Complete Summary

GUIDELINE TITLE

Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

BIBLIOGRAPHIC SOURCE(S)

Goodin DS, Frohman EM, Hurwitz B, O'Connor PW, Oger JJ, Reder AT, Stevens JC. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2007 Mar 27;68(13):977-84. [57 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- March 16, 2005, Avonex (interferon beta-1a): Revisions to the WARNINGS, PRECAUTIONS/Drug Interactions and ADVERSE REACTIONS/Post-Marketing Experience sections and Medication Guide regarding reports of severe hepatic injury, including cases of hepatic failure.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Multiple sclerosis

GUIDELINE CATEGORY

Management
Technology Assessment
Treatment

CLINICAL SPECIALTY

Neurology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the clinical and radiographic impact of neutralizing antibodies to interferon-beta in the treatment of multiple sclerosis

TARGET POPULATION

Individuals being treated for multiple sclerosis with interferon beta (IFN beta)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Treatment with interferon beta (IFN beta): IFN beta-1a, IFN beta-1b
2. Measurement of seroprevalence and titers of neutralizing antibodies (NAbs) to interferon beta
3. Clinical and radiologic assessment of multiple sclerosis activity

MAJOR OUTCOMES CONSIDERED

- Persistence of neutralizing antibodies (NAb) to interferon beta (IFN beta)
- Clinical impact of NAb to IFN beta on severity of multiple sclerosis (MS)
- Radiographic impact of Nab to IFN beta on severity of MS
- Rate of NAb production

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A panel of neurologists analyzed the evidence relating to neutralizing antibodies (NAbs) using a literature search with the key words antibodies and interferon beta. The MEDLINE database was searched from 1966 to 2005. In addition, the reference lists of the articles identified were reviewed to identify articles not found by the computer search. Using these methods 627 articles were identified.

NUMBER OF SOURCE DOCUMENTS

Twenty-seven articles in the English language reporting clinical or radiographic outcomes in both antibody positive and antibody negative patients were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE 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) clearly defined; b) exclusion/inclusion criteria clearly defined; c) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; and 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 randomized controlled trial in a representative population that lacks one criteria 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).

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The entire panel classified the level of evidence provided by each article. Several studies were classified as providing Class II evidence, despite a randomized placebo-controlled trial design. This is because evidence associated with NAb status is always post hoc and because patients can never be randomized with respect to their ultimate Nab status. Therefore, one can never exclude the possibility that there are patient-specific factors, which both predispose certain patients to the development of Nabs and, in an unrelated manner, make them more or less susceptible to multiple sclerosis (MS) attacks. If so, this will make Nabs artificially appear to increase or decrease the MS attack rate, underscoring the fact that evidence of an association cannot prove causation.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

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.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Draft guidelines were reviewed for accuracy, quality, and thoroughness by the American Academy of Neurology (AAN) members, topic experts, and pertinent physician organizations.

Final guidelines were approved by the Therapeutics and Technology Subcommittee on July 28, 2006; by the Practice Committee on November 11, 2006; and by the AAN Board of Directors on January 4, 2007.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the strength of the recommendations (A, B, C, U) and classification of the evidence (Class I through Class IV) are provided at the end of the "Major Recommendations" field.

1. Treatment of multiple sclerosis (MS) with interferon beta (IFN beta) (Avonex, Betaseron, or Rebif) is associated with the production of neutralizing antibodies (Nabs) to the IFN beta molecule (**Level A**).
2. 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 IFN beta treatment (**Level B**).
3. It is probable that the rate of NAb production is less with IFN beta-1a treatment compared to IFN beta-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 IFN beta is difficult to determine.
4. It is probable that the seroprevalence of Nabs to IFN beta 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 IFN beta-1a (as it is currently formulated for intramuscular injection) is less immunogenic than the current IFN beta preparations (either IFN beta-1a or IFN beta-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**).
5. Although the finding of sustained high-titer NAbs (>100 to 200 NU/mL) has been associated with a reduction in the therapeutic effects of IFN beta on radiographic and clinical measures of multiple sclerosis 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**).

Definitions:

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) clearly defined; b) exclusion/inclusion criteria clearly defined; c) adequate accounting for dropouts and crossovers with numbers sufficiently low to

have minimal potential for bias; and 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 randomized controlled trial in a representative population that lacks one criteria 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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

A better understanding of the impact of the development of neutralizing antibodies (NAbs) in patients treated with interferon beta (IFN beta) for multiple sclerosis on:

- Reduction in biologic action and effectiveness of IFN beta
- Persistence of NAB positivity
- Differences in seroprevalence between different IFN beta agents

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Goodin DS, Frohman EM, Hurwitz B, O'Connor PW, Oger JJ, Reder AT, Stevens JC. Neutralizing antibodies to interferon beta: assessment of their clinical and radiographic impact: an evidence report: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2007 Mar 27;68(13):977-84. [57 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Mar 27

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Therapeutics and Technology Assessment Subcommittee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: D.S. Goodin, MD; E.M. Frohman, MD, FAAN; B. Hurwitz, MD; P.W. O'Connor, MD; J.J. Oger, MD, FRCPC, FAAN; A.T. Reder, MD; and J.C. Stevens, MD, FAAN

Therapeutics and Technology Assessment Subcommittee Members: Janis Miyasaki, MD, FAAN (*Co-Chair*); Yuen T. So, MD, PhD (*Co-Chair*); Carmel Armon, MD, MHS, FAAN (*ex-officio*); Vinay Chaudhry, MD, FAAN; Richard M. Dubinsky, MD, MPH, FAAN; Douglas S. Goodin, MD (*ex-officio, facilitator*); Mark Hallett, MD, FAAN; Cynthia L. Harden, MD; Kenneth J. Mack, MD, PhD; Fenwick T. Nichols III, MD; Michael A. Sloan, MD, MS, FAAN; James C. Stevens, MD; Paul W. O'Connor, MD, FAAN

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate

those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. With regards to this specific report, all authors have stated that they have nothing to disclose.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the American Academy of Neurology Web site.
- Supplemental material. Overview of interferon biology. St. Paul (MN): American Academy of Neurology. Electronic copies: Available from the American Academy of Neurology Web site.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI Institute on May 14, 2007.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 9/22/2008