Complete Summary

GUIDELINE TITLE

Guidelines on use of anti-IFN-beta antibody measurements in multiple sclerosis: report of an EFNS Task Force on IFN-beta antibodies in multiple sclerosis.

BIBLIOGRAPHIC SOURCE(S)

Sorensen PS, Deisenhammer F, Duda P, Hohlfeld R, Myhr KM, Palace J, Polman C, Pozzilli C, Ross C, EFNS Task Force on Anti-IFN-beta Antibodies in Multiple Sclerosis. Guidelines on use of anti-IFN-beta antibody measurements in multiple sclerosis: report of an EFNS Task Force on IFN-beta antibodies in multiple sclerosis. Eur J Neurol 2005 Nov;12(11):817-27. [85 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Multiple sclerosis (MS)

GUIDELINE CATEGORY

Evaluation
Prevention
Screening
Technology Assessment

CLINICAL SPECIALTY

Allergy and Immunology
Family Practice
Internal Medicine
Neurology

INTENDED USERS

Clinical Laboratory Personnel
Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate differences in immunogenicity of interferon-beta (IFN-beta) products
- To evaluate the reliability and give recommendations on binding antibodies (BABs) and neutralizing antibodies (NABs) assays
- To evaluate the impact of NABs on clinical efficacy and give recommendation on the clinical use of measurement of IFN-b antibodies
- To review the evidence on prevention of NAB development and the management of patients with NABs

TARGET POPULATION

Patients with multiple sclerosis receiving interferon-beta therapy

INTERVENTIONS AND PRACTICES CONSIDERED

1. Interferon-beta (IFN-beta) antibody screening with binding antibody (BAB) assays (e.g., enzyme-linked immunosorbent assay [ELISA], Western blot [WB])
2. IFN-beta antibody screening with neutralizing antibody (NAB) assays such as cytopathic effect (CPE) assay, MxA induction assay, and calculation of NAB titre using Kawade formula
3. Discontinuing NAB measurements in NAB-negative patients and repeating NAB measurements in NAB-positive patients at intervals of 3 to 6 months
4. Discontinuing (IFN-beta) therapy in patients with high NAB titres
5. Prevention and treatment of NABs with intravenous methylprednisolone

MAJOR OUTCOMES CONSIDERED

- Influence of interferon-beta (IFN-beta) formulation, dosage, and route of administration on the immunogenicity of IFN-beta products
- Sensitivity and specificity of binding antibody (BAB) and neutralizing antibody (NAB) assays
- Correlation of NABs against IFN-beta with disease relapses, magnetic resonance imaging (MRI) outcomes, and disease progression
- Effectiveness of steroid treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

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

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The task force systematically searched the Medline database for available information published in English up to September 2004. Key words included: interferon beta (IFN-beta), multiple sclerosis, immunogenicity, antibodies, binding antibody assays, neutralizing antibody assays. Articles related to this topic from the authors' personal literature databases were also included.

A PubMed search using "binding antibodies assay interferon beta" found that 21 of the 55 articles were relevant for detection of binding antibodies (BABs) with IFN-beta treatment.

PubMed was searched using the terms "neutralizing antibodies interferon beta assay." Thirty-four of 54 articles covered methods of neutralizing antibody (NAB) detection and were included.

PubMed was searched for "IFN-beta antibodies and multiple sclerosis'" Of 236 articles, 103 were original articles or review articles on antibodies against IFN-beta or controlled clinical trials of IFN-beta in which measurements of antibodies were performed. For assessment of the impact of NABs the task force selected randomized controlled trials of IFN-beta in multiple sclerosis (MS) with blindly analysed NABs and controlled non-randomized studies with blind evaluation of NABs of at least 3-year duration (see Table 4 in the original guideline document).

NUMBER OF SOURCE DOCUMENTS

Binding antibodies – 21 articles
Neutralizing antibodies – 34 articles
Measurement of antibodies against interferon-beta in multiple sclerosis – 103 articles

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

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons

with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. 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–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

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

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

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

For each specific issue at least one member of the task force assessed all published papers and omitted those that did not fulfill given criteria, read and rated the remaining articles according to the guidance for preparation of neurological management guidelines by the European Federation of Neurological Societies (EFNS) Scientific task forces – revised recommendations 2004 (see the

"Rating Scheme for the Strength of the Evidence" and the "Rating Scheme for the Strength of the Recommendations" fields).

Only trials of sufficient duration (≥3 years) and blind evaluation of neutralizing antibody (NAB) status were graded as class I evidence for effects of NABs. Trials of less sufficient duration (2–3 years) and blind evaluation of NAB status were graded as class II evidence, and trials of inappropriate duration (<2 years) and/or no blind evaluation of NAB status were classified as class III evidence regarding clinical effects of NABs.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Each paragraph of the guidelines was drafted by one member of the task force and circulated to the other members. After appropriate revision the guidelines were finalized and consensus was reached amongst all task force members at meeting.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Rating of Recommendations for a Therapeutic Intervention

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

COST ANALYSIS

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

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (Hughes RAC, Barnes MP, Baron J, Brainin M [2001]. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces. *Eur J Neurol* 8:549-550).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C) are defined at the end of the "Major Recommendations" field.

Measurements of Binding and Neutralizing Antibodies

Binding Antibodies

There are no existing recommendations on binding antibody (BAB) assays. There is class I evidence that interferon-beta (IFN-beta) BAB assays have a very high sensitivity and specificity, and can be reliably used for IFN-beta antibody screening before performing a neutralizing antibody (NAB) assay (**Level A recommendation**). Different BAB assays should be evaluated and compared using a large number of serum samples in order to identify the method with the best sensitivity and specificity for NAB detection (**Level B recommendation**).

Neutralizing Antibodies

Measurements of binding and neutralizing antibodies against IFN-beta should be performed in specialized laboratories (**Level A recommendation**). Measurement of NABs with a validated cytopathic effect (CPE) assay is still the gold standard. It is recommended that A549 cells are used with a fixed amount of IFN-beta (the preparation used by the patient) for stimulation and serial dilution of the test sera. The stimulated cells can either be challenged with encephalomyocarditis (EMC) viruses or MxA production determined. Standard curves should be obtained using increasing amounts of IFN-beta until saturation is reached. The NAB titre should be calculated using the Kawade formula (Level A recommendation).

Titres above 20 to 60 (depending on the IFN-beta preparation used in the assay) are associated with a loss of IFN-beta bioactivity (**class I evidence**). As the European Medicines Association (EMEA) currently validates a NAB assay based upon the MxA production of A549 cells (MxA induction assay), it is recommended

to use the EMEA protocol. (This recommendation is only based on class IV evidence, but consensus was reached to offer this advice as good practice.) Validation of simpler NAB assay methods is strongly recommended such as the in vivo biological response to IFN-beta administration (**Level A recommendation**).

Clinical Use of Measurements of Antibodies against IFN-beta

It is recommended that patients treated with IFN-beta are tested for the presence of NABs at 12 and 24 months of therapy (**Level A recommendation**). Measurements of NABs can be discontinued in those patients remaining NAB-negative during this period but should be resumed if disease activity increases (**Level B recommendation**). There is class I evidence that the presence of NABs significantly hampers the effect of IFN-beta on the relapse rate and on both active lesions and burden of disease seen on magnetic resonance imaging (MRI). In patients with NABs, NAB measurements should be repeated at intervals of 3 to 6 months and therapeutic options should be re-evaluated (**Level A recommendation**). Therapy with IFN-beta should be discontinued in patients with high titres of NABs (e.g., titres >100 in patients using IFN-beta-1b) sustained at repeated measurements with 3- to 6-month intervals (**Level A recommendation**).

Prevention and Treatment of NABs

Limited evidence is available on managements that reduce NAB formation to IFN-beta in multiple sclerosis (MS). Monthly 1 g intravenous (i.v.) methylprednisolone (MP) administration has been revealed to be safe and able to minimize the formation of NABs over time (**Level C recommendation**). However, no effect has been observed in reducing the amplitude of NABs titres once NABs have been formed. Further studies are warranted to strengthen these results and to expand the knowledge in such an intriguing matter.

Principal Recommendations Regarding Measurements of Antibodies against IFN-beta and the Clinical Use of NAB Measurements

- BAB assays can be reliably used for IFN-beta antibody screening before performing a NAB assay (**Level A recommendation**).
- Measurements of binding and neutralizing antibodies against IFN-beta should be performed in specialized laboratories (**Level A recommendation**).
- Measurement of NABs should be performed with a validated CPE assay or MxA production assay using serial dilution of the test sera. The NAB titre should be calculated using the Kawade formula (**Level A recommendation**).
- Tests for the presence of NABs should be performed at 12 and 24 months of therapy (**Level A recommendation**).
- Measurements of NABs can be discontinued in those patients remaining NAB-negative during this period but should be resumed if disease activity increases (**Level B recommendation**).
- In patient with NABs, measurements should be repeated after 3 to 6 months (**Level A recommendation**).
- Therapy with IFN-beta should be discontinued in patients with high titres of NABs sustained at repeated measurements with 3- to 6-month intervals (**Level A recommendation**).

Definitions:

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

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e. 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–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

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Rating of Recommendations for a Diagnostic Measure

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Rating of Recommendations for a Therapeutic Intervention

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Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

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 selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate measurement of binding antibodies (BABs) and neutralizing antibodies (NABs) against interferon-beta (IFN-beta) and the clinical use of measurement of INF-beta antibodies

POTENTIAL HARMS

Western blot method had a low false-negative rate when screening for neutralizing antibody (NAB)-positivity.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

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)

Sorensen PS, Deisenhammer F, Duda P, Hohlfeld R, Myhr KM, Palace J, Polman C, Pozzilli C, Ross C, EFNS Task Force on Anti-IFN-beta Antibodies in Multiple Sclerosis. Guidelines on use of anti-IFN-beta antibody measurements in multiple sclerosis: report of an EFNS Task Force on IFN-beta antibodies in multiple sclerosis. Eur J Neurol 2005 Nov;12(11):817-27. [85 references] PubMed

ADAPTATION

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

DATE RELEASED

2005 Nov

GUIDELINE DEVELOPER(S)

European Federation of Neurological Societies - Medical Specialty Society

SOURCE(S) OF FUNDING

European Federation of Neurological Societies

GUIDELINE COMMITTEE

European Federation of Neurological Societies Task Force on IFN-beta antibodies in multiple sclerosis

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Task Force Members: P. S. Sørensen, Danish Multiple Sclerosis Research Centre, Department of Neurology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; F. Deisenhammer, Department of Neurology, University of Innsbruck, Innsbruck, Austria; P. Duda, Outpatient Clinic Neurology-Neurosurgery, University Hospitals, Basel, Switzerland; R. Hohlfeld, Institute for Clinical Neuroimmunology, University of Munich, Klinikum Grosshadern, Munich, Germany; K.-M. Myhr, Department of Neurology, Haukeland University Hospital, Bergen, Norway; J. Palace, Multiple Sclerosis Group, Radcliffe Infirmary, Oxford, UK; C. Polman, Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands; C. Pozzilli, Department of Neurological Sciences, II Faculty of Medicine, University "La Sapienza", Rome, Italy; C. Rossi, Institute for Inflammation Research, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark for the EFNS Task Force on Anti-IFN-b Antibodies in Multiple Sclerosis

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available to registered users from the European Federation of Neurological Societies Web site.

Print copies: Available from Prof. Per Soelberg Sorensen, MD, DMSci, Department of Neurology 2082, Danish MS Research Center, Copenhagen University Hospital, Rigshospitalet, DK 2100 Copenhagen, Denmark; Phone: + 45 3545 2080; Fax: + 45 3545 2626; E-mail: pss@rh.dk

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site.
- Guideline papers. European Federation of Neurological Societies. Electronic copies: Available from the European Federation of Neurological Societies Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on December 6, 2006. The information was verified by the guideline developer on January 2, 2007.

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