

Imaging Plus Biomarker Predicted Dementia in AD

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CHICAGO — A combination of specialized brain imaging and cerebrospinal amyloid β_{42} measurements powerfully predicts the presence—and absence—of Alzheimer's-type dementia.

For several years researchers have focused on $A\beta_{42}$ in cerebrospinal fluid (CSF) as a possible biomarker of Alzheimer's disease (AD): Higher levels indicate the

protein is still soluble, whereas lower levels suggest that it might be building up in the brain as neuropathologic plaque. But an unpredictable overlap of CSF $A\beta_{42}$ among controls, Alzheimer's patients, and those with mild cognitive impairment has confounded any definitive conclusions, Anne Fagan, Ph.D., said at the International Conference on Alzheimer's Disease.

“Over the years, many people have looked at the level of this protein in CSF in nondemented and Alzheimer's sub-

jects,” said Dr. Fagan of Washington University, St. Louis. “Although the mean levels are different, there has always been a question over why there is this tremendous amount of overlap, with many controls showing $A\beta_{42}$ levels as low as those we see among Alzheimer's patients, and some Alzheimer's patients showing levels as high as those of normal controls.”

The advent of Pittsburgh imaging compound B (PIB), an imaging agent that lights up amyloid plaques during positron emis-

sion tomography scanning, has allowed Dr. Fagan to more fully explore the associations of $A\beta_{42}$ in the brain and the CSF. She presented the results of a prospective study of 132 subjects, all of whom underwent PIB scanning and a lumbar puncture for CSF $A\beta_{42}$ levels within a 2-year period. These volunteers had a mean age of 66 years; 113 were cognitively normal, 14 had very mild Alzheimer's dementia, and 5 had mild Alzheimer's dementia.

Dr. Fagan and her colleagues found what she called “a striking inverse relationship between the levels of amyloid in the brain and levels of $A\beta_{42}$ in the CSF.”

Of the 37 subjects whose PIB-PET scans showed high levels of brain amyloid, 36 (97%) had low CSF $A\beta_{42}$. Conversely, 80 of the 95 with low levels of brain amyloid (84%) had high CSF $A\beta_{42}$. These relationships were strong regardless of cognitive status at the time of testing. “Low CSF $A\beta_{42}$



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DR. FAGAN

appears to be an excellent marker for the presence of brain amyloid, regardless of whether people have dementia or not. The presence of low CSF $A\beta_{42}$ combined with PIB-positivity in the brain may be antecedent biomarkers of Alzheimer's disease, predicting who will develop future dementia.”

Indeed, some independent clinical follow-up data on the cohort seem to confirm this, Dr. Fagan said. Three subjects who were cognitively normal at the time of testing, but were PIB-positive and had low CSF $A\beta_{42}$, have since developed a diagnosis of very mild Alzheimer's dementia.

Four who had a diagnosis of very mild Alzheimer's at the time of testing, but who were PIB-negative and had high CSF $A\beta_{42}$ have had their diagnoses changed to either “no dementia” or “non-Alzheimer's dementia.” “This seems to say that high CSF $A\beta_{42}$ and cortical PIB-negativity may be useful for a differential diagnosis, identifying possible Alzheimer's misdiagnoses in the very early stages.”

Finally, Dr. Fagan noted, four subjects who were cognitively normal at the time of testing and were PIB-negative but had low CSF $A\beta_{42}$ have since undergone additional PIB scans. “One subject is now PIB-positive, indicating the presence of cortical amyloid, and two others may have PIB-positivity in some select brain regions. Levels of CSF $A\beta_{42}$ may decrease prior to cortical amyloid becoming detectable by PIB, and thus may be a very sensitive biomarker for the earliest, preclinical stages of Alzheimer's.”

The potential clinical impact of such an early diagnostic tool could be profound. “Our goal is to push the disease diagnosis back to a much earlier time, hopefully into this preclinical stage,” Dr. Fagan said at the meeting sponsored by the Alzheimer's Association.

BETASERON® (INTERFERON BETA 1b) FOR INJECTION

10011479

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

Betaseron (Interferon beta-1b) is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

CONTRAINDICATIONS

Betaseron is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, Albumin (Human), USP, or any other component of the formulation.

WARNINGS

Depression and Suicide

Betaseron (Interferon beta-1b) should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression and suicide have been reported to occur with increased frequency in patients receiving interferon compounds, including Betaseron. Patients treated with Betaseron should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. If a patient develops depression, cessation of Betaseron therapy should be considered.

In the four randomized controlled studies there were three suicides and eight suicide attempts among the 1532 patients in the Betaseron treated groups compared to one suicide and four suicide attempts among the 965 patients in the placebo groups.

Injection Site Necrosis

Injection site necrosis (ISN) has been reported in 4% of patients in controlled clinical trials (see **ADVERSE REACTIONS**). Typically, injection site necrosis occurs within the first four months of therapy, although post-marketing reports have been received of ISN occurring over one year after initiation of therapy. Necrosis may occur at a single or multiple injection sites. The necrotic lesions are typically three cm or less in diameter, but larger areas have been reported. Generally the necrosis has extended only to subcutaneous fat. However, there are also reports of necrosis extending to and including fascia overlying muscle. In some lesions where biopsy results are available, vasculitis has been reported. For some lesions debridement and, infrequently, skin grafting have been required.

As with any open lesion, it is important to avoid infection and, if it occurs, to treat the infection. Time to healing was varied depending on the severity of the necrosis at the time treatment was begun. In most cases healing was associated with scarring.

Some patients have experienced healing of necrotic skin lesions while Betaseron therapy continued; others have not. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis. For patients who continue therapy with Betaseron after injection site necrosis has occurred, Betaseron should not be administered into the affected area until it is fully healed. If multiple lesions occur, therapy should be discontinued until healing occurs.

Patient understanding and use of aseptic self-injection techniques and procedures should be periodically reevaluated, particularly if injection site necrosis has occurred.

Anaphylaxis

Anaphylaxis has been reported as a rare complication of Betaseron use. Other allergic reactions have included dyspnea, bronchospasm, tongue edema, skin rash and urticaria (see **ADVERSE REACTIONS**).

Albumin (Human), USP

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

Information for Patients

All patients should be instructed to carefully read the supplied Betaseron Medication Guide. Patients should be cautioned not to change the dose or schedule of administration without medical consultation.

Patients should be made aware that serious adverse reactions during the use of Betaseron have been reported, including depression and suicidal ideation, injection site necrosis, and anaphylaxis (see **WARNINGS**). Patients should be advised of the symptoms of depression or suicidal ideation and be told to report them immediately to their physician. Patients should also be advised of the symptoms of allergic reactions and anaphylaxis.

Patients should be advised to promptly report any break in the skin, which may be associated with blue-black discoloration, swelling, or drainage of fluid from the injection site, prior to continuing their Betaseron therapy.

Patients should be informed that flu-like symptoms are common following initiation of therapy with Betaseron. In the controlled clinical trials, antipyretics and analgesics were permitted for relief of these symptoms. In addition, gradual dose titration during initiation of Betaseron treatment may reduce flu-like symptoms.

Female patients should be cautioned about the abortifacient potential of Betaseron (see **PRECAUTIONS, Pregnancy-Teratogenic effects**).

Instruction on Self-injection Technique and Procedures

Patients should be instructed in the use of aseptic technique when administering Betaseron. Appropriate instruction for reconstitution of Betaseron and methods of self-injection should be provided, including careful review of the Betaseron Medication Guide. The first injection should be performed under the supervision of an appropriately qualified health care professional.

Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. A puncture resistant container for disposal of used needles and syringes should be supplied to the patient along with instructions for safe disposal of full containers. Patients should be advised of the importance of rotating areas of injection with each dose, to minimize the likelihood of severe injection site reactions, including necrosis or localized infection.

Laboratory Tests

In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential white blood cell counts, platelet counts and blood chemistries, including liver function tests, are recommended at regular intervals (one, three, and six months) following introduction of Betaseron therapy, and then periodically thereafter in the absence of clinical symptoms. Thyroid function tests are recommended every six months in patients with a history of thyroid dysfunction or as clinically indicated. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Drug Interactions

No formal drug interaction studies have been conducted with Betaseron. In the placebo controlled studies in MS, corticosteroids or ACTH were administered for treatment of relapses for periods of up to 28 days in patients (N=664) receiving Betaseron.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis: Interferon beta-1b has not been tested for its carcinogenic potential in animals.

Mutagenesis: Betaseron was not mutagenic when assayed for genotoxicity in the Ames bacterial test in the presence or absence of metabolic activation. Interferon beta-1b was not mutagenic to human peripheral blood lymphocytes in vitro, in the presence or absence of metabolic inactivation. Betaseron treatment of mouse BALBc-3T3 cells did not result in increased transformation frequency in an in vitro model of tumor transformation.

Impairment of fertility: Studies in normally cycling, female rhesus monkeys at doses up to 0.33 mg/kg/day (32 times the recommended human dose based on body surface area, body surface dose based on 70 kg female) had no apparent adverse effects on either menstrual cycle duration or associated hormonal profiles (progesterone and estradiol) when administered over three consecutive menstrual cycles. The validity of extrapolating doses used in animal studies to human doses is not known. Effects of Betaseron on normally cycling human females are not known.

Pregnancy-Teratogenic effects

Pregnancy Category C: Betaseron was not teratogenic at doses up to 0.42 mg/kg/day when given to pregnant female rhesus monkeys on gestation days 20 to 70. However, a dose related abortifacient activity was observed in these monkeys when Interferon beta-1b was administered at doses ranging from 0.028 mg/kg/day to 0.42 mg/kg/day (2.8 to 40 times the recommended human dose based on body surface area comparison). The validity of extrapolating doses used in animal studies to human doses is not known. Lower doses were not studied in monkeys. Spontaneous abortions while on treatment were reported in patients (n=4) who participated in the Betaseron PRMS clinical trial. Betaseron given to rhesus monkeys on gestation days 20 to 70 did not cause teratogenic effects; however, it is not known if teratogenic effects exist in humans. There are no adequate and well-controlled studies in pregnant women. If the patient becomes pregnant or plans to become pregnant while taking Betaseron, the patient should be apprised of the potential hazard to the fetus and it should be recommended that the patient discontinue therapy.

Nursing Mothers

It is not known whether Betaseron is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Betaseron, a decision should be made to either discontinue nursing or discontinue the drug, taking into account the importance of drug to the mother.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Clinical studies of Betaseron did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

ADVERSE REACTIONS

In all studies, the most serious adverse reactions with Betaseron were depression, suicidal ideation and injection site necrosis (see **WARNINGS**). The incidence of depression of any severity was approximately 30% in both Betaseron-treated patients and placebo-treated patients. Anaphylaxis and other allergic reactions have been reported in patients using Betaseron (see **WARNINGS**). The most commonly reported adverse reactions were lymphopenia (lymphocytes <1500/mm³), injection site reaction, asthenia, flu-like symptom complex, headache, and pain. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Betaseron, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were depression, flu-like symptom complex, injection site reactions, leukopenia, increased liver enzymes, asthenia, hypertonia, and myasthenia.

Because clinical trials are conducted under widely varying conditions and over varying lengths of time, adverse reaction rates observed in the clinical trials of Betaseron cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to Betaseron in the four placebo controlled trials of 1407 patients with MS treated with 0.25 mg or 0.16 mg/m², including 1261 exposed for greater than one year. The population encompassed an age range from 18-65 years. Sixty-four percent (64%) of the patients were female. The percentages of Caucasian, Black, Asian, and Hispanic patients were 94.8%, 3.5%, 0.1%, and 0.7%, respectively.

The safety profiles for Betaseron-treated patients with SPMS and RRMS were similar. Clinical experience with Betaseron in other populations (patients with cancer, HIV positive patients, etc.) provides additional data regarding adverse reactions; however, experience in non-MS populations may not be fully applicable to the MS population.

Table 1 enumerates adverse events and laboratory abnormalities that occurred among all patients treated with 0.25 mg or 0.16 mg/m² Betaseron every other day for periods of up to three years in the four placebo controlled trials (Study 1-4) at an incidence that was at least 2.0% more than that observed in the placebo patients (System Organ Class, MedDRA v. 8.0).

System Organ Class MedDRA v. 8.0 ^a Adverse Reaction	Placebo (n=965)	Betaseron (n=1407)
Blood and lymphatic system disorders		
Lymphocytes count decreased (<1500/mm ³) ^x	66%	86%
Absolute neutrophil count decreased (<1500/mm ³) ^x	5%	13%
White blood cell count decreased (<3000/mm ³) ^x	4%	13%
Lymphadenopathy	3%	6%
Nervous system disorders		
Headache	43%	50%
Insomnia	16%	21%
Incoordination	15%	17%
Vascular disorders		
Hypertension	4%	6%
Respiratory, thoracic and mediastinal disorders		
Dyspnea	3%	6%
Gastrointestinal disorders		
Abdominal pain	11%	16%
Hepatobiliary disorders		
Alanine aminotransferase increased (SGPT > 5 times baseline) ^x	4%	12%
Aspartate aminotransferase increased (SGOT > 5 times baseline) ^x	1%	4%
Skin and subcutaneous tissue disorders		
Rash	15%	21%
Skin disorder	8%	10%
Musculoskeletal and connective tissue disorders		
Hypertonia	33%	40%
Myalgia	14%	23%
Renal and urinary disorders		
Urinary urgency	8%	11%
Reproductive system and breast disorders		
Metrorrhagia [*]	7%	9%
Impotence ^{**}	6%	8%
General disorders and administration site conditions		
Injection site reaction (various kinds) ^o	26%	78%
Asthenia	48%	53%
Flu-like symptoms (complex) [§]	37%	57%
Pain	35%	42%
Fever	19%	31%
Chills	9%	21%
Peripheral edema	10%	12%
Chest pain	6%	9%
Malaise	3%	6%
Injection site necrosis	0%	4%

[#] except for “injection site reaction (various kinds)” and “flu-like symptom complex” the most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

^x laboratory abnormality

^{*} pre-menopausal women

^{**} men

^o “Injection site reaction (various kinds)” comprises all adverse events occurring at the injection site (except injection site necrosis), i.e. the following terms: injection site reaction, injection site hemorrhage, injection site hypersensitivity, injection site inflammation, injection site mass, injection site pain, injection site edema and injection site atrophy.

[§] “Flu-like symptom complex” denotes flu syndrome and/or a combination of at least two AEs from fever, chills, myalgia, malaise, sweating.

Injection Site Reactions

In four controlled clinical trials, injection site reactions occurred in 78% of patients receiving Betaseron with injection site necrosis in 4%. Injection site inflammation (42%), injection site pain (16%), injection site hypersensitivity (4%), injection site necrosis (4%), injection site mass (2%), injection site edema (2%) and non-specific reactions were significantly associated with Betaseron treatment (see **WARNINGS** and **PRECAUTIONS**). The incidence of injection site reactions tended to decrease over time. Approximately 69% of patients experienced the event during the first three months of treatment, compared to approximately 40% at the end of the studies.

Flu-Like Symptom Complex

The rate of flu-like symptom complex was approximately 57% in the four controlled clinical trials. The incidence decreased over time, with only 10% of patients reporting flu-like symptom complex at the end of the studies. For patients who experienced a flu-like symptom complex in Study 1, the median duration was 7.5 days.

Laboratory Abnormalities

In the four clinical trials, leukopenia was reported in 18% and 6% [of patients in Betaseron- and placebo-treated groups, respectively]. No patients were withdrawn or dose reduced for neutropenia in Study 1. Three percent (3%) of patients in Studies 2 and 3 experienced leukopenia and were dose-reduced. Other abnormalities included increase of SGPT to greater than five times baseline value (12%), and increase of SGOT to greater than five times baseline value (4%). In Study 1, two patients were dose reduced for increased hepatic enzymes; one continued on treatment and one was ultimately withdrawn. In Studies 2 and 3, 1.5% of Betaseron patients were dose-reduced or interrupted treatment for increased hepatic enzymes. In Study 4, 1.7% of patients were withdrawn from treatment due to increased hepatic enzymes, two of them after a dose reduction. In Studies 1-4, nine (0.6%) patients were withdrawn from treatment with Betaseron for any laboratory abnormality, including four (0.3%) patients following dose reduction (see **PRECAUTIONS, Laboratory tests**).

Menstrual Irregularities

In the four clinical trials, 97 (12%) of the 783 pre-menopausal females treated with Betaseron and 79 (15%) of the 528 pre-menopausal females treated with placebo reported menstrual disorders. One event was reported as severe, all other reports were mild to moderate severity. No patients withdrew from the studies due to menstrual irregularities.

Postmarketing Experience

The following adverse events have been observed during postmarketing experience with Betaseron and are classified within body system categories:

Blood and lymphatic system disorders: Anemia, Thrombocytopenia

Endocrine disorders: Hypothyroidism, Hyperthyroidism, Thyroid dysfunction

Metabolism and nutrition disorders: Hypocalcemia, Hyperuricemia, Triglyceride increased, Anorexia, Weight decrease

Psychiatric disorders: Confusion, Depersonalization, Emotional lability

Nervous system disorders: Ataxia, Convulsion, Paresthesia, Psychotic symptoms

Cardiac disorders: Cardiomyopathy

Vascular disorders: Deep vein thrombosis, Pulmonary embolism

Respiratory, thoracic and mediastinal disorders: Bronchospasm, Pneumonia

Gastrointestinal disorders: Pancreatitis, Vomiting

Hepatobiliary disorders: Hepatitis, Gamma GT increased

Skin and subcutaneous tissue disorders: Pruritus, Skin discoloration, Urticaria

Renal and urinary disorders: Urinary tract infection, Urosepsis

General disorders and administration site conditions: Fatal capillary leak syndrome^{*}.

^{*}The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of this syndrome.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Serum samples were monitored for the development of antibodies to Betaseron during Study 1. In patients receiving 0.25 mg every other day 56/124 (45%) were found to have serum neutralizing activity at one or more of the time points tested. In Study 4, neutralizing activity was measured every 6 months and at end of study. At individual visits after start of therapy, activity was observed in 16.5% up to 25.2% of the Betaseron treated patients. Such neutralizing activity was measured at least once in 75 (29.9%) out of 251 Betaseron patients who provided samples during treatment phase; of these, 17 (22.7%) converted to negative status later in the study.

Based on all the available evidence, the relationship between antibody formation and clinical safety or efficacy is not known.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Betaseron using a biological neutralization assay that measures the ability of immune sera to inhibit the production of the interferon-inducible protein, MxA. Neutralization assays are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing activity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Betaseron with the incidence of antibodies to other products may be misleading.

Anaphylactic reactions have rarely been reported with the use of Betaseron.

DRUG ABUSE AND DEPENDENCE

No evidence or experience suggests that abuse or dependence occurs with Betaseron therapy; however, the risk of dependence has not been systematically evaluated.

OVERDOSAGE

Safety of doses higher than 0.25 mg every other day has not been adequately evaluated. The maximum amount of Betaseron that can be safely administered has not been determined.

Rx Only.

REFERENCES

References furnished upon request.

U.S. Patent No. 4,588,585; 4,961,969; 5,702,699; 6,994,847

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