

# Transient Neurological Attacks Raise Vascular Risk

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Adults who suffered transient neurological attacks with nonfocal symptoms were at increased risk of developing major vascular disease and dementia in a study of more than 6,000 adults aged 55 years and older.

The findings challenge the perception that nonfocal transient neurological attacks (TNAs) are harmless. "TNAs with

nonfocal symptoms were almost as frequent as focal TNAs, and had an equally unfavorable overall subsequent clinical course with a slightly higher risk of stroke and a higher risk of vascular dementia than persons without TNA," the investigators wrote. The authors defined TNA as an episode of neurological dysfunction lasting less than 24 hours (usually from 2 to 15 minutes).

Although focal TNAs (better known as transient ischemic attacks or TIAs) have

been characterized, a variety of diagnoses have been applied to nonfocal and mixed TNAs (focal and nonfocal symptoms in the same attack). Focal and mixed TNAs are often considered benign and have not been well studied, Dr. Michiel J. Bos of Erasmus University Medical Centre in Rotterdam, the Netherlands, and colleagues, noted.

To study the incidence and prognosis of each of these three types of TNA, the investigators followed 6,062 community-

dwelling adults with no history of stroke, myocardial infarction, or dementia. The participants were part of the Rotterdam Study, an ongoing population-based cohort study.

The subjects enrolled between 1990 and 1993 and were followed until Jan. 1, 2005. The median age of the patients at baseline was 68 years, and 3,758 (62%) were women (JAMA 2007;298:2877-85).

A total of 548 individuals experienced TNAs during the study period of 60,535 person-years. Categorized by their symptoms, 282 TNAs were considered focal, 228 were nonfocal, and 38 were mixed.

Overall, focal and nonfocal TNAs occurred with similar frequency, with incidence rates of 4.7 per 1,000 person-years



**Occurrence of a TNA is a rally cry for extensive evaluation in these patients and further research.**

DR. JOHNSTON

and 3.8 per 1,000 person-years, respectively. The incidence rates for both types increased with age. The incidence rate for mixed TNAs was much lower—0.6 per 1,000 person years—and the incidence was not clearly associated with age.

Those who met criteria for focal TNAs had a higher risk of subsequent stroke (hazard ratio 2.14) than did those without TNA, after adjustment for age and sex, but there was no observable difference in the risk for MI or dementia.

The participants with nonfocal TNAs were at greater risk of both stroke (HR, 1.56) and dementia (HR, 1.59), compared with subjects without TNAs. And they were at especially high risk for vascular dementia (HR, 5.05). There was no difference in risk for MI in this subgroup.

Those with mixed TNAs also were at increased risk of stroke (HR, 2.48), ischemic heart disease (HR, 2.26), vascular death (HR, 2.54), and dementia (HR, 3.46), compared with individuals who didn't experience TNAs. Notably, the risk of vascular dementia was much higher among those with mixed TNAs (HR, 21.5).

The clinical implication of the findings is that nonfocal TNAs deserve to be taken seriously, Dr. S. Claiborne Johnston, a neurologist at the University of California, San Francisco, wrote in an accompanying editorial (JAMA 2007;298:2912-3).

"The study argues that, whatever is causing these events, the prognosis justifies greater attention," according to Dr. Johnston.

"Even though TNA is likely to be only of transient utility because clinicians must quickly move to more specific diagnoses to provide appropriate treatment for patients, this entity should be considered a rally cry for more extensive evaluation or consultation in these patients, as well as for further research," he wrote.

None of the researchers or Dr. Johnston reported any financial conflicts related to this study.

## 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 one year after initiation of therapy. Necrosis may occur at a single or multiple injection sites. The necrotic lesions are typically 3 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 myeloid suppression 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 formation.

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 RMS 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/mm<sup>3</sup>), 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, hypotonia, 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/m<sup>2</sup>, 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 RMS 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/m<sup>2</sup> 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 in the placebo patients (System Organ Class, MedDRA v. 8.0).

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

<sup>†</sup> 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.

<sup>x</sup> laboratory abnormality

\* pre-menopausal women

\*\* men

<sup>o</sup> "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.

<sup>§</sup> "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 526 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, Urorspias

General disorders and administration site conditions: Fatal capillary leak syndrome<sup>†</sup>.

<sup>†</sup>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%) 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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