This is a summary of the American Academy of Neurology’s evidence report that reviews the available evidence and assesses the clinical and radiographic impact of neutralizing antibodies (NAbs) to interferon beta (IFNβ).

Please refer to the full evidence report for detailed findings and supporting evidence at www.aan.com.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

• Treatment of MS with IFNβ (Avonex, Betaseron, or Rebif) is associated with the production of NAbs to the IFNβ molecule (Level A).

• It is probable that the presence of NAbs, especially in persistently high-titers, is associated with a reduction in the radiographic and clinical effectiveness of IFNβ treatment (Level B).

• It is probable that the rate of NAb production is less with IFNβ-1a treatment compared to IFNβ-1b treatment (Level B). However, because of the variability of the prevalence data, and because NAbs disappear in the majority of patients even with continued treatment (especially in those with low-titer NAbs), the magnitude and persistence of any difference in seroprevalence between these forms of IFNβ is difficult to determine.

• It is probable that the seroprevalence of NAbs to IFNβ is affected by one or more of the following: its formulation, dose, route of administration, or frequency of administration (Level B). Regardless of the explanation, it seems clear that IFNβ-1a (as it is currently formulated for intramuscular injection) is less immunogenic than the current IFNβ preparations (either IFNβ-1a or IFNβ-1b) given multiple times per week subcutaneously (Level A). Because NAbs may disappear in many patients with continued therapy, the persistence of this difference is difficult to determine (Level B).

• Although the finding of sustained high-titer NAbs (> 100-200 NU/mL) has been associated with a reduction in the therapeutic effects of IFNβ on radiographic and clinical measures of MS disease activity, there is insufficient information on the utilization of NAb testing to provide specific recommendations regarding when to test, which test to use, how many tests are necessary, and which cutoff titer to apply (Level U).

RECOMMENDATIONS

Due to a paucity of evidence, it is impossible to make recommendations on this controversial issue.

FUTURE RESEARCH RECOMMENDATIONS

• In order to incorporate NAb testing into clinical practice, future research must specifically address issues such as the assay system applied and the stratification of risk for losing IFNβ-efficacy based on the degree of test abnormality.

• The methods of NAb measurement need to be standardized in order to facilitate cross-trial comparisons.

• Future clinical trials need to include a long-term ascertainment of NAb status and its clinical impact.

• Future clinical trials need to include a determination of IFNβ-responsiveness in individuals at study onset in order to link the biological activity in both NAb-positive and NAb-negative groups with clinical and radiographic outcomes.

• Because of the small number of NAb-positive patients generally available in RCTs, and because patients can’t be randomized with respect to their ultimate NAb status, conclusive data will need to be compiled from large-scale post-marketing surveys.
This summary is evidence-based. The AAN uses the following definitions for the level of recommendation and classification of evidence.

**Classification of Evidence for Therapeutic Intervention:**

**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 cross-overs 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.  

**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 criterion a-d.  

**Class III:** All other controlled trials including well defined natural history controls or patients serving as own controls in a representative population, where outcome is independently assessed or independently derived by objective outcome measurement.*  

**Class IV:** Evidence from uncontrolled studies, case series, case reports, or expert opinion.  

*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

**Classification of Recommendations:**

**A=** Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)  

**B=** Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)  

**C=** Possibly effective, ineffective, or harmful for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)  

**U=** Data inadequate or conflicting; given current knowledge, treatment is unproven.

This is an educational service of the American Academy of Neurology. It is designed to provide members with evidence report recommendations to assist with decision-making in patient care. It is based on an assessment of current scientific and clinical information, and is not 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 the circumstances involved. Physicians are encouraged to carefully review the full AAN evidence report so they understand all recommendations associated with care of these patients.

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