

Practice advisory on selection of patients with multiple sclerosis for treatment with Betaseron

Report of the Quality Standards Subcommittee of the American Academy of Neurology

Background and overview. The Food and Drug Administration (FDA) recently approved Betaseron (human interferon-beta) for use in selected patients with multiple sclerosis (MS), basing their decision on a well-designed clinical trial.^{1,2} In that trial, the drug was demonstrated to reduce the relapse rate of certain relapsing-remitting patients and to decrease magnetic resonance imaging (MRI) evidence of MS activity in the brain. The results of the trial pertain only to the relapsing-remitting patient group, since other forms of MS were not represented in the trial. Moreover, the trial demonstrated no beneficial effect of the drug on ultimate disability of MS over the 2 to 3 years of the study. Longer follow-up of the study patients, as well as other studies, are planned or are in progress.

Justification. The Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN) is charged with developing evidence-based practice parameters in neurology. In addition, as new therapeutic information emerges, the QSS will publish rapid practice advisories based on the best available scientific evidence and expert consensus. The large number of MS patients, many cared for by neurologists, justifies QSS consideration of Betaseron. Given the newness and high cost of Betaseron, neurologists differ as to which patients should be treated with the drug. Theoretical and laboratory evidence^{3,4} suggests that Betaseron may offer substantial prospects for improving the health outcome of MS patients. The selection of MS patients who are most likely to benefit from Betaseron could be more consistent if a practice advisory were available. Thus, a practice advisory could have substantial economic impact by identifying which patients are unlikely to benefit from Betaseron.

Government agencies have played an important role in the development of Betaseron. For example, the FDA based its approval, in part, on the recommendation of a scientific advisory panel, but that

recommendation was not unanimous (five in favor, two opposed). Also, the initiative of government to reduce health care costs while broadening health care availability makes consideration of a practice advisory for this new costly treatment for MS timely. Scientific evidence supporting general use of Betaseron is limited, but for some MS patients, a widely held consensus for treatment exists. For other MS patients, opinion is mixed.

Process. A Medline search was conducted for all articles published in English from 1980 to 1994 with the key words "Betaseron," "interferon-beta," and "multiple sclerosis." Forty-three articles were identified. Of these, the recently completed trial that led to FDA approval,^{1,2} two randomized controlled trials with small numbers,^{5,6} and three pilot studies⁷⁻⁹ were read in their entirety, and each was reviewed for the following elements: author, year, treatment, number of subjects, type of MS, age range, outcome measure, whether retrospective or prospective, blinded evaluation, and statistical analysis.

In addition to the literature review, opinion regarding Betaseron treatment was sought from recognized experts in MS therapy. Such individuals were identified by soliciting candidate experts from the National Multiple Sclerosis Society, including its Medical Advisory Board, to which only individuals with long-standing scientific and medical contributions to MS research and treatment are appointed. To these individuals, we sent a letter of explanation of the QSS responsibility and a list of potential applications of Betaseron therapy in MS. After evaluation of these statements from experts, the QSS members reached a consensus by group discussion. The consensus of all statements was forwarded to each expert for additional comment and criticism, and these revised comments were used to formulate the final consensus-based treatment recommendations.

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Scientific evidence. *Class I (randomized, controlled clinical trials [RCCT]).* The large, multicenter RCCT that recently led to FDA approval of Betaseron for MS demonstrated that subcutaneous drug, given every other day for 2 years, could reduce the rate and severity of exacerbations.¹ In addition, a greater increase in lesion area occurred in placebo compared with treated patients during follow-up.² Of two dosages tested against placebo, the higher dose (8 million international units [MIU] of interferon-beta) was more effective than the lower dose (1.6 MIU). Approximately one-quarter of all patients, regardless of treatment arm, worsened by at least one Kurtzke EDSS unit by the end of 3 study years. Consequently, the study did not determine that Betaseron could arrest progression in MS.

Two other randomized, controlled clinical trials have been reported, both using intrathecal interferon-beta. The first, by Jacobs et al,⁵ reported a significant reduction in exacerbation rate at 2 years of follow-up. In that study, 24 patients received nine to 10 intrathecal treatments during an initial 6-month treatment period. Indomethacin and "false" lumbar punctures were used in that study to improve blinding. A second small trial by Milanese et al⁶ in 16 relapsing-remitting and progressive MS patients reported an increase in exacerbations after a similar intrathecal dosing schedule and approximately 22 months of follow-up.

Class II (pilot studies; unblinded controlled studies). Pilot studies have been reported using three different routes of administration of interferon-beta. Jacobs et al^{7,10,11} reported an earlier series of unblinded, controlled studies. In this series, 20 patients were treated with intrathecal drug, each study providing later follow-up. The improvement in exacerbation rate in the treated patients led these authors to "cross-over" controls to active treatment.¹¹ These newly treated patients were also thought to have a decreased exacerbation rate after 2 more years of follow-up. Huber et al⁸ used intravenous interferon-beta for 6 months to treat nine MS patients. They followed the patients for an average of 1.2 years. No impact on exacerbation rate or CSF IgG synthesis was found. Knobler et al⁹ randomized 30 relapsing-remitting MS patients to placebo or to one of four subcutaneous doses of Betaseron given thrice weekly for an initial 24-week period. The highest dose used, 16 MIU, produced intolerable side effects; the 8-MIU dose was then used in all treatment groups between 24 weeks and 3 years. After 3 years, all patients could continue to receive Betaseron for another 3 years. Overall, adverse events were infrequent except for injection site inflammation, and the authors reported a trend toward a decrease in exacerbation rate. However, when looked at over the entire 6-year treatment period, an apparent decline of exacerbation rate over time was probably due to selective drop-out of patients with high exacerbation rates.

Class III (case reports; expert opinion). The FDA approved Betaseron for ambulatory patients with

relapsing-remitting MS.¹² Consensus opinion among MS experts and the QSS committee was that if the drug is effective in reducing the number and severity of exacerbations, as shown in the one class I study on which FDA approval was based,^{1,2} then any MS patient who experienced true exacerbations should be able to receive the drug. This would include patients of any age or EDSS level and patients with relapsing-progressive MS, even though all such patients were not studied in the trial. For example, a wheelchair-bound patient (EDSS = 7.0) with minimal upper extremity involvement, who is experiencing exacerbation in the upper extremities, could potentially benefit from receiving Betaseron. The same group reached consensus on the need for withdrawal criteria. If reasonable evidence suggests that the drug was not preventing exacerbations or if disease progression appeared to be steady in spite of the drug, then withdrawal should be considered.

This group could not reach consensus on the use of Betaseron in chronic progressive MS. No class I or class II evidence is yet available to support the use of Betaseron in such patients, and progression occurred equally among treated and placebo patients in the Betaseron trial. A minority of experts thought that the MRI data² might support the use of Betaseron in all MS patients.

Recommendations. The following analysis of scientific studies as well as QSS and MS expert opinion is presented to assist the clinician considering the use of Betaseron for MS patients.

A. Patients for whom class I experimental evidence and expert consensus suggest Betaseron may be helpful:

MS patients with a relapsing-remitting disease course who

1. Have clinically definite or laboratory-supported definite MS¹³;
2. Are aged 18 to 50 years;
3. Are ambulatory with EDSS¹⁴ ≤ 5.5 (no unilateral or bilateral constant assistance required);
4. Have had at least two acute exacerbations during the previous 2 years, consisting of the appearance of new symptoms or worsening of old symptoms lasting at least 24 hours in the absence of fever, and preceded by stability or improvement for at least 30 days.

B. Patients for whom no class I evidence exists, but for whom expert consensus suggests Betaseron may be helpful:

1. Relapsing-remitting and age > 50 years;
2. Relapsing-remitting and EDSS¹⁴ ≥ 6.0 (at least unilateral constant assistance required);
3. Patients with relapsing-progressive disease who also meet criteria A.1 and A.4 above.

C. Patients for whom neither class I evidence nor expert consensus exists to

support therapy with Betaseron:

1. MS patients with a primary chronic progressive disease course.

D. Expert consensus suggests Betaseron should *not* be given to patients in whom:

1. Concurrent illness is likely to alter compliance or substantially reduce life expectancy, eg, dementia, alcoholism, malignancy, or other chronic illness;
2. Pregnancy is planned or occurs.

E. For those patients who have been started on Betaseron, expert consensus suggests that the following criteria should be considered for *cessation* of Betaseron treatment:

1. Steady progression of disability for 6 months;
2. Treatment with at least three courses of ACTH or corticosteroids during a 1-year period was required despite Betaseron therapy;
3. Severe depression or suicidal ideation while on Betaseron¹²;
4. Consistent noncompliance in taking the medication as prescribed by the physician;
5. Severe drug toxicity;
6. Planned pregnancy or becoming pregnant.

Additional comments. The FDA announcement stresses that Betaseron is the first biotechnology product to be licensed under the FDA's accelerated approval regulations.¹² Such expedited approval relies solely or in part on surrogate end points for evidence of effectiveness. The product's sponsor (the drug company) is required to conduct controlled postmarketing studies to verify the relationship between the clinical end points (eg, progression) and the surrogate end point (MRI). In the case of Betaseron, postmarketing studies will require an investigation of the ability of the MRI end point to predict subsequent progression.¹⁵ The published study² did not demonstrate such a relationship.

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DEFINITIONS

Classification of evidence

Class I. Evidence provided by one or more well-designed randomized controlled clinical trials.

Class II. Evidence provided by one or more well-designed clinical studies such as case-control studies, cohort studies, and so forth.

Class III. Evidence provided by expert opinion, nonrandomized historical controls, or one or more case reports.

Strength of recommendations

Standards. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on class I evidence or, when circumstances preclude randomized clinical trials, overwhelming evidence from class II studies that directly addresses the question at hand or from decision analysis that directly addresses all the issues).

Guidelines. Recommendations for patient management that may identify a particular strategy or range of management strategies and that reflect moderate clinical certainty (ie, based on class II evidence that directly addresses the issue, decision analysis that directly addresses the issue, or strong consensus of class III evidence).

Practice options or advisories. Other strategies for patient management for which there is unclear clinical certainty (ie, based on inconclusive or conflicting evidence or opinion).

Practice parameters. Results, in the form of one or more specific recommendations, from a scientifically based analysis of a specific clinical problem.

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

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