

Interferon beta-1b, Betaseron

DESCRIPTION

Betaseron® (Interferon beta-1b) is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques. Interferon beta-1b is manufactured by bacterial fermentation of a strain of *Escherichia coli* that bears a genetically engineered plasmid containing the gene for human interferon beta_{ser17}. The native gene was obtained from human fibroblasts and altered in a way that substitutes serine for the cystine residue found at position 17. Interferon beta-1b has 165 amino acids and an approximate molecular weight of 18,500 daltons. It does not include the carbohydrate side chains found in the natural material.

The specific activity of Betaseron is approximately 32 million international units (IU)/mg Interferon beta-1b. Each vial contains 0.3 mg of Interferon beta-1b. The unit measurement is derived by comparing the antiviral activity of the product to the World Health Organization (WHO) reference standard of recombinant human interferon beta. Mannitol, USP and Albumin (Human), USP (15 mg each/vial) are added as stabilizers.

Lyophilized Betaseron is a sterile, white to off-white powder, for subcutaneous injection after reconstitution with the diluent supplied (Sodium Chloride, 0.54% Solution).

CLINICAL PHARMACOLOGY

General

Interferons (IFNs) are a family of naturally occurring proteins, produced by eukaryotic cells in response to viral infection and other biologic agents. Three major groups of interferons have been distinguished: alpha, beta, and gamma. Interferons alpha and beta comprise the Type I interferons and interferon gamma is a Type II interferon. Type I interferons have considerably overlapping but also distinct biologic activities. The bioactivities of IFNs are mediated by their interactions with specific receptors found on the surfaces of human cells. Differences in bioactivities induced by IFNs likely reflect divergences in the signal transduction process induced by IFN-receptor binding.

Biologic Activities

The mechanism of action of Interferon beta-1b in patients with multiple sclerosis is unknown. Interferon beta-1b receptor binding induces the expression of interferon-induced proteins that are responsible for the pleiotropic bioactivities of Interferon beta-1b. A number of these proteins (including neopterin, β_2 -microglobulin, MxA protein, and IL-10) have been measured in blood fractions from Betaseron-treated patients and Betaseron-treated healthy volunteers. Immunomodulatory effects of Interferon beta-1b include the enhancement of suppressor T cell activity, reduction of pro-inflammatory cytokine production, down-regulation of antigen presentation, and inhibition of lymphocyte trafficking into the central nervous system. It is not known if these effects play an important role in the observed clinical activity of Betaseron in multiple sclerosis (MS).

Pharmacokinetics

Because serum concentrations of Interferon beta-1b are low or not detectable following subcutaneous administration of 0.25 mg or less of Betaseron, pharmacokinetic information in patients with MS receiving the recommended dose of Betaseron is not available. Following single and multiple daily

subcutaneous administrations of 0.5 mg Betaseron to healthy volunteers (N=12), serum Interferon beta-1b concentrations were generally below 100 IU/mL. Peak serum Interferon beta-1b concentrations occurred between one to eight hours, with a mean peak serum interferon concentration of 40 IU/mL. Bioavailability, based on a total dose of 0.5 mg Betaseron given as two subcutaneous injections at different sites, was approximately 50%.

After intravenous administration of Betaseron (0.006 mg to 2.0 mg), similar pharmacokinetic profiles were obtained from healthy volunteers (N=12) and from patients with diseases other than MS (N=142). In patients receiving single intravenous doses up to 2.0 mg, increases in serum concentrations were dose proportional. Mean serum clearance values ranged from 9.4 mL/min•kg⁻¹ to 28.9 mL/min•kg⁻¹ and were independent of dose. Mean terminal elimination half-life values ranged from 8.0 minutes to 4.3 hours and mean steady-state volume of distribution values ranged from 0.25 L/kg to 2.88 L/kg. Three-times-a-week intravenous dosing for two weeks resulted in no accumulation of Interferon beta-1b in sera of patients. Pharmacokinetic parameters after single and multiple intravenous doses of Betaseron were comparable.

Following every other day subcutaneous administration of 0.25 mg Betaseron in healthy volunteers, biologic response marker levels (neopterin, β₂-microglobulin, MxA protein, and the immunosuppressive cytokine, IL-10) increased significantly above baseline six-12 hours after the first Betaseron dose. Biologic response marker levels peaked between 40 and 124 hours, and remained elevated above baseline throughout the seven-day (168-hour) study. The relationship between serum Interferon beta-1b levels or induced biologic response marker levels and the clinical effects of Interferon beta-1b in multiple sclerosis is unknown.

CLINICAL STUDIES

The safety and efficacy of Betaseron have been assessed in three multicenter trials. Study 1 evaluated Betaseron in relapsing-remitting MS (RRMS) patients and Studies 2 and 3 assessed Betaseron in secondary progressive MS (SPMS) patients.

The effectiveness of Betaseron in relapsing-remitting MS (Study 1) was evaluated in a double blind, multiclinic, randomized, parallel, placebo controlled clinical investigation of two years duration. The study enrolled MS patients, aged 18 to 50, who were ambulatory EDSS of = 5.5, exhibited a relapsing-remitting clinical course, met Poser's criteria¹ for clinically definite and/or laboratory supported definite MS and had experienced at least two exacerbations over two years preceding the trial without exacerbation in the preceding month. Patients who had received prior immunosuppressant therapy were excluded.

An exacerbation was defined as the appearance of a new clinical sign/symptom or the clinical worsening of a previous sign/symptom (one that had been stable for at least 30 days) that persisted for a minimum of 24 hours.

Patients selected for study were randomized to treatment with either placebo (N=123), 0.05 mg of Betaseron (N=125), or 0.25 mg of Betaseron (N=124) self-administered subcutaneously every other day. Outcome based on the 372 randomized patients was evaluated after two years.

Patients who required more than three 28-day courses of corticosteroids were removed from the study. Minor analgesics (acetaminophen, codeine), antidepressants, and oral baclofen were allowed ad libitum but chronic nonsteroidal anti-inflammatory drug (NSAID) use was not allowed.

The primary/protocol-defined outcome measures were 1) frequency of exacerbations per patient and 2)

proportion of exacerbation free patients. A number of secondary clinical and magnetic resonance imaging (MRI) measures were also employed. All patients underwent annual T2 MRI imaging and a subset of 52 patients at one site had MRIs performed every six weeks for assessment of new or expanding lesions.

The study results are shown in Table 1.

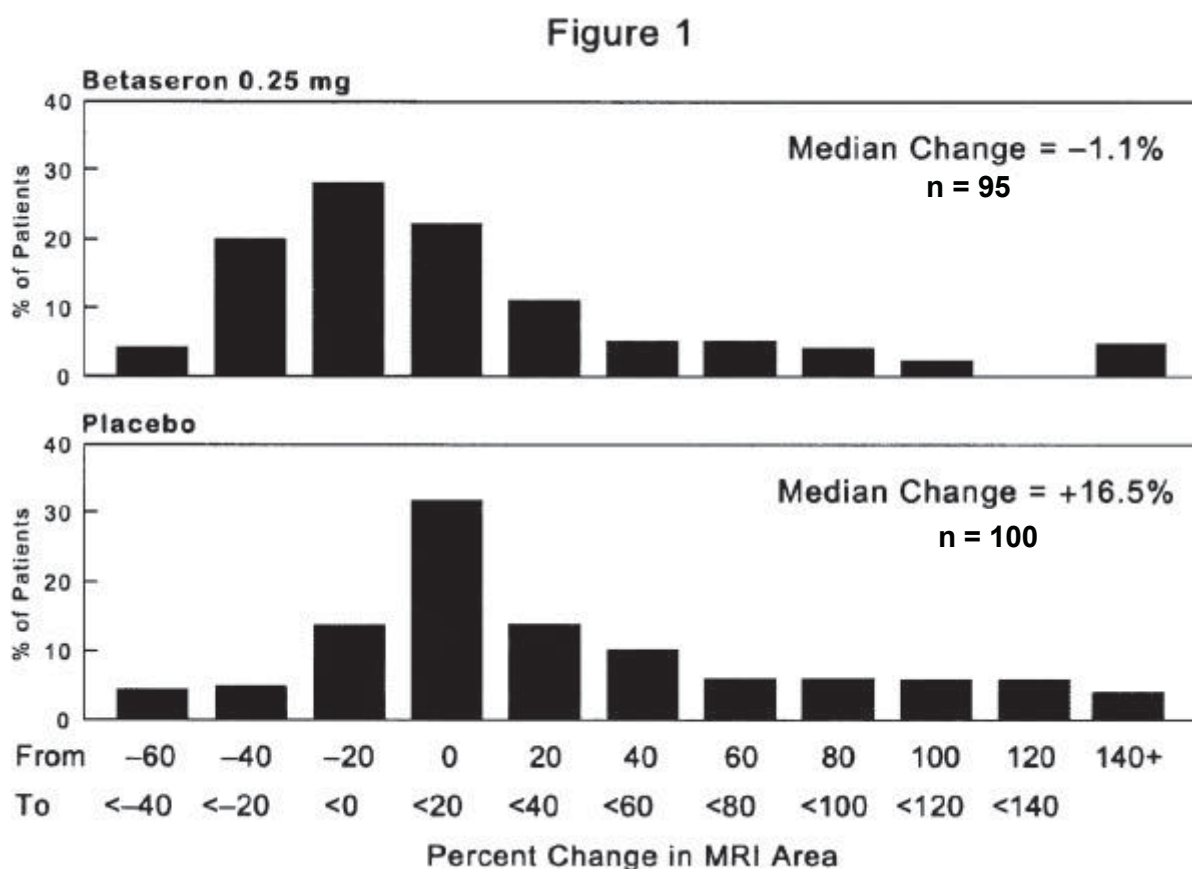
TABLE 1							
Two Year RRMS Study Results Primary and Secondary Clinical Outcomes							
Efficacy Parameters		Treatment Groups			Statistical Comparisons p-value		
Primary End Points		Placebo (N=123)	0.05 mg (N=125)	0.25 mg (N=124)	Placebo vs 0.05 mg	0.05 mg vs 0.25 mg	Placebo vs 0.25 mg
Annual exacerbation rate		1.31	1.14	0.90	0.005	0.113	0.0001
Proportion of exacerbation-free patients [†]		16%	18%	25%	0.609	0.288	0.094
Exacerbation frequency per patient	0 [†]	20	22	29	0.151	0.077	0.001
	1	32	31	39			
	2	20	28	17			
	3	15	15	14			
	4	15	7	9			
	≥5	21	16	8			
Secondary Endpoints^{††}							
Median number of months to first on-study exacerbation		5	6	9	0.299	0.097	0.010
Rate of moderate or severe exacerbations per year		0.47	0.29	0.23	0.020	0.257	0.001
Mean number of moderate or severe exacerbation days per patient		44.1	33.2	19.5	0.229	0.064	0.001
Mean change in EDSS score [‡] at endpoint		0.21	0.21	-0.07	0.995	0.108	0.144
Mean change in Scripps score ^{‡‡} at endpoint		-0.53	-0.50	0.66	0.641	0.051	0.126
Median duration in days per exacerbation		36	33	35.5	ND	ND	ND
% change in mean MRI lesion area at endpoint		21.4%	9.8%	-0.9%	0.015	0.019	0.0001
<p>ND Not done</p> <p>[†] 14 exacerbation free patients (0 from placebo, six from 0.05 mg, and eight from 0.25 mg) dropped out of the study before completing six months of therapy. These patients are excluded from this analysis.</p> <p>^{††} Sequelae and Functional Neurologic Status, both required by protocol, were not analyzed individually but are included as a function of the EDSS.</p> <p>[‡] EDSS scores range from 1-10, with higher scores reflecting greater disability</p> <p>^{‡‡} Scripps neurologic rating scores range from 0-100, with smaller scores reflecting greater disability.</p>							

Of the 372 RRMS patients randomized, 72 (19%) failed to complete two full years on their assigned treatments.

Over the two-year period, there were 25 MS-related hospitalizations in the 0.25 mg Betaseron-treated group compared to 48 hospitalizations in the placebo group. In comparison, non-MS hospitalizations were evenly distributed among the groups, with 16 in the 0.25 mg Betaseron group and 15 in the placebo group. The average number of days of MS-related steroid use was 41 days in the 0.25 mg Betaseron group and 55 days in the placebo group ($p=0.004$).

MRI data were also analyzed for patients in this study. A frequency distribution of the observed percent changes in MRI area at the end of two years was obtained by grouping the percentages in successive intervals of equal width. Figure 1 displays a histogram of the proportions of patients, which fell into each of these intervals. The median percent change in MRI area for the 0.25 mg group was 1.1% which was significantly smaller than the 16.5% observed for the placebo group ($p=0.0001$).

Distribution of Change in MRI Area



In an evaluation of frequent MRI scans (every six weeks) on 52 patients at one site, the percent of scans with new or expanding lesions was 29% in the placebo group and 6% in the 0.25 mg treatment group ($p=0.006$).

The exact relationship between MRI findings and clinical status of patients is unknown. Changes in

lesion area often do not correlate with changes in disability progression. The prognostic significance of the MRI findings in this study has not been evaluated.

Studies 2 and 3 were multicenter, randomized, double-blind, placebo controlled trials conducted to assess the effect of Betaseron in patients with SPMS. Study 2 was conducted in Europe and Study 3 was conducted in North America. Both studies enrolled patients with clinically definite or laboratory-supported MS in the secondary progressive phase, and who had evidence of disability progression (both Study 2 and 3) or two relapses (Study 2 only) within the previous two years. Baseline Kurtzke expanded disability status scale (EDSS) scores ranged from 3.0 to 6.5.² Patients in Study 2 were randomized to receive Betaseron 0.25 mg (n=360) or placebo (n=358). Patients in Study 3 were randomized to Betaseron 0.25 mg (n=317), Betaseron 0.16 mg/m² of body surface area (n=314, mean assigned dose 0.30 mg), or placebo (n=308). Test agents were administered subcutaneously, every other day for three years.

The primary outcome measure was progression of disability, defined as a 1.0 point increase in the EDSS score, or a 0.5 point increase for patients with baseline EDSS \geq 6.0. In Study 2, time to progression in EDSS was longer in the Betaseron treatment group (p=0.005), with estimated annualized rates of progression of 16% and 19% in the Betaseron and placebo groups, respectively. In Study 3, the rates of progression did not differ significantly between treatment groups, with estimated annualized rates of progression of 12%, 14%, and 12% in the Betaseron fixed dose, surface area-adjusted dose, and placebo groups, respectively.

Multiple analyses, including covariate and subset analyses based on sex, age, disease duration, clinical disease activity prior to study enrollment, MRI measures at baseline and early changes in MRI following treatment were evaluated in order to interpret the discordant study results. No demographic or disease-related factors enabled identification of a patient subset where Betaseron treatment was predictably associated with delayed progression of disability.

In Studies 2 and 3, like Study 1, a statistically significant decrease in the incidence of relapses associated with Betaseron treatment was demonstrated. In Study 2, the mean annual relapse rates were 0.42 and 0.63 in the Betaseron and placebo groups, respectively (p<0.001). In Study 3, the mean annual relapse rates were 0.16, 0.20, and 0.28, for the fixed dose, surface area-adjusted dose, and placebo groups, respectively (p<0.02).

MRI endpoints in both Study 2 and Study 3 showed lesser increases in T2 MRI lesion area and decreased number of active MRI lesions in patients in the Betaseron groups. The exact relationship between MRI findings and the clinical status of patients is unknown. Changes in MRI findings often do not correlate with changes in disability progression. The prognostic significance of the MRI findings in these studies is not known.

Safety and efficacy of treatment with Betaseron beyond three years are not known.

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.

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.

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