these are generally mild and subside with continued therapy. Metabolic and hematological abnormalities following treatment with glatiramer acetate were not noted either in the pivotal trial or in the six-year open-label study (22, 124). A few patients treated with glatiramer acetate in the pivotal trial (15.2%) experienced what was called an "immediate post-injection reaction," as did a smaller number (3.2%) of placebo-treated patients (22). This reaction may have caused unblinding. This reaction consisted of flushing and/or chest pain together with a variable secondary symptom complex including palpitations, anxiety, and/or dyspnea (22). It came on within minutes of injection, was self-limited (lasting less that 30 minutes), and was without sequelae. It did not recur in the majority of patients and its cause is unknown. No evidence of neutralizing antibodies to glatiramer acetate has been reported, although it is unclear what specific biologic effect could be tested for evidence of such neutralization.

- In conclusion, on the basis of Class I evidence, glatiramer acetate has been demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with RRMS (Type A recommendation). The evidence of a benefit to treatment on measures of disease severity, however, is less robust, in part because the Class I evidence using glatiramer acetate is limited. There is only one Class I study that has both clinical and MRI outcomes available for review. This trial did demonstrate a significant benefit of treatment on MRI measures of disease severity such as the T2 disease burden. The duration of the trial (9 months), however, was too short to evaluate disability progression. The longer duration pivotal trial did not include MRI outcomes and the effect of glatiramer acetate on slowing sustained disability progression did not achieve statistical significance in this study. It is considered possible, nonetheless, that treatment of MS patients with glatiramer acetate produces a beneficial effect on disability progression in patients with RRMS (Type C recommendation).
- As a result, and on the basis of the same Class I evidence, it is appropriate to consider for glatiramer acetate treatment any patient who has RRMS (Type A recommendation). While it may be that glatiramer acetate is also helpful in patients with progressive disease, there is no convincing evidence to support this

hypothesis (Type U recommendation). Again, as with other currently available therapies, the decision to begin treatment needs to be tempered by the facts that the magnitude of the reported treatment benefit is modest, that the attack rate and disease severity measures used as outcomes the clinical trials have an uncertain relationship with long-term outcome, and that some patients with MS, even without specific therapy, will have a relatively benign disease course.

Immunosuppressive Treatments

CYCLOPHOSPHAMIDE

Cyclophosphamide (Cytoxan) is an alkylating agent that has potent immunosuppressive and cytotoxic properties. Often it has prominent side effects such as alopecia, nausea, vomiting, and hemorrhagic cystitis. Other side effects include sterility, myelosuppression, and a long-term risk of malignancy.

In 1983, the first randomized, controlled trial of this agent in the treatment of MS was published (127). It involved 58 patients with chronic progressive MS (SPMS and PPMS) who were divided into three treatment groups. Twenty patients received i.v. ACTH for 21 days; 20 patients received ACTH and i.v. cyclophosphamide (400–500 mg/day for 10–14 days); and 18 patients received ACTH and low-dose oral cyclophosphamide in addition to 5 courses of plasma exchange over two weeks. No benefit to plasma exchange was noted in this trial. However, grouping patients who improved and those who remained stable (i.e., changed by less than 1 EDSS point) into a "stabilized" group, these authors reported a benefit to therapy at both 6 and 12 months ($p < 0.002$). This study was not blinded and no true placebo group was included and, thus, it provides only Class III evidence in favor of a treatment effect.

In 1987, the results of a nonrandomized trial of cyclophosphamide in patients with chronic progressive MS (SPMS and PPMS) were reported (128). There were 27 treated and 24 untreated patients in this study. Treated patients either received i.v. cyclophosphamide (500 mg/day for 10–14 days) in addition to i.v. ACTH or oral prednisone, or they received oral cyclophosphamide (700 mg/m^2/ week for 6 weeks) in addition to oral prednisone. The authors reported a benefit to treatment at both the 1 and 2 year time-points ($p = 0.002$ and $p = 0.009$). This study, however, was nonrandomized, the treatment regimen varied considerably, and the outcome assessment was not done by blinded observers. As a result this study provides only Class III evidence in favor of a treatment effect.

In 1988, the results of a randomized, placebo-controlled, blinded evaluation of cyclophosphamide in the treatment of 44 patients with chronic progressive MS (SPMS and PPMS) were reported (129). The 22 treated patients received i.v. cyclophosphamide (400–500 mg) five times per week until the white blood cell count dropped to below 4,000/µl. Placebo patients received i.v. folic acid (1 mg) on the same schedule for 2 weeks. This study found no trend in favor of treatment at either the 1 or 2 year time points. This study is quite small but, nonetheless, provides some Class I evidence against any value of pulse cyclophosphamide treatment in progressive MS.

In 1992, the results of the Canadian multicenter trial of cyclophosphamide and plasma exchange in the treatment of progressive MS (SPMS and PPMS) were reported (130). This trial involved 168 patients who were randomized into three treatment arms. Fifty-five patients received i.v. cyclophosphamide (1000 mg) on alternate days until either the white blood cell count dropped to below 4,500/µl or the patient had received 9 courses of treatment. These patients also received 40 mg/day of oral prednisone for 10 days. The 57 patients in the plasma exchange group were given oral cyclophosphamide (1.5–2.0 mg/kg) and oral prednisone on alternate days for 22 weeks with the dose of cyclophosphamide, adjusted to achieve a white blood cell count of 4,000–5,000/µl. In addition, these patients received a plasma exchange of 1 plasma volume (40 ml/kg) weekly for 20 weeks. Placebo patients received oral cyclophosphamide placebo, prednisone placebo, and sham plasma exchange on the same schedule. Patients were followed for

up to 3 years and at no time point was there a significant difference in outcome between treatment arms. After 3 years, the cumulative failure rate was actually less in the placebo arm than in the two active treatment arms. This study provides Class I evidence that neither pulse cyclophosphamide treatment nor plasma exchange alters the course of progressive MS.

In 1993, 256 progressive MS patients (SPMS and PPMS) were evaluated (131). Patients were randomized to receive an induction treatment with i.v. cyclophosphamide, either 500 mg/day for 8–18 days until the white blood cell count dropped below 4,000/μl (groups 1 and 2), or 600 mg/m^2 given on days 1, 2, 4, 6, and 8 (groups 3 and 4). All groups were also given ACTH. Groups 2 and 4 subsequently received boosters of i.v. cyclophosphamide (700 mg/m^2) every other month for two years, whereas groups 1 and 3 were not given booster treatment. Outcome assessment was not blinded.

Patients were followed for up to 3 years and Kaplan-Meyer analysis for treatment failure showed no significant benefit to booster treatment over three years ($p = 0.18$). A subgroup analysis, dividing patients into those younger and older than 41 years, suggested a benefit to treatment in younger patients ($p = 0.003$) but no such benefit in the older population. This subgroup, however, was not prospectively identified so that the validity of the observation is questionable. This study provides Class III evidence of a benefit to booster treatment in younger patients. Because all patients received induction with cyclophosphamide, this study cannot be used to assess the value of induction or the benefit of therapy compared to no therapy.

- Based on consistent Class I evidence, pulse cyclophosphamide treatment does not seem to alter the course of progressive MS (Type B recommendation)
- Based on one Class III study, it is possible that younger patients with progressive MS may derive some benefit from pulse plus booster cyclophosphamide treatment (Type U recommendation)

METHOTREXATE

Methotrexate (Rheumatrex) is an inhibitor of dihydrofolate. It has anti-inflammatory properties, decreases proinflammatory cytokines, and augments suppressor cell function. It is already in use for other inflammatory neurological conditions, such as myasthenia gravis and demyelinating peripheral neuropathies. Patients may experience nausea, headache, stomatitis, or diarrhea but these rarely necessitate discontinuation of treatment. Following prolonged treatment (> 2 years), some patients develop liver damage and some experts recommend a percutaneous liver biopsy after two years of treatment to detect drug-related hepatic toxicity. The long-term risk of developing non-Hodgkin's lymphoma following therapy is slightly increased.

In 1993, the results of an 18-month, double-blind, randomized, placebo-controlled pilot study of low-dose methotrexate (7.5 mg/wk) in MS were reported (132). The study population, however, was small (45 individuals) and was not focused on any specific disease category (Class II evidence). The results of this trial suggested a possible benefit to treatment in RRMS but not in progressive MS.

In 1995, the effect of low-dose oral methotrexate (7.5mg/wk) in 60 chronic progressive MS patients (SPMS and PPMS) treated for two years was assessed (42). Treatment failure was defined using a composite outcome measure including two measures sensitive to ambulation (EDSS and AI) and two measures of upper extremity function (9HPT and the Box and Block Test). The trial was randomized, placebo-controlled, and double-blinded (Class II). These authors found a benefit to therapy on the composite outcome ($p = 0.011$).

This result, however, was driven entirely by the findings on the 9HPT ($p = 0.007$), whereas none of the other composite measures showed any significant benefit to treatment. Outcome was also assessed by MRI scans in 56 of the 60 patients, including measures of T2 lesion burden, Gd-enhancement, and new T2 lesions (133). A subgroup analysis of 35 patients (not prospec-

tively defined) with scans performed every 6 weeks suggested a reduction in T2 disease burden favoring treatment with methotrexate ($p = 0.036$) although, considering the entire cohort, no significant difference was noted between the placebo and treated groups with respect to any MRI outcome measure. In sum, this trial provides equivocal evidence of a treatment effect for methotrexate in progressive MS.

- Based on limited, although somewhat conflicting, Class II evidence, it is considered possible that methotrexate favorably alters the disease course in patients with progressive MS (Type C recommendation).

AZATHIOPRINE

Azathioprine (Imuran) is a nucleoside analogue of 6-mercaptopurine that impairs deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis. The clinical benefits may be delayed and expected changes such as lymphopenia or an increase in the mean corpuscular volume may not be observed for three to six months (134). Side effects to treatment include lymphopenia, anemia, transaminitis, alopecia, pancreatitis, and the reactivation of latent viral infections including warts and herpetic infections. There is concern regarding the possible long-term risk of developing malignancy (particularly lymphoma) in those treated with this agent (135).

Studies of this agent in the treatment of MS have yielded mixed results, perhaps related to differences in trial design, study duration, and the number of patients studied. One retrospective meta-analysis of all randomized, blinded controlled trials of azathioprine in MS involving 793 patients in seven studies demonstrated a reduction in relapses (136). From this meta-analysis, the odds ratio for remaining relapse-free at the conclusion of two years of azathioprine therapy was calculated to be 2.04 (137).

In 1988, the British and Dutch Multiple Sclerosis Azathioprine Trial Group reported the results of a three-year, randomized, double-blind trial of azathioprine (2.5 mg/kg daily) or placebo (138) in 354 patients with MS (Class I evidence). After three years, there was a slight improvement in both the mean EDSS score and the AI in the azathioprine-treated patients compared to controls, although there was no significant difference in attack rate between groups (138). These authors concluded that the beneficial effects of treatment azathioprine were small and that such treatment could not be generally recommended to patients with MS.

In a three-arm placebo-controlled, randomized, double-blind trial, 98 MS patients with progressive MS (SPMS and PPMS) were evaluated (139). Patients in the first arm were treated with oral azathioprine (beginning at 2.2 mg/kg increasing as necessary to achieve a white blood cell count of 3,000-4,000/μl) in addition to a course of IVMP. Patients in the second arm were treated similarly with azathioprine but got i.v. placebo instead of IVMP. The third arm received both oral and i.v. placebo. Patients were followed over 36 months of treatment. Intent-to-treat analysis demonstrated no statistically significant difference in the rates of progression among the three treatment arms. Nevertheless, the azathioprine treatment groups had half the relapse rate of the placebo group. Therapeutic effects on disability were not demonstrated.

- On the basis of several, but somewhat conflicting, Class I and II studies, it is considered possible that azathioprine reduces the relapse rate in patients with MS (Type C recommendation). Its effect on disability progression has not been demonstrated (Type U recommendation)

CLADRIBINE

Cladribine (Leustatin) is an adenosine deaminase-resistant purine neucleoside. It is a potent immunosuppressive agent that is relatively selective for lymphocytes. It has been used to treat a variety of lymphoid malignancies but seems to be especially effective in the treatment of hairy-cell leukemia. Side effects include long-term leukopenia, fever, fatigue, nausea, and diarrhea.

A small-randomized study of the use of cladribine in MS was reported in 1994 from the

Scripps Clinic (140). There were 51 patients with chronic progressive MS (SPMS and PPMS) who were treated with either cladribine (0.01mg/kg/day i.v. for seven days in four monthly courses) or placebo. Patients were followed for a year and then crossed over (141). In analyzing the data for the first year, 24 pairs of patients were identified who were matched on the basis of age, sex, and disease severity. Outcome measures included the EDSS score, the SNRS score, and the volume of disease measured from magnetic resonance imaging (MRI). No attack rate data were reported.

This trial reported significant benefit in EDSS and SNRS outcome between the cladribine and placebo groups ($p = 0.004$ and $p = 0.001$ respectively). The authors also noted a beneficial effect on the outcomes of total MRI lesion volume ($p < 0.002$) and Gd-enhancing lesion volume ($p < 0.001$). There are concerns, however, about this trial due to its small size and related to the use of a paired data analysis, coupled with the authors' decision to replace cladribine dropouts but not placebo dropouts (50). Also, interpretation of the MRI lesion volume data is complicated by the fact that the largest difference in lesion volume between groups was seen at baseline. Following treatment the two groups were not statistically different, and, in fact, the lesion volume was slightly greater in the cladribine-treated group (140). This trial provides some Class II data that cladribine favorably affects the course of progressive MS.

In another small trial from the Scripps clinic (142), these same authors examined the value of cladribine treatment in RRMS. The 52 patients were randomized to receive either cladribine (0.07 mg/kg/day for 5 days in six monthly courses) or placebo. Patients were followed for 18 months. These authors found that the relapse rate was reduced in the treated group compared to controls, although this was not statistically significant. There was also no significant difference between groups on the measures of EDSS or SNRS. MRI measures, by contrast, were favorably affected by treatment. Indeed, enhancing lesions were completely suppressed in the cladribine-treated group at 6 months. At seven months, the frequency of enhancing lesions was significantly greater in the placebo ($p = 0.0001$) and remained so at the end of the trial ($p = 0.002$). In sum, this is a small Class I study which provides evidence of a treatment effect on MRI outcomes but also provides no evidence of a clinical benefit to treatment in RRMS.

A multicenter placebo-controlled trial of cladribine in progressive MS (SPMS and PPMS) from North America was also reported recently (143). In this trial 159 patients were randomized to receive either cladribine (0.07 mg/kg/day for 5 days in 2 or 6 monthly cycles) or placebo. Patients were followed for only 12 months. At the end of the trial there was no difference in mean EDSS or SNRS change between groups. Again, by contrast, MRI measures were favorably affected by treatment. There was a greater than 90% reduction in the number of Gd-enhanced T1 lesions ($p < 0.003$) and a slight reduction in the T2 volume of disease (-4%; $p = 0.029$) in the high-dose group compared to placebo. This study provides Class I evidence for a treatment effect on MRI outcomes, but not on clinical outcomes in progressive MS.

- On the basis of consistent Class I and Class II evidence, it is concluded that cladribine reduces Gd-enhancement in patients with both relapsing and progressive forms of MS (Type A recommendation).
- Cladribine treatment does not, however, appear to alter favorably the course of the disease, either in terms of attack rate or disease progression (Type C recommendation).

CYCLOSPORINE

Cyclosporine (Sandimmune) is a cyclic undecapeptide that has potent immunosuppressive activity related to a selective inhibitory effect on helper T-lymphocytes. Frequent side effects to therapy include nephrotoxicity, hypertension, hirsutism, headache, gingival hyperplasia, edema, paresthesias, abdominal discomfort, and nausea. There is also an increased susceptibility to future malignancies.

In 1989, the results of the British/Dutch placebo-controlled, randomized cyclosporine trial were reported (144). This trial included patients with active MS (37 from Amsterdam and 43 from London) defined as having at least two attacks in the previous two years or a progression of disability over the last year. Patients received an average of 7.5 mg/kg/day in London and 5 mg/kg/day in Amsterdam. In London, after six months of therapy, there seemed to be a benefit to treatment on reducing the categorical 1-point EDSS change from baseline ($p = 0.03$), but, at the one- and two-year marks, this benefit was no longer apparent. In Amsterdam, there was never a benefit to therapy and in neither city was there an effect on relapse rate over the two years of study. Moreover, side effects to therapy were common. Thus half of the treated patients developed hypertension and renal function was adversely affected in almost all patients. In summary, this trial provides Class II evidence that cyclosporine is ineffective in the treatment of patients with active MS. Because of its small size, these results cannot exclude a benefit to therapy, although the toxicity of this agent is too great to warrant the pursuit of this possibility.

In 1990, the results of a large multicenter study of cyclosporine in the treatment of chronic progressive MS (SPMS and PPMS) were reported (145). This trial involved 554 patients randomized to treatment with either cyclosporine (initiated at a dose of 6 mg/kg and adjusted to maintain a trough level of 300-600 ng/ml) or placebo (Class I study). Patients were followed for 2 years. No significant benefit to treatment was seen on the measures used: time to sustained progression and time to dependency in activities of daily living.

A significant difference in mean EDSS favoring the treated group was noted at the time of exit from the study ($p = 0.001$) although the magnitude of the between-group difference (0.27 EDSS points) was quite small. The authors also reported a decrease in the probability of becoming wheelchair bound with therapy ($p = 0.038$). Notably, 44% of the cyclosporine-treated patients dropped out of the study, a quarter of them because of adverse reactions to the medication. In addition, abnormalities of creatinine were found, at some time, in 84% of cyclosporine-treated patients and, at any one time, in 62%. Because of the frequent occurrence of potentially observable adverse reactions to therapy such as hirsutism (66.5%), gingival hyperplasia (32.7%), and edema (25.8%), there are some concerns about the adequacy of the observer blinding in this trial.

- Based on Class I and II evidence, it is considered possible that cyclosporine provides some therapeutic benefit in progressive MS (Type C recommendation). However, the frequent occurrence of adverse reactions to treatment, especially nephrotoxicity, together with the small magnitude of the potential benefit makes the risk/benefit of this therapeutic approach unacceptable (Type B recommendation).

MITOXANTRONE

Mitoxantrone (Novantrone) is a chemotherapeutic agent widely used for treatment of cancer. It exerts its antineoplastic action by intercalating into DNA and producing both DNA strand-breaks and interstrand cross-links. Compared to other forms of chemotherapy, it is relatively easy to use and has minimal side effects at the time of delivery. Nevertheless, patients treated with mitoxantrone are at increased risk of cardiac toxicity as manifested by cardiomyopathy, reduced left ventricular ejection fraction, and irreversible congestive heart failure. Therefore, a lifetime cumulative dose of more than 140 mg/m^2 is not recommended (146). There is also substantial concern that mitoxantrone may increase the likelihood of developing malignancies in the future (147). Mitoxantrone was recently approved for use in MS by the FDA on the basis of a phase III clinical trial in Europe.

In 1994, the results of a randomized, double-blind, placebo controlled trial of mitoxantrone (8 mg/m^2 per month for 1 year) in 25 patients with RRMS were reported (148). Mean baseline EDSS score was 3.7 in the treated group and 3.5 in the placebo group. A reduction in the clinical attack

rate (-68%; $p = 0.014$) was noted 1 year following treatment. The number of Gd-enhancing lesions seen on MRI and the percentage of patients with a 1-point EDSS deterioration were also reduced, although these changes were not significant. This study provides Class II data that mitoxantrone reduces the clinical attack rate in patients with RRMS. It demonstrated no significant effect on measures of disease severity.

In 1997, the results of a randomized, controlled trial of mitoxantrone in 42 patients with "active" MS (RRMS or SPMS) were reported (149). Patients were treated with either mitoxantrone (20 mg, i.v./month) and IVMP (1 g, i.v./month) or with IVMP alone. At 6 months, the percentage of patients in the mitoxantrone group without enhancing lesions was significantly greater than the comparable percentage in the control group ($+59.2\%$; $p < 0.001$). The clinical relapse rate was also reduced (-77%; $p < 0.01$), as was the confirmed 1-point EDSS progression rate (-83%; $p < 0.01$). There are concerns about this trial, however, because the number of subjects studied is small and because the study was not blinded for clinical outcomes. Thus, this study provides only Class III clinical data in favor of efficacy. By contrast, the MRI data is Class II because the interpreting radiologists were blinded to treatment assignment.

In 1997, another study (150) reported the results of a multicenter, randomized, single-blind, placebo-controlled trial of mitoxantrone (8 mg/m^2 per month for 1 year) in 51 RRMS patients. After two years, the rate of confirmed 1-point EDSS deterioration in the mitoxantrone group was reduced compared to placebo (-80%; $p = 0.02$). However, 5 of the 8 patients who experienced confirmed EDSS progression in the first year of the trial reverted to a non-progressive status (i.e., their EDSS scores improved) in the second year. Also, the mean EDSS score was not different between groups at any point during the study. The changes in attack rate measures were more convincing, with the attack rate being reduced in the treated group compared to controls (-66%; $p = 0.0002$). Similarly, there was a reduction in the number of new lesions in the treatment group compared to placebo (-52%; $p < 0.05$). Although quite small, this study, nevertheless, provides Class II evidence that mitoxantrone reduces the clinical attack rate in RRMS. The evidence for an effect on the progression of the disease, however, is equivocal.

- On the basis of generally consistent Class II and III studies, it is concluded that mitoxantrone probably reduces the attack rate in patients with relapsing forms of MS. There is concern, however, that the potential toxicity of mitoxantrone may outweigh the clinical benefits early in the course of disease (Type B recommendation).
- On the basis of several Class II and III observations, it is considered possible that mitoxantrone has a beneficial effect on disease progression in MS. Perhaps with publication of the phase III clinical trial results, the evidence in favor of a treatment effect may become stronger. At the moment, however, this clinical benefit has not been established (Type C recommendation).

Other Immune Therapies

INTRAVENOUS IMMUNE GLOBULIN (IVIg)

Following a number of preliminary studies, the results of an Austrian cooperative study of IVIg in MS were reported (151). This trial was randomized, multicenter, double-blind, and placebo-controlled and studied 148 RRMS patients (Class I evidence). Patients were randomly assigned to receive either monthly IVIg (0.15-0.2 g/kg) or placebo for 2 years. These authors reported that treatment with IVIg reduced the clinical attack rate (-49%; $p = 0.006$). The difference in final unconfirmed proportion with 1-point EDSS progression was also reduced, although this outcome was not significant. The unconfirmed EDSS change at 2 years, however, was less in treated patients (-0.35 EDSS points; $p = 0.008$).

A small crossover study of IVIg in MS (Class II evidence) has also been reported (152). In this trial, 26 patients with RRMS were treated with either IVIg (1 gm/kg/day for 2 days) or placebo every month for 6 months. The results were

mixed. For patients who completed both treatment arms (n = 18), the total number of enhancing lesions seen on MRI (-64%; p = 0.03) and the number of new lesions (-60%; p = 0.01) were reduced in patients treated with IVIg. This study, however, found no differences in T2 lesion load, clinical attack rate, or EDSS progression. Also, the high dropout rate makes this trial hard to interpret.

In 1998 (153), IVIg (0.4 gm/kg/day for 5 days and then monthly for 1 day) was compared with placebo over a period of 2 years. This trial (Class II) reported significant reductions in the clinical attack rate but no between-group differences on other outcomes including EDSS and MRI. An original investigator on this trial has raised serious concerns with regard to the conduct of this study (154).

- In summary, the studies of IVIg, to date, have generally involved small numbers of patients, have lacked complete data on clinical and MRI outcomes, or have used methods that have been questioned. It is, therefore, considered only possible that IVIg reduces the attack rate in RRMS (Type C recommendation). With regard to slowing disease progression, the current evidence suggests that IVIg is of little benefit (Type C recommendation).

PLASMA EXCHANGE

The use of plasma exchange to treat MS has been investigated in several clinical trials. As discussed earlier, both the Class III Harvard trial (127) and the Class I Canadian cooperative trial (130) did not provide evidence of a therapeutic benefit from plasma exchange in the treatment of progressive MS.

In a pilot trial (155), 20 chronically progressive definite MS patients with evidence of a continuous decline for at least two years before study entry were randomized in a double-blind, placebo-controlled study of PP versus sham exchange. There were no obvious differences between the groups with respect to EDSS, either pre- or post-exchange, or after six months of follow up.

In 1985 another study (156) evaluated the use of plasma exchange in 55 patients with progressive MS. This trial was randomized and double-blinded with 26 patients treated with plasma exchange and 29 patients treated with sham exchange, once weekly for twenty weeks. All patients also received oral cyclophosphamide, prednisone, and IVIg with each exchange for 21 weeks. Outcome measures included changes in the Kurtzke Disability Status Scale and the Canter scale. Plasma exchange was reported to produce a significantly better outcome at 5 and 11 months ($p < 0.007$). The statistical methods used to arrive at this observation, however, are unclear. The authors undertook multiple statistical comparisons between groups. A chi-square analysis of the results presented in their Table 4 results in a p-value of only 0.12 at each of these time points. As a result this study, although Class I, provides little or no evidence in favor of a treatment effect.

In 1989 (157), 116 MS patients were studied, 40 of whom had a progressive course and 76 of whom had a relapsing course. The trial was randomized and double-blind, with 59 patients treated with true plasma exchange and 57 treated with sham exchange. All patients also received ACTH and cyclophosphamide. The clinical outcome measures were the EDSS, the Functional Systems Scale (FSS), and the AI. Despite numerous statistical comparisons, no statistically significant differences on any of the outcome measures were observed. This trial provides no evidence in favor of a treatment effect.

A recent controlled clinical trial (158) reported that patients with a recent (within approximately 2 months) severe episode of demyelination (not necessarily from MS), and who also failed to respond to i.v. glucocorticoids, may benefit from a series of plasma exchanges involving 1.1-plasma volumes (54 ml/kg) every other day for 14 days. Patients included in the study had either no or only minimal neurological dysfunction prior to their attack. The trial was randomized, sham-controlled, double-masked, and crossover in design for nonresponders. Moderate or greater improvement was observed in 8 of 19 (42%) of those who

received active treatment versus only 1 of 17 (5.9%) receiving sham treatment. These findings were only marginally significant.

- On the basis of consistent Class I, II, and III studies, plasma exchange is of little or no value in the treatment of progressive MS (Type A recommendation).
- On the basis of a single small Class I study, it is considered possible that plasma exchange may be helpful in the treatment of severe, acute episodes of demyelination in previously nondisabled individuals (Type C recommendation).

SULFASALAZINE

Sulfasalazine is a safe oral agent that has both anti-inflammatory and immunomodulatory properties. A Mayo Clinic/Canadian multicenter trial compared sulfasalazine (2,000 mg/day) to placebo in patients with RRMS, SPMS, and PPMS (159). This study reported an early benefit to therapy (in terms of confirmed EDSS progression) in patients with a progressive course. By three years, however, there was no discernable difference in outcome between the placebo and active treatment arms. Other outcome measures were also equivocal. Although the annualized attack rate was lower in the treated patients ($p = 0.03$), other attack-rate measures, such as the percentage of relapse-free patients and the median time to first relapse, were unaffected. The percent of T2-active MRI scans was reduced in the treated group at 30 months ($p = 0.025$), although there was no consistent trend in this direction at 24 months or 36 months. The T2 volume of disease was unaffected by therapy.

- Based on this single Class I study, it is concluded that treatment of MS with sulfasalazine provides no therapeutic benefit in MS (Type B recommendation).

CONCLUSION

In conclusion, there are now several medications available to practitioners that can favorably alter the course of disease in patients with MS. It is likely, with improvements in our understanding of the pathogenesis of this disease, that an even larger array of agents will be available in the near future. The evidence for or against the effectiveness of different therapeutic strategies, however, varies widely between the different agents. In many cases the lack of convincing evidence is due to the poor quality of the available clinical trials. In the case of off-patent drugs, there is often little or no industry support for double-blind, randomized clinical trials. In other cases the lack of convincing evidence is due to the relative ineffectiveness of the medication under study.

Nevertheless, on a day-to-day basis, physicians must decide whether to recommend medical procedures to their patients, and it is unclear how best to guide them in this regard. Ideally, one would like conclusive evidence, such as the results of randomized clinical trials, regarding the balance between the benefit and harm of each treatment option. Unfortunately, however, such conclusive evidence is often lacking. Moreover, even when high-quality randomized trials are available, the patients included in the clinical trial often reflect only a minority of the patients who might benefit from the medication or procedure being studied. In these circumstances, physicians must still decide whether, in their judgment, a specific patient might derive benefit from a specific therapy.

Evidence-based assessments are helpful to physicians in making these judgments, but they cannot be the sole guide to medical practice. Appropriateness criteria based on a consensus of a panel of clinical experts may also provide a valuable guide to current practice (160). The continued quest for better evidence to judge the value of different therapeutic strategies should not delay the application of existing strategies to current patients. To wait until the evidence is perfect might result in a missed opportunity to prevent or delay harm to our patients—harm that could be irreparable. As one example, there is no Class I data to support the use of penicillin to treat infections and yet to withhold such treatment until Class I evidence became available would be unconscionable. This is not to undervalue the usefulness of evidence-based assessments such as the present document. Rather, it is to underscore that physicians, in recommending treatments to individual patients, need to consider information from a wide range of venues.

Also, it is important to recognize that the use of many of these disease-modifying agents requires skills development and sustained adherence, on the part of the patient, to long-term treatment if he or she is to derive the maximum benefits from therapy. Achieving such long-term adherence can be quite difficult, and wide variations in success have been reported between different studies (161). Clearly, the education provided to the patient by physicians, nurses, and staff is an important component of assuring adherence with these therapies. So too is similar education provided to the family, especially in circumstances where the patient has cognitive problems. This latter component of the educational process is helpful both to ensure that the information was received accurately and also for the encouragement and support that family members can provide to the patient.

Lastly, it is important to note that, while this review has focused on the currently existing disease modifying strategies in MS, the field of MS therapeutics is quite active and constantly evolving. It is anticipated that this document will stimulate rather than slow the process of developing new strategies that build upon what is known today. Indeed, many combination trials of various medications are currently underway and the results of these trials are eagerly anticipated. These trials include combinations of IFNβ with

previously studied agents such as glatiramer acetate, glucocorticoids, cyclophosphamide, methotrexate, azathioprine, and IVIg. They also include the study of newer, as yet untested, agents such as retinoid, interleukin 10, natalizumab, and mycophenolate mofetil, both alone and in combination. It is hoped that these newer combination therapies will be able to build on the successes of the past, and that successful control of MS will be achieved incrementally through this approach.

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APPENDIX A: LIST OF ABBREVIATIONS

adrenocorticotropic hormone (ACTH)

ambulation index (AI)

area under the curve (AUC)

brain parenchymal fraction (BPF)

central nervous system (CNS)

cerebrospinal fluid (CSF)

clinically definite MS (CDMS)

cytopathic effect (CPE)

enzyme-linked immunosorbent assays (ELISAa)

extended disability status scale (EDSS)

Food and Drug Administration (FDA)

functional systems scale (FSS)

gadolinium (Gd)

immunoglobulin gamma (IgG)

integrated disability status scale (IDSS)

interferon beta-1a (IFNb-1a)

interferon beta-1b (IFNb-1b)

intravenous immunoglobulin (IVIg)

intravenous methylprednisolone (IVMP)

magnetic resonance imaging (MRI)

millions of international units (MIU)

multiple sclerosis (MS)

MS functional composite (MSFC)

neutralizing antibody (NAb)

nine-hole peg test (9HPT)

not significant (ns)

Optic Neuritis Treatment Trial (ONTT)

Paced Auditory Serial Addition Test (PASAT)

primary progressive MS (PPMS)

Prevention of Relapses and Disability by Interferon-ß-1a Subcutaneously in Multiple Sclerosis Study (PRISMS)

relapsing/progressive MS (RPMS)

relapsing/remitting MS (RRMS)

secondary progressive MS (SPMS)

Scripps Neurologic Rating Scale (SNRS)

Secondary Progressive Efficacy Clinical Trial of Rebif® in MS Study (SPECTRIMS)

United States (US)

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