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250 µg or 500 µg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study

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250 µg or 500 µg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study

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Summary

Background The aim of the Betaferon Efficacy Yielding Outcomes of a New Dose (BEYOND) trial was to compare the efficacy, safety, and tolerability of 250 µg or 500 µg interferon beta-1b with glatiramer acetate for treating relapsing-remitting multiple sclerosis.

Methods Between November, 2003, and June, 2005, 2447 patients with relapsing-remitting multiple sclerosis were screened and 2244 patients were enrolled in this prospective, multicentre, randomised trial. Patients were randomly assigned 2:2:1 by block randomisation with regional stratification to receive one of two doses of interferon beta-1b (250 µg or 500 µg) subcutaneously every other day or 20 mg glatiramer acetate subcutaneously every day. The primary outcome was relapse risk, defined as new or recurrent neurological symptoms separated by at least 30 days from the preceding event and that lasted at least 24 h. Secondary outcomes were progression on the expanded disability status scale (EDSS) and change in T1-hypointense lesion volume. Clinical outcomes were assessed quarterly for 2·0–3·5 years; MRI was done at screening and annually thereafter. Analysis was by per protocol. This study is registered, number NCT00099502.

Findings We found no differences in relapse risk, EDSS progression, T1-hypointense lesion volume, or normalised brain volume among treatment groups. Flu-like symptoms were more common in patients treated with interferon beta-1b ($p<0·0001$), whereas injection-site reactions were more common in patients treated with glatiramer acetate ($p=0·0005$). Patient attrition rates were 17% (153 of 888) on 250 µg interferon beta-1b, 26% (227 of 887) on 500 µg interferon beta-1b, and 21% (93 of 445) for glatiramer acetate.

Interpretation 500 µg interferon beta-1b was not more effective than the standard 250 µg dose, and both doses had similar clinical effects to glatiramer acetate. Although interferon beta-1b and glatiramer acetate had different adverse event profiles, the overall tolerability to both drugs was similar.

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Introduction

250 µg interferon beta-1b (Betaferon) given subcutaneously every other day was the first therapy with proven effectiveness for relapsing-remitting multiple sclerosis. The clinical efficacy of interferon beta-1b is dose-dependent,[1] but the ceiling of this dose response has not been established. A randomised, double-blind, pilot study compared the tolerability of the licensed dose of interferon beta-1b (250 µg) with a 500 µg dose. Although this study showed that the higher dose was well tolerated, the clinical efficacy was not assessed.[2]

Multiple sclerosis is characterised by recurrent clinical and subclinical disease activity. Interferon beta-1b reduces the number and volume of gadolinium-enhancing[3] and T2-weighted lesions.[4–7] Glatiramer acetate has also been shown to reduce multiple sclerosis disease activity, but its pharmacological and pharmacodynamic properties differ from those of interferon beta-1b. More data have been published on the efficacy of interferon beta-1b than on that of glatiramer acetate, but compared with placebo glatiramer acetate reduces relapse rate and the development of new gadolinium-enhancing and T2-weighted lesions.[8,9] In the Rebif versus Glatiramer Acetate in Relapsing MS Disease (REGARD) study,[10] no differences were seen between glatiramer acetate and interferon beta-1a in clinical outcome or in T2-weighted lesion number and volume. Although the volume of gadolinium-enhancing lesions was similar between treatment arms, patients treated with interferon beta-1b had significantly fewer gadolinium-enhancing lesions.[10] The effect of glatiramer acetate on gadolinium-enhancing lesions might be delayed by 5 months and could be smaller than the effect of interferon beta.[9] However, without a clinical trial that compares interferon beta-1b with glatiramer acetate, whether these treatments have different effects (timing, magnitude, or both) on clinical and MRI measures is unknown.

The Betaferon Efficacy Yielding Outcomes of a New Dose (BEYOND) trial was a phase 3 clinical trial in treatment-naive patients with early relapsing-remitting multiple sclerosis that compared the efficacy, safety, and tolerability of 500 µg interferon beta-1b on clinical and MRI measures with that of 250 µg interferon beta-1b (the currently approved dose).

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The BEYOND trial also compared the efficacy, safety, and tolerability of both doses of interferon beta-1b with 20 mg glatiramer acetate.

Methods

Patients

BEYOND was a randomised, parallel-group, multicentre, phase 3 study. Treatment-naive patients with relapsing-remitting multiple sclerosis who met the 2001 McDonald and International Panel diagnostic criteria[11] were enrolled at 198 centres in 26 countries worldwide. Study participants were aged 18–55 years, had had at least one relapse in the year before entry into the study, and had a baseline expanded disability status scale (EDSS) score of 0–5.[12] Women of childbearing capability had a negative pregnancy test and agreed to take adequate contraceptive measures during the trial. Patients were excluded if they: had signs or symptoms that were better explained by a disease other than multiple sclerosis; had progressive forms of multiple sclerosis or had heart disease; were treatment-experienced or had participated in previous trials of drugs for multiple sclerosis; had a history of severe depression, alcohol or drug misuse, or had made suicide attempts or had current suicidal ideations; had serious or acute liver, renal, or bone marrow dysfunction, monoclonal gammaglobinopathy, or uncontrolled epilepsy; had intolerance, contraindication, or allergy to any of the drugs used in the study; were unable to have MRI; or were unable to administer the study drug or have it administered by a care giver. Patients were followed up for at least 2 years. Patients who were randomly assigned early in BEYOND continued on a schedule of clinic visits every 3 months until the last patient had reached the 2-year endpoint. This "filling of the triangle" design was introduced about 2 years after the first patient had started treatment because of lower than expected event rates. Consequently, some patients who were randomised early in the study were followed up for 3·5 years.

BEYOND was done according to good clinical practice and the International Conference on Harmonisation (ICH) guidelines. The institutional review boards of all participating centres approved the study protocol, and patients provided written informed consent before entry into the trial. An independent data and safety monitoring board oversaw study conduct and did interim analyses to assess the benefit to risk ratios of the treatments.

Randomisation and masking

Patients were randomly assigned in a 2:2:1 ratio to either 250 µg or 500 µg interferon beta-1b subcutaneously every other day or 20 mg glatiramer acetate subcutaneously every day by the central randomisation group by use of SAS-based block randomisation with regional stratification. To ensure masking between the two doses of interferon beta-1b, medication was identical in appearance, packaging, and labelling. Physicians and

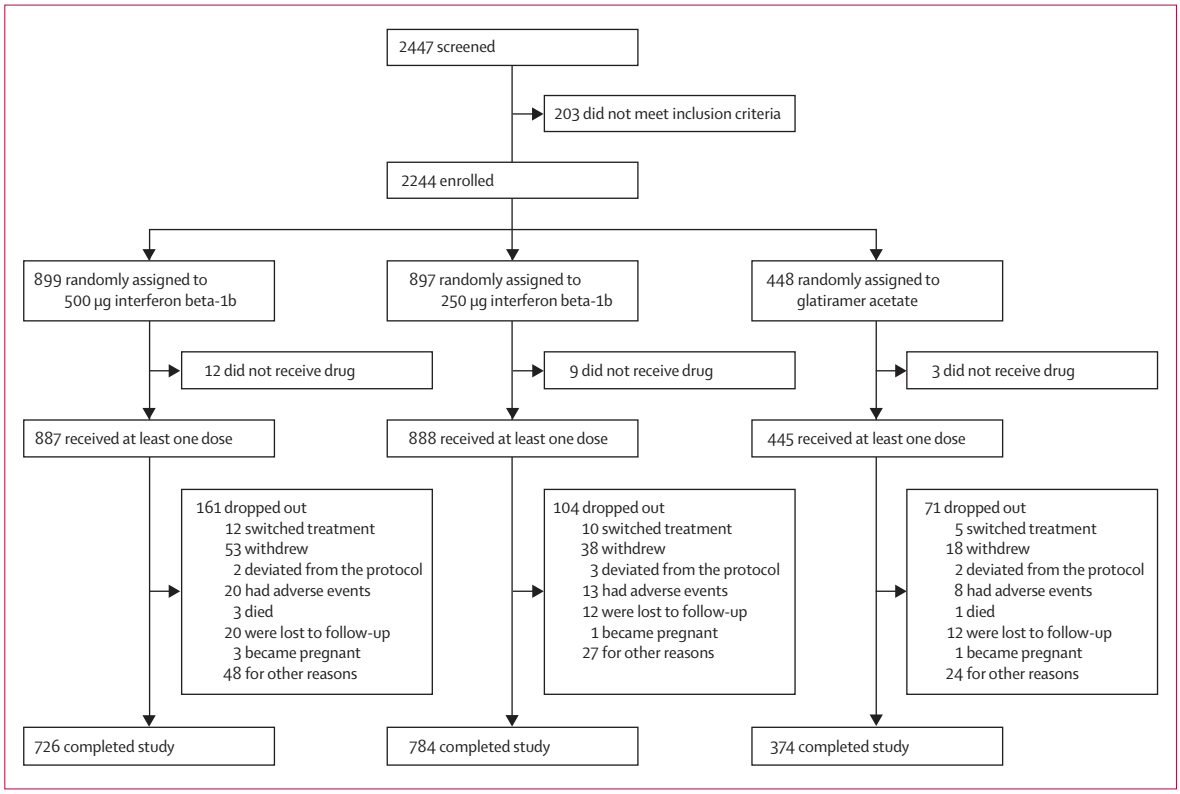

Figure 1: **Trial profile**

patients were double-blind to comparisons between the two doses.

Dose titration was done to optimise tolerability to interferon beta-1b. Dose volume was increased by 0·25 mL every 2 weeks until full dose was reached after week 6. The titration period could be extended to week 13 at the investigator's discretion. Ibuprofen or acetaminophen were given at the same time as random assignment to interferon beta-1b, at least during the first 3 months, to reduce flu-like symptoms. The treating physicians and the patients were therefore aware of treatment assignments. The evaluating physicians were masked to all randomisations. Autoinjector use was mandatory for all patients.

Procedures

Patients received 250 μg or 500 μg interferon beta-1b subcutaneously every other day or 20 mg glatiramer acetate subcutaneously every day. Clinic visits were scheduled every 3 months to assess relapse, EDSS and functional system scale, safety, and tolerability. The occurrence of new neurological symptoms and adverse events was assessed by telephone, 6 weeks after each visit. The unmasked, treating physicians were responsible for overall medical care; the masked evaluating physicians did all neurological assessments and ascertained functional system and EDSS scores. EDSS scores were evaluated in the event of new, recurrent, or worsening of neurological symptoms, and at scheduled visits. The evaluating physicians were not involved in the care of patients and had no access to patient files or previous assessments. In BEYOND, relapse was defined as new or recurrent neurological abnormalities that were separated by at least 30 days from the onset of the preceding event, lasted at least 24 h, and occurred without fever or infection. A neurological event was deemed as a relapse only if it was associated with an increase in EDSS or functional system scores—as determined by the masked, evaluating physician—that was appropriate to the reported symptoms. To assess the severity of relapses, a preplanned algorithm was developed that distinguished between major and minor relapses (webappendix). MRI was done at baseline and annually thereafter. T2-weighted and T1-weighted images (with and without 0·1 mmol/kg gadolinium-diethylene triamine penta-acetic acid [DTPA]) of the whole brain were taken. MRI scans were assessed, masked to treatment allocation, by MF at the Neuroimaging Research Unit, Milan, Italy. Observers identified the T1-weighted and T2-weighted lesions, and a semi-automated local thresholding technique was used to quantify lesion volume. Normalised brain volume at baseline was assessed with SIENAX (structural image evaluation, using

See Online for webappendix

	500 μg IFNB-1b (n=899)	250 μg IFNB-1b (n=897)	Glatiramer acetate (n=448)
Women	629 (70%)	627 (70%)	306 (68%)
White	809 (90%)	830 (93%)	406 (91%)
Age at screening (years)	35·9 (36, 28–43)	35·8 (35, 28–43)	35·2 (35, 27–43)
Disease duration (years)	5·4 (3, 1–8)	5·3 (3, 1–7)	5·1 (3, 1–7)
Relapses in past year	1·6 (1, 1–2)	1·6 (1, 1–2)	1·6 (1, 1–2)
Previous relapses	3·5 (3, 2–4)	3·5 (3, 2–4)	3·7 (3, 2–4)
Two or more relapses in past 2 years	641 (71%)	620 (69%)	329 (73%)
EDSS score	2·33 (2, 1·5–3·0)	2·35 (2, 1·5–3·0)	2·28 (2, 1·5–3·0)
Multiple sclerosis diagnosis*			
Two or more relapses and two or more clinical lesions	790 (88%)	763 (85%)	397 (89%)
Two or more relapses and one clinical lesion and dissemination in space or two or more T2 lesions and a positive CSF	57 (6%)	62 (7%)	34 (8%)
One relapse and two or more clinical lesions and dissemination in time	28 (3%)	45 (5%)	10 (2%)
One relapse and one clinical lesion and dissemination in time and space or two or more T2 lesions and a positive CSF	24 (3%)	24 (3%)	7 (2%)
MRI			
T2 lesion volume (cm^3)	8·6 (6·0, 2·3–11·7)	9·3 (5·7, 2·2–12·0)	9·2 (5·9, 2·2–13·1)
14 or more T2 lesions	767 (85%)	758 (85%)	377 (84%)
T1-hypointense lesion volume (cm^3)	1·6 (0·6, 0·2–1·7)	1·9 (0·6, 0·2–1·8)	1·7 (0·6, 0·1–2·0)
Number of gadolinium-enhancing lesions	2·3 (0, 0–2)	2·3 (0, 0–2)	1·8 (0, 0–2)
One or more gadolinium-enhancing lesions	405 (45%)	413 (46%)	202 (45%)
Volume of gadolinium-enhancing lesions (cm^3)	0·3 (0, 0–0·2)	0·3 (0, 0–0·2)	0·2 (0, 0–0·2)
Normalised brain volume (cm^3)	1490 (1489, 1420–1566)	1489 (1491, 1423–1565)	1496 (1498, 1415–1572)

Data are number (%) or mean (median, IQR). IFNB-1b=interferon beta-1b. EDSS=expanded disability status scale. *Multiple sclerosis was diagnosed according to the 2001 McDonald/International Panel criteria.[11]

Table 1: **Baseline characteristics of all randomised patients**

normalisation, of atrophy: state) and longitudinal brain volume percentage change was assessed with SIENA (structural image evaluation, using normalisation, of atrophy: rate).

Treating physicians recorded the intensity and frequency of adverse events and assessed whether they were related to treatment. Patients covered their injection sites during neurological examination and did not discuss any adverse events with the evaluating physician. Categorisation of serious adverse events conformed to ICH guidelines.

Statistical analysis

For power calculations, hazard ratios for recurrent relapses relative to 250 µg interferon beta-1b were assumed to be 0·825 for 500 µg interferon beta-1b and 1·244 for glatiramer acetate. If at least 840 patients were assigned to each dose of interferon beta-1b and at least 420 patients were assigned to glatiramer acetate, this would give BEYOND a power of more than 80% to detect differences of these magnitudes among groups. Analyses were done with SAS, version 9.1.3 (CA, USA).

Relapse risk was chosen as the primary endpoint and was assessed with the Andersen–Gill model for time to recurring events, which includes correction for the inter-dependency of multiple events.[13] Supportive relapse-based outcomes were predefined as time to first relapse (analysed by Cox proportional hazard model), proportion of patients who were relapse free at 2 years (analysed by Kaplan–Meier estimates), and annualised relapse rate (assessed by hazard ratios derived from generalised linear Poisson regression).

To assess the robustness of the treatments for the risk of relapse, prespecified subgroup analyses were done. These included stratification by median age (years), sex, median disease duration (years), geographical region, baseline EDSS score (≤2 or >2), number of relapses in the year before enrolment (one, two, or more), gadolinium-enhancing lesions at screening, median T2-lesion volume at screening, and diagnostic category (one, two, or more relapses with one or more clinical lesions). EDSS progression, measured as a 1-point change in the score that was sustained for 3 months, was a secondary outcome.

	500 µg IFNB-1b *vs* 250 µg IFNB-1b		500 µg IFNB-1b *vs* glatiramer acetate		250 µg IFNB-1b *vs* glatiramer acetate	
	HR (95% CI)	p*	HR (95% CI)	p*	HR (95% CI)	p*
Primary analysis (unadjusted)	0·93 (0·81–1·07)	0·16	0·98 (0·82–1·18)	0·43	1·06 (0·89–1·26)	0·73
With covariate adjustment†	0·94 (0·82–1·08)	0·20	1·00 (0·83–1·19)	0·48	1·06 (0·89–1·27)	0·74
Per-protocol analysis A‡	0·94 (0·81–1·09)	0·21	1·00 (0·83–1·20)	0·50	1·06 (0·89–1·27)	0·74
Per-protocol analysis B§	0·95 (0·80–1·13)	0·29	0·91 (0·74–1·11)	0·18	0·95 (0·78–1·15)	0·30

IFNB-1b=interferon beta-1b. EDSS=expanded disability status scale. *One-sided p value. †Pre-planned, excluding observation time after a major protocol violation or a 3-month interval in which less than 50% of study drug was taken. ‡Baseline covariates: sex, age, disease duration, EDSS, number of relapses in previous year, number of gadolinium-enhancing lesions, and T2 lesion volume. §Post-hoc, excluding observation time after a major protocol violation or a 3-month interval in which less than 100% of drug dose was taken.

Table 2: **Outcome variables and relapse risk**

	Recorded values			p		
	500 µg IFNB-1b	250 µg IFNB-1b	Glatiramer acetate	500 µg IFNB-1b *vs* 250 µg IFNB-1b	500 µg IFNB-1b *vs* glatiramer acetate	250 µg IFNB-1b *vs* glatiramer acetate
Supportive relapse-based outcomes*						
Annualised relapse rate†	0·33	0·36	0·34	0·10	0·42	0·79
Days to first relapse (25th percentile)‡	348	283	271	0·07	0·30	0·75
Proportion relapse free (year 2)§	539 (60%)	520 (58%)	262 (59%)	0·11	0·17	0·72
Secondary outcome measures						
Change in days to confirmed progression on EDSS (10th percentile)‡¶	190	274	268	0·84	0·45	0·35
Change in T1-hypointense lesion volume from screening (cm^3)‖	36·0% (10·2%)	23·1% (8·2%)	40·6% (10·6%)	0·18	0·54	0·68
Other clinical outcomes§						
Annualised rate of major relapse†	0·18	0·19	0·18	0·48	0·71	0·36
At least one major relapse (year 2)§	236 (26%)	244 (27%)	120 (27%)	0·34	0·43	0·56
Confirmed EDSS progression (year 2)§	200 (22%)	244 (27%)	92 (21%)	0·55	0·71	0·68
At least one MS-related admission to hospital**	155 (17%)	178 (20%)	87 (19%)	0·16	0·33	0·89
At least one MS-related steroid course**	288 (32%)	309 (34%)	144 (32%)	0·29	1·00	0·43
Other MRI outcomes (last available scan)						
Change in T2 lesion volume from screening‖	22% (12%)	19% (10%)	25% (17%)	0·56	0·0008	0·0001
Cumulative number of new T2 lesions‖	3·3 (1·0)	3·3 (1·0)	4·6 (1·0)	0·25	0·0009	0·011
Cumulative volume of gadolinium-enhancing lesions (cm^3)‖	0·11 (0·0)	0·12 (0·0)	0·14 (0·0)	0·87	0·028	0·017
Cumulative number of gadolinium-enhancing lesions‖	1·0 (0·0)	0·9 (0·0)	1·2 (0·0)	0·80	0·07	0·12
Change in percentage brain volume from screening‖	–0·64% (–0·52%)	–0·65%(–0·50%)	–0·61% (–0·50%)	0·74	0·33	0·46

Data are mean (median) and number (%). HR=hazard ratio. EDSS=expanded disability status scale. MS=multiple sclerosis. IFNB-1b=interferon beta-1b. *One-sided p values. †Generalised linear Poisson regression. ‡Log-rank test. §χ^2 test. ¶Two-sided p values. ‖Two-sided, non-parametric regression. **Fisher's exact test.

Table 3: **Outcome variables**

Because 250 µg interferon beta-1b has a large effect on inflammatory MRI measures (ie, new T2-hyperintense gadolinium-enhancing lesions),[1] it seemed unlikely that 250 µg or 500 µg interferon beta-1b would differ on these MRI endpoints. Therefore, the relative change in volume of T1-hypointense lesions from screening to last available scan was a secondary outcome. Other MRI variables (eg, development of new T2 lesions, relative change in T2-lesion volume, change in brain volume, and change in volume and number of gadolinium-enhancing lesions) were assessed and analysed with non-parametric regression models with baseline scan as a covariate.

The frequencies of adverse events or severe adverse events were presented as summary statistics (eg, number and mean) and analysed with Fisher's exact test. The titres of neutralising antibodies to interferon beta-1b were measured every 3 months. These findings will be reported elsewhere. This study is registered, number NCT00099502.

Role of the funding source

The sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors who were members of the publication committee had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between November, 2003, and June, 2005, 2447 patients were screened and 2244 patients were randomly assigned to receive 500 µg interferon beta-1b (899 patients), 250 µg interferon beta-1b (897 patients), or glatiramer acetate (448 patients). Figure 1 shows the trial profile. Randomisation was regionally balanced (webappendix), and patients in all treatment groups had similar demographic and clinical characteristics at baseline (table 1).

24 patients who were randomly assigned did not receive treatment. Of the 2220 patients who received treatment, 336 (15%) discontinued treatment prematurely. This difference was not significant among the treatment groups (104 [12%] in the 250 µg interferon beta-1b group, 161 [18%] in the 500 µg interferon beta-1b group, and 71 [16%] in the glatiramer acetate group). Almost 90% (799) of the patients treated with 250 µg interferon beta-1b and 87% (771) of the patients treated with 500 µg interferon beta-1b reached the full dose within the dose titration window (by week 13). 3% (27) of patients in the 250 µg interferon beta-1b group and 6% (54) of patients in the 500 µg interferon beta-1b group did not reach full dose.

Relapse risk before and after covariate adjustment was similar among the groups (table 2). This result was seen in all populations and subgroups analysed (data not shown) and extended to all clinical outcomes (table 3).

All patients had an MRI at baseline, but owing to technical reasons the MRI scans for 18 patients could not be assessed. The number of patients available for analysis of at least one post-baseline MRI measure decreased with time (2053 at year 1, 1930 at year 2, and 316 at year 3). MRI scans from 2096 patients were included in the last available scan analysis for at least one post-baseline MRI measure.

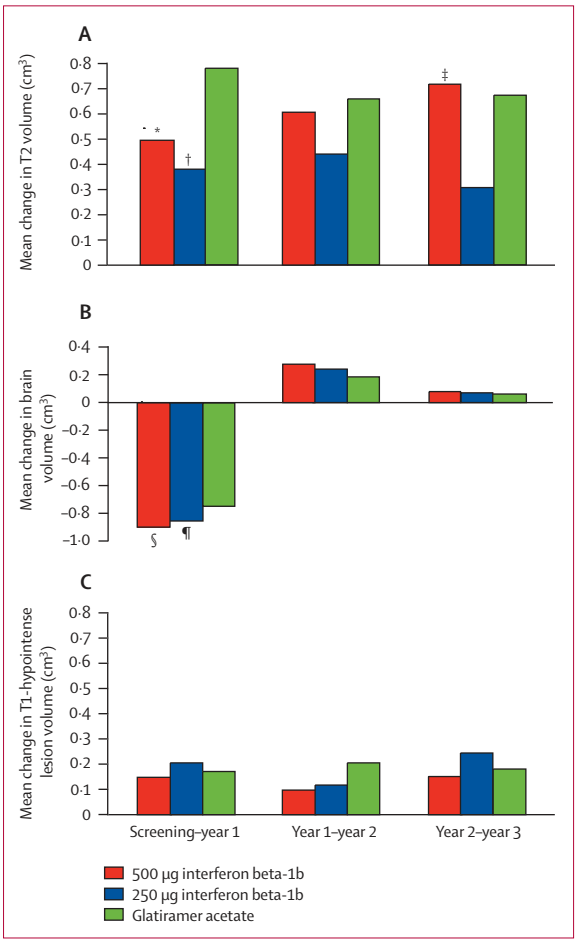

Figure 2: **Yearly changes in MRI parameters**
(A) Mean change in T2 lesion volume. (B) Mean change in brain volume. (C) Mean change in T1-hypointense lesion volume. *p=0·01 versus glatiramer acetate. †p=0·04 versus glatiramer acetate. ‡p=0·04 versus 250 µg interferon beta-1b. §p=0·007 versus glatiramer acetate. ¶p=0·02 versus glatiramer acetate.

No differences were found in the change in T1-hypointense lesion volume among treatment groups when comparing baseline with either last available scan or annual time points (table 3). Change in total MRI disease burden was significantly lower in the patients in both interferon beta-1b dose groups compared with the patients who received glatiramer acetate (high dose p=0·0008; low dose p=0·0001; table 3). A significant decrease was seen in T2 lesion volume for patients in either interferon beta-1b dose group compared with the patients in the glatiramer acetate group during year 1 (250 µg interferon beta-1b *vs* glatiramer acetate p=0·04; 500 µg interferon beta-1b *vs* glatiramer acetate, p=0·01) but not during years 2 or 3 (figure 2). The cumulative volume but not the cumulative number of gadolinium-enhancing lesions from baseline to last available scan

was significantly lower (p=0·028) for 500 µg interferon beta-1b compared with glatiramer acetate (table 3).

The overall median change in brain volume from baseline to last available scan was similar in each group, although during year 1, but not during years 2 or 3, patients treated with interferon beta-1b had a significantly greater reduction in mean brain volume than did patients treated with glatiramer acetate (250 µg interferon beta-1b *vs* glatiramer acetate p=0·02; 500 µg interferon beta-1b *vs* glatiramer acetate p=0·007; figure 2). MRI parameters did not differ between patients in either interferon beta-1b group (table 3).

	500 µg IFNB-1b (n=887)	250 µg IFNB-1b (n=888)	Glatiramer acetate (n=445)	p
Influenza-like illness	401 (45%)	359 (40%)	25 (6%)	<0·0001
Pyrexia	111 (13%)	80 (9%)	20 (5%)	0·003
Any injection-site reaction	485 (55%)	427 (48%)	259 (58%)	0·0005
Injection-site reaction	215 (24%)	194 (22%)	107 (24%)	0·37
Injection-site erythema	183 (21%)	162 (18%)	79 (18%)	0·88
Injection-site pain	91 (10%)	74 (8%)	74 (17%)	<0·0001
Injection-site pruritus	16 (2%)	11 (1%)	34 (8%)	<0·0001
Injection-site induration	14 (2%)	7 (1%)	20 (5%)	<0·0001
Injection-site swelling	7 (1%)	10 (1%)	16 (4%)	0·005
Injection-site irritation	10 (1%)	11 (1%)	13 (3%)	0·047
Headache	293 (33%)	280 (32%)	122 (27%)	0·13
Fatigue	210 (24%)	193 (22%)	95 (21%)	0·89
Nasopharyngitis	175 (20%)	162 (18%)	107 (24%)	0·014
Depression	153 (17%)	151 (17%)	64 (14%)	0·24
Raised concentration of alanine aminotransferase	142 (16%)	99 (11%)	16 (4%)	<0·0001
Raised concentration of aspartate aminotransferase	112 (13%)	76 (9%)	11 (3%)	<0·0001
Arthralgia	110 (12%)	121 (14%)	49 (11%)	0·19
Influenza	110 (12%)	96 (11%)	46 (10%))	0·85
Back pain	108 (12%)	103 (12%)	51 (11%)	1·00
Paraesthesia	104 (12%)	122 (14%)	69 (16%)	0·41
Urinary tract infection	104 (12%)	91 (10%)	47 (11%)	0·85
Insomnia	100 (11%)	102 (12%)	29 (7%)	0·005
Upper respiratory tract infection	100 (11%)	79 (9%)	48 (11%)	0·28
Pain in extremity	99 (11%)	95 (11%)	57 (13%)	0·27
Raised concentration of gamma-glutamyltransferase	92 (10%)	57 (6%)	4 (1%)	<0·0001
Hypoaesthesia	81 (9%)	78 (9%)	45 (10%)	0·42
Nausea	70 (8%)	83 (9%)	49 (11%)	0·33

Data are shown as number (%). Data were based on the safety analysis set, which included all patients who received at least one dose of the study drug. Adverse event terminology conforms to Medical Dictionary for Regulatory Activities, version 10.0. IFNB=interferon beta-1b.

Table 4: **Adverse events in at least 10% of patients in one treatment arm**

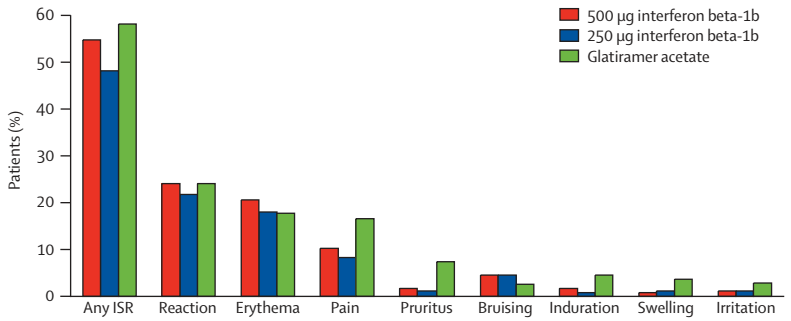

Figure 3: **Proportion of patients with at least one injection-site reaction**
Only adverse events with a frequency of at least 2% are shown. ISR=injection site reaction.

Drug treatment was well tolerated and the incidence of severe adverse events was similar among the groups (11% [100] in the 250 µg interferon beta-1b group, 16% [138] in the 500 µg interferon beta-1b group, and 13% [57] in the glatiramer acetate group). Table 4 lists adverse events that were reported by at least 10% of patients in one or more treatment group. Flu-like symptoms (p<0·0001) and elevated liver enzymes (p<0·0001) were significantly more common in patients treated with interferon beta-1b than in those treated with glatiramer acetate. The proportion of patients who had any flu-like symptom at least once was 59% (527) in the 250 µg interferon beta-1b group and 64% (565) in the 500 µg interferon beta-1b group compared with 24% (108) in the glatiramer acetate group. By contrast, the proportion of patients who had any injection-site reaction at least once was significantly higher in the patients treated with glatiramer acetate than in patients treated with interferon beta-1b (p=0·0005; figure 3, table 4). The significantly higher incidences of pain, pruritus, induration, swelling, and irritation at the injection site with glatiramer acetate (figure 3, table 4) could explain this difference. Lipoatrophy occurred only in the patients treated with glatiramer acetate. Similarly, post-injection reactions (eg, dyspnoea, chest pain, flushing, chest discomfort, or post-procedural complications) mostly occurred in the patients treated with glatiramer acetate (17% [75] in the glatiramer acetate group, 5% [46] in the 250 µg interferon beta-1b, and 6% [49] in the 500 µg interferon beta-1b group). Individually, each of these adverse events occurred in fewer than 10% of the patients treated with glatiramer acetate. The occurrence of injection site reactions and flu-like symptoms reduced over time (figure 4).

Discussion

The BEYOND study showed that the efficacy of 500 µg interferon beta-1b on clinical and MRI measures is similar to that seen with the licensed dose (250 µg). Moreover, there were no differences between interferon beta-1b and glatiramer acetate with respect to the primary outcome variable (relapse risk) or other supportive clinical efficacy outcomes (ie, annualised relapse rate, time to first relapse, relapse-free status, or progression on the EDSS). There were no differences among treatments in relapse-based or disability-based outcomes in any BEYOND subgroups, stratified by baseline disease activity, severity, or duration.

Compared with the original interferon beta-1b trial,[1] the relapse rate in BEYOND was lower than anticipated. This is probably attributable to several factors. First, 31% of the patients in BEYOND had an EDSS score of less

than 2 at baseline compared with 18% in the original trial.[1] Moreover, the mean disease duration in BEYOND was 5·3 years compared with 8·0 years in the earlier trial.[1] Thus, BEYOND enrolled participants earlier in the disease course than those who participated in the original study. Because early treatment seems to have a greater effect on disease course compared with delayed treatment,[14] this might have resulted in the lower than expected event rates in all treatment groups. Second patients were selected for inclusion in the BEYOND study according to the McDonald diagnostic criteria, which enables diagnosis at milder or earlier stages of the disease. Enrolling patients at an earlier stage of the disease can make the reported disease course seem milder than it is—the "Will Rogers phenomenon".[15] Third, there might have been selection bias: only treatment-naive patients were enrolled in BEYOND; therefore, patients with active disease who were prescribed aggressive treatment would have been excluded, which would skew the BEYOND study population to patients with mild disease.

There was no measurable difference in T1-hypointense lesion volume, the primary MRI study outcome, between treatment arms. Chronic T1-hypointense lesions are thought to be indicative of areas of greater tissue damage (eg, matrix destruction or axonal loss),[16,17] but our analyses did not distinguish between acute and chronic T1-hypointense lesions. Thus, whether there are treatment-specific differences in the development of chronic T1-hypointense lesions, a potentially better surrogate of disability in multiple sclerosis, remains unclear.[18]

Although there were no differences between interferon beta-1b and glatiramer acetate in measures of clinical disease or T1-hypointense lesions, there were differences for some of the other MRI outcomes (table 3). For example, the development of T2-weighted lesions was better controlled in the patients treated with interferon beta-1b than it was in those treated with glatiramer acetate. This effect was shown for both doses of interferon beta-1b, which contributed to the robustness of the finding. The difference between interferon beta-1b and glatiramer acetate for T2 burden of disease was most pronounced during year 1. Although the relevance of these findings is unclear, some data suggest that early development of a greater T2 burden of disease in patients with clinically isolated syndrome[19] or relapsing-remitting multiple sclerosis[20] predicts worse long-term outcome, including onset of long-term disability, early development of secondary progressive multiple sclerosis, and poor cognitive status.[20,21]

The cumulative volume of gadolinium-enhancing lesions from baseline to last available scan was significantly lower for both doses of interferon beta-1b than it was for glatiramer acetate. Because only the volume of cumulative gadolinium-enhancing lesions—and not the number—differed, interferon beta-1b might be more effective for retarding the formation of large lesions. Because only annual MRI scans were done during BEYOND, the superiority of interferon beta-1b over glatiramer acetate for controlling the permeability of the blood–brain barrier is likely to be underestimated by our data. The REGARD study also showed that patients treated with interferon beta-1a had a reduced number of gadolinium-enhancing lesions within 6 months of starting treatment compared with those treated with glatiramer acetate.[10] The differences between interferon beta-1b and glatiramer acetate seen in the BEYOND study are in contrast with the findings of the Betaseron versus Copaxone in MS with triple-dose gadolinium and 3T MRI Endpoints (BECOME) study. However, unlike BEYOND, which measured the numbers of T2-hyperintense and gadolinium-enhancing lesions separately, BECOME looked at a composite of these lesions.[22]

Significantly greater decreases in whole-brain volume were measured between screening and year 1 for interferon beta-1b than were for glatiramer acetate. This decline is probably a consequence of reductions in the amount of inflammatory infiltrate (oedema) in the brain. The potent anti-inflammatory effects of products derived from interferon beta have been reported.[23,24] Because such decreases in brain volume are attributable more to water loss than they are to tissue loss, this phenomenon is known as pseudoatrophy. The decline for the two doses

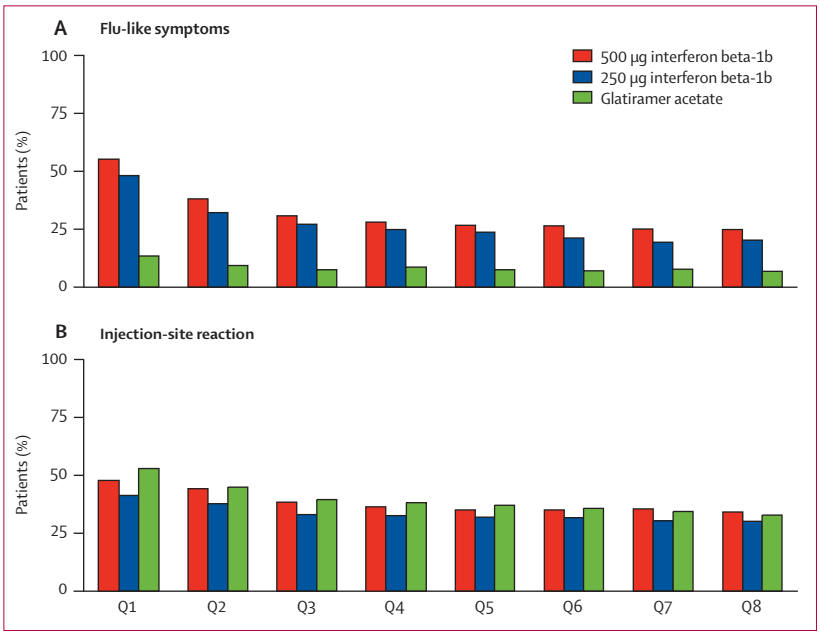

Figure 4: **Frequency of flu-like symptoms and injection-site reactions over time**
Flu-like symptoms (eg, increased body temperature, chills, cold sweats, feeling cold, body temperature change, malaise, myalgia, pyrexia, and hyperhidrosis) were more common with interferon beta-1b, whereas injection-site reactions (eg, anaesthesia, atrophy, bruising, dermatitis, discolouration, discomfort, eczema, erythema, haematoma, haemorrhage, hypersensitivity, induration, infection, inflammation, mass, necrosis, nodule, oedema, pain, papule, paraesthesia, phlebitis, pruritus, pustule, rash, reaction, swelling, urticaria, warmth, vessel puncture site haematoma, and vessel puncture-site reaction) were more prevalent with glatiramer acetate. The occurrence of these adverse events subsided with time in the three treatment groups. Occurrences are presented for each quarter (Q). Because all patients completed 2 years of treatment, data are presented up to Q8.

of interferon beta-1b is greater than the decline seen for glatiramer acetate, indicating that the anti-inflammatory effects of interferon beta-1b are more profound.

Adherence to study treatment was highest in the 250 µg interferon beta-1b group, although this difference was not significant. Interferon beta-1b and glatiramer acetate were well tolerated, and the adverse event profiles of 250 µg interferon beta-1b and glatiramer acetate were similar to those reported in previous studies. The tolerability of 500 µg interferon beta-1b reported here differs from the results of a pilot study done in 1993, which showed a dose-dependent increase in the incidence of adverse events with interferon beta-1b.[25] This is probably related to the effectiveness of modern methods for giving drugs, which can increase tolerability (eg, dose titration, autoinjector use, and simultaneous treatment with non-steroidal anti-inflammatory drugs [NSAIDs]).

As expected, flu-like symptoms and abnormalities in liver function were more common with interferon beta-1b than they were with glatiramer acetate. Nevertheless, flu-like symptoms decreased over time after effective management with dose titration and NSAIDs. By contrast, the occurrence of any injection-site reaction (eg, pain, swelling, induration, itching, and irritation) and lipoatrophy was more commonly associated with glatiramer acetate than with interferon beta-1b. The development of a systemic reaction, described as immediate post-injection reaction after glatiramer acetate use, is well known.[26] Although none of the adverse events in BEYOND were coded as such, and the time to adverse events was not recorded, the higher incidences of dyspnoea, chest pain, flushing, chest discomfort, and post-procedural complication in patients treated with glatiramer acetate shows the difference in immediate post-injection reactions between groups. In light of the absence of differences in clinical efficacy, the lower adherence rate for glatiramer acetate might be caused by the increased incidence of injection-site or systemic reactions and the higher frequency of injections.

We did not show the superiority of 500 µg interferon beta-1b over the licensed dose for either clinical or subclinical disease measures. Therefore, 250 µg interferon beta-1b seems to be the dose with maximum efficacy for treatment-naive patients who are in the early stages of relapsing-remitting multiple sclerosis. No differences in clinical efficacy were seen when interferon beta-1b was compared with glatiramer acetate.

Contributors

POC planned, designed, and undertook the study, analysed the data, did extensive preparation for, reviewed, and revised the manuscript, and was a member of the steering committee. MF was a study site investigator, principal investigator for the analysis of the MRI data, reviewed and revised the manuscript, and was a member of the steering committee. BA designed the study, analysed and interpreted the data, wrote the manuscript, and was a member of the steering committee. GC undertook the study, collected, analysed, and interpreted the data, and reviewed the manuscript. SC designed the study, collected, analysed, and interpreted the data, developed the figures for and wrote the manuscript, and was a member of the steering committee. DG designed the study, collected, analysed, and interpreted the data, reviewed and revised the manuscript, and was a member of the steering committee. HPH collected, analysed, and interpreted the data, reviewed and revised the manuscript, and was member of the steering committee. DJ served on the steering committee and planned the study, analysed and interpreted the data, implemented the study, and wrote and reviewed the manuscript. VF designed and undertook the study and collected the data. MG designed the study and analysed and interpreted the data. LK undertook the study, standardised the neurological analyses, trained the neurological personnel, analysed and interpreted the data, reviewed the manuscript, and was a member of the steering committee. FB designed the study and analysed and interpreted the data. VK designed the study, analysed and interpreted the data, and developed, revised, and reviewed the manuscript. CK designed and coordinated the study and was a member of the steering committee. RS designed the study and generated the study protocol, conducted the study, collected, analysed, and interpreted the data, and reviewed and revised the manuscript. CP did the study, collected, analysed, and interpreted the data, and reviewed and revised the manuscript. TB conceptualised, designed, and planned the study, oversaw the conduct of the study analysed and interpreted the data, and wrote, reviewed, and revised the manuscript.

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Conflicts of interest

POC has received either personal compensation (for consultation, service on a scientific advisory board, or from speaking) or financial support for scholarly activities from pharmaceutical companies that develop products for multiple sclerosis, including Biogen Idec, Sanofi–Aventis, EMD Serono, Abbott Labs, Teva Pharmaceuticals, Bayer, Bio-MS, Genentech, Genzyme, Roche, and Novartis. MF has received personal compensation and research support from Teva Pharmaceutical Industries, Merck–Serono, Bayer Schering Pharma AG, Biogen-Dompè, and Genmab. BA has served as a consultant for Bayer HealthCare Pharmaceuticals. GC has received personal compensation for activities with Teva Neuroscience, Merck Serono, Bayer–Schering, Novartis, Sanofi–Aventis Pharmaceuticals, and Biogen-Dompè as a consultant,

speaker, or member of the scientific advisory board. SC has received honoraria from Bayer HealthCare Pharmaceuticals, and from other pharmaceutical companies (Genmab, Merck, and Merck Serono) for speaking and consulting. DG has received honoraria for activities with Bayer, EMD Serono, and Teva Neuroscience. HPH has received personal compensation for activities with Schering, Teva, Serono, and Biogen. LK has received research support from Bayer–Schering Pharma, Bayhill, Biogen Idec, Centocor, Eisai, Genmab, Genzyme, GlaxoSmithKline, Merck–Serono, Novartis, Sanofi–Aventis, Roche, Teva, UCB Pharma, and Wyeth. DJ has received honoraria for speaking and consulting from and funded research with Bayer, Serono, Pfizer, TEVA, Novartis, Biogen, and GlaxoSmithKline. RS, MG, and CP are salaried employees of Bayer Schering Pharma AG/Bayer HealthCare Pharmaceuticals and own stock in Bayer AG, the owner of Bayer Schering Pharma AG/Bayer HealthCare Pharmaceuticals. VF, MG, FB, CK, VK, and TB are salaried employees of Bayer Schering Pharma AG/Bayer HealthCare Pharmaceuticals.

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