AMERICAN ACADEMY OF NEUROLOGY

Special Article

Disease modifying therapies in multiple sclerosis

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines

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Overview. *Clinical types of MS.* MS is a chronic recurrent inflammatory disorder of the 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] The symptoms of MS vary, depending in part on 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.[6] The first, relapsing–remitting MS (RRMS), is characterized by self-limited attacks of neurologic dysfunction. These attacks develop acutely, evolving over days to weeks. Over the next several weeks to months, most patients experience a recovery of function that is often (but not always) complete. Between attacks the patient is neurologically and symptomatically stable. The second clinical course, secondary progressive MS (SPMS), begins as RRMS, but at some point the attack rate is reduced and the course becomes characterized by a steady deterioration in function unrelated to acute attacks. The third clinical type, primary progressive MS (PPMS), is characterized by a steady decline in function from the beginning without acute attacks. The fourth type, progressive–relapsing MS (PRMS), also begins with a progressive course although these patients also experience occasional attacks.

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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 (2 or 3 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. For a discussion of these issues, interested readers should consult the full-length assessment on the Neurology Web site at www.neurology.org.

Scope of this guideline. The purpose of this assessment is to consider the clinical utility of these disease-modifying agents including the anti-inflammatory, immunomodulatory, and immunosuppressive treatments that are currently available. Symptomatic and reparative therapies will not be considered.

Before considering the evidence from individual

Approved by the TTA Subcommittee August 3, 2001. Approved by the Practice Committee August 4, 2001. Approved by the AAN Board of Directors October 20, 2001.

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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%.[7-10] For a one-tailed comparison, this minimum Type I error rate is actually 21%.[7-10] 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.[7-10] 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.[11-15] 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.[16] For example, one recent trial[17] found that after 2 years of treatment, sustained disability progression was nonsignificantly reduced by 12%. Clearly, such a result cannot be used to reject a true 12% reduction in this measure, and, in fact, this nonsignificant observation is still compatible with an even more robust treatment effect.[16] The issue is the statistical power (i.e., 1-β) of the clinical trial to detect group differences and this, in turn, is related to the number of subjects studied.[16] In this particular trial,[17] 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 likelihood of the observed 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. Consequently, reports of substantial improvement following the use of such agents should be viewed with caution.

A synopsis of the conclusions and recommendations for all the treatments considered is provided in the Summary. The actual analysis of the evidence (table), however, is provided here only for the immunomodulatory treatments. Readers interested in the analysis of the evidence for other therapies should consult the full-length assessment on the Neurology Web site at www.neurology.org.

Analysis of the evidence. *Immunomodulatory treatments.* Interferon beta. *Clinical trial results.* The multicenter study of IFNβ-1b (Betaseron; Berlex Laboratories, Montville, NJ) in RRMS[18-20] was randomized, double-blind, and placebo-controlled (Class I evidence). It included 372 patients with RRMS who had scores on the extended disability status scale (EDSS) ≤5.5 and who had experienced at least two attacks in the prior 2 years. Patients were randomized to receive placebo, low-dosage (1.6 million of International Units [MIU]; 50 μg), or high-dosage (8 MIU; 250 μg) IFNβ-1b subcutaneously (SC) every other day for 2 years. After 2 years, compared with placebo, treatment with high-dosage IFNβ-1b reduced the clinical relapse rate (−34%; $p < 0.0001$), which was the primary endpoint 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 with placebo-treated patients. The high dosage 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 3 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; Biogen, Cambridge, MA) trial[21-23] also was multicenter, randomized, and

Table *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 dropouts 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.

patients with RRMS who had an EDSS score of 1.0–3.5, and who had experienced at least two attacks in the 3 years prior to entering the study. Patients were treated either with placebo or IFNβ-1a, 6 MIU/wk (30 μg/wk), intramuscularly (IM) for 2 years. This trial was stopped earlier than originally designed, so only 57% (172 patients) completed the full 2 years on study medication. Compared with placebo, treatment with Avonex for 2 years produced a reduction in the confirmed 1-point EDSS progression rate (−37%; $p = 0.02$), which was the primary endpoint 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 with placebo-treated patients. The total volume of T2 disease burden seen on MRI also was reduced compared with 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%, not significant) was less than the reduction in patients who had completed 2 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.[21,24,25] Nevertheless, the authors provide no statistical evidence of a difference between the 1-year and 2-year data, and, in addition, the other IFNβ trials in RRMS did not observe such a delay in therapeutic benefit.[18-20,24,26,27] Most important, however, this subgroup of patients (who had a 32% reduction in attack rate over 2 years) had a similar

Such an observation indicates that this particular subgroup of patients (i.e., the 2-year completers) is not representative of the study cohort as a whole. As a result of this anticipated bias, the validity of any separate analysis on this subgroup of patients is questionable. A re-analysis of the trial data (for the subgroup of 2-year completers only) using the "brain parenchymal fraction" to measure brain atrophy[28] showed no statistically significant reduction in brain atrophy after 2 years of treatment ($p = 0.30$). A subgroup 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 brain parenchymal fraction presented in the article's figure.[28] Therefore, the validity of this observation is uncertain.

In summary, this trial provides (Class I) evidence that IFNβ-1a reduces the biologic 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 2 years. In addition, there was a reduction in the confirmed 1-point EDSS progression rate, although there was no statistically significant concomitant benefit on either MRI disease

The IFNβ-1a (Rebif; Serono International SA, Geneva, Switzerland) trial[26,27] was a similarly randomized, multicenter, double-blind, and placebo-controlled study (Class I evidence). A total of 560 patients with RRMS with an EDSS score ≤5.0 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 dosages of either 22 μg (6 MIU) or 44 μg (12 MIU) SC three times weekly. After 2 years, there was a significant beneficial effect of treatment with either dose on both clinical and MRI outcome measures. Thus, compared with placebo, treatment with IFNβ-1a, 132 μg/wk (36 MIU/wk), reduced the clinical attack rate (−32%; $p < 0.005$), which was the primary endpoint 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%; $p < 0.05$) also were reduced in the IFNβ-1a arm compared with placebo.

In summary, this trial provides (Class I) evidence that IFNβ-1a reduces the biologic 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; Schering AG, Berlin, Germany) trial in SPMS[29] was a randomized, placebo-controlled, double-blinded study conducted among 32 European centers (Class I evidence). Included were 718 patients with an EDSS of 3.0–6.5. Patients had to have either two relapses or more than a 1.0 point increase in EDSS in the prior 2 years. Those included were randomized to receive either placebo or IFNβ-1b, 250 μg (8 MIU) SC, every other day for up to 3 years. Compared with treatment with placebo, treatment with 28 MIU/wk Betaferon reduced the confirmed 1-point EDSS progression rate (−22%; $p = 0.0008$), the primary endpoint 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%; $p = 0.0001$) all were significantly reduced in the IFNβ-1b arm compared with 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 2 years before entering the study 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 [illegible] 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 3-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 also has been reported in preliminary form.[30] This trial failed to find a statistically significant reduction in the confirmed 1-point EDSS progression rate (the primary endpoint 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 found 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[31,32] also failed to find a statistically significant reduction in the confirmed 1-point EDSS progression rate (the primary endpoint of the trial). Like the IFNb-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 found on T2-weighted MRI. Also, when the results of this trial were reanalyzed 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 reanalysis 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 patients with SPMS 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.[33] Using the MS functional composite as the primary outcome, this trial found that, compared with placebo, treatment with IFNβ-1a, 60 μg/wk, IM was beneficial over a 2-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 MS functional composite outcome was due primarily to the results from the Nine-Hole Peg Test 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 [illegible]

the subsequent rate of conversion to clinically definite MS (CDMS).[34,35] The IFNβ-1a (Avonex) trial[34] 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 (≥3 mm) on T2-weighted MRI scans, at least one of which needed to be ovoid in appearance or periventricular in location. Patients initially were treated with intravenous methylprednisolone, 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, IM) or placebo throughout the study. Using a Cox proportional hazard 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 after 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 the number of enhancing lesions (−67%; $p < 0.0001$) all were reduced using IFNβ-1a when compared with placebo. The IFNβ-1a (Rebif) trial[35] also was 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, SC) or placebo throughout the study. The proportion of patients converting to CDMS was less in the treated group compared with placebo (−24%; $p = 0.047$). In addition, the median number of T2 active lesions seen on MRI also was reduced in the treated compared with placebo patients ($p < 0.001$). The T2 disease burden also was reduced in the treated arm compared with 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) also would 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.

Effects of IFNβ type, route of administration, and dose on clinical outcome. The total dosage of IFNβ

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 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 microgram for microgram basis. Also, the conversion of IFNβ-1a to IFNβ-1b doses can be calculated using published data,[36] with the result that 6 MIU Avonex (30 μg) is equivalent to approximately 7-9 MIU Betaseron (220-280 μg).

IFNβ induces the expression of many gene products and interferon-specific markers, including 2',5'-oligoadenylate synthetase (2',5'-OAS), neopterin, tryptophan, β_2-microglobulin, and human Mx protein.[37] These markers reflect a range of biologic activities of IFNβ, including MHC Class-I gene expression, antiviral and antiproliferative actions, and monocyte activation. These markers have been used as indicators of the biologic activity of IFNβ. The relative dose of the different preparations also can be assessed from another recent publication[38] in which antiviral protein (MxA) stimulation was studied in the untreated blood from 10 healthy volunteer subjects. 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[39] initially suggested that IM administration of IFNβ-1a caused a substantially greater area under the concentration-time curve for IFNβ activity in the serum compared with SC administration. By contrast, a different study[36] compared the effects of IFNβ-1a given SC and IM and IFNβ-1b given SC on neopterin, human Mx protein, and 2',5'-OAS in 75 healthy volunteer subjects. 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 biologic effects between the two types of IFNβ or between the different routes of administration. Similar results have been found by other investigators.[40,41] Thus, the balance of the evidence favors the view that the route of IFNβ administration is not of clinical importance.

The previously cited study[38] also examined the levels of MxA in the peripheral blood in 237 patients with CDMS after administration of IFNβ. There were 78 patients receiving IFNβ-1b (Betaseron) at a dosage of 8 MIU (250 μg) every other day; 71 patients receiving IFNβ-1a (Rebif) at a dosage of 6 MIU

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