ORIGINAL RESEARCH

ExtaviJect® 30G device for subcutaneous self-injection of interferon beta-1b for multiple sclerosis: a prospective European study

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Background: The ExtaviJect® 30G autoinjector was developed to facilitate parenteral self-administration of interferon beta-1b (Extavia®), a first-line disease-modifying therapy in patients with multiple sclerosis. Our aim was to assess patient compliance with treatment when using the autoinjector, patients' and nurses' experiences of using the device, its tolerability, and patient satisfaction.

Methods: This was a 12-week, real-world, prospective, observational, noninterventional study conducted in nine European countries. Questionnaires were used to measure patient compliance and to assess patients' and nurses' experiences. All adverse events were recorded by severity, including injection site reactions or pain. Patient satisfaction and health-related quality of life were assessed using the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) and EuroQol-5 Dimension (EQ-5D) instruments, respectively.

Results: Of 582 patients enrolled, 568 (98%) received at least one injection and attended the first follow-up visit at 6 weeks, and 542 (93%) attended the second follow-up visit at 12 weeks. For the whole study, 548 of 568 (97%) patients were compliant with treatment. Among the various questions assessing whether the device was easy and quick to use accurately, without fear of the needle, 56%–98% of patients and 59%–98% of nurses were in agreement. There were nine serious adverse events (four disease-related) reported among the 227 (39%) patients reporting adverse events. Scores increased in the TSQM-9 convenience domain between weeks 6 and 12 (P=0.0009), and in the EQ-5D visual analog scale between baseline and week 12 ($P<0.0001$), indicating improvement in health-related quality of life.

Conclusion: ExtaviJect 30G was convenient to use and was associated with high levels of compliance.

Keywords: autoinjector, injections, subcutaneous, interferon beta, multiple sclerosis, relapsing-remitting, patient preference, self-administration

Introduction

Subcutaneous interferon beta-1b is widely used for the treatment of multiple sclerosis (MS). Its clinical benefits have been demonstrated in numerous randomized, controlled Phase III studies in patients with clinically isolated syndrome, relapsing-remitting MS, and relapsing secondary progressive MS.[1–5] Recently, a long-term follow-up study found a clinically important survival benefit associated with early interferon beta-1b treatment.[6] Comparing survival rates among patients randomized to interferon beta-1b therapy with those simultaneously randomized to receive placebo during their first 2 years of therapy, a 47% reduction in all-cause mortality was found in the former group at 21 years.[6]

There is also a wealth of evidence supporting the long-term safety and tolerability of interferon beta-1b,[7] which has accumulated since its first clinical use over 25 years ago and also from 1.3 million patient-years of exposure since it first received marketing authorization (data on file; Novartis Pharma AG, Basel, Switzerland; Bayer Schering Pharma AG, Berlin, Germany). Among the most common side effects of injectable disease-modifying therapies experienced by patients with MS are injection site pain (ISP) and injection site reactions (ISRs).[8–10] Rates of ISP and ISRs associated with subcutaneous administration of interferons are generally higher than those associated with intramuscular administration, and are also higher for subcutaneous administration of interferon beta-1a than for high-dose, high-frequency administration of interferon beta-1b.[8,11] Furthermore, studies investigating the role of needle diameter in ISP/ISRs have shown that administration of interferon formulations using thinner needles is clinically advantageous.[11,12] A study of 120 healthy volunteers found that less ISP was associated with needles of a smaller compared with a larger outer diameter.[12]

Improvements in injection-related tolerance and satisfaction among patients who self-administer interferons can be achieved by using autoinjectors.[9,12–18] Use of autoinjectors has also been shown to be a strong predictor of adherence[17] and, in a crossover study of patients self-administering interferon beta-1b, use of autoinjectors was associated with a lower incidence of ISRs (32%) than manual injections performed without an autoinjector.[18]

The ExtaviJect® 30G autoinjector (Novartis Pharma AG, Basel, Switzerland; Figure 1) was developed to facilitate high-dose, high-frequency subcutaneous administration of Extavia® (interferon beta-1b; Novartis Pharma AG). This autoinjector has a thin, 30-gauge (30G) needle and includes features designed to make administration simpler and quicker than with some other autoinjectors, such as a needle cap that can remain in place while the syringe is being loaded. Therefore, it was hoped that patient satisfaction and adherence would be improved using ExtaviJect 30G, compared with using other devices or self-administration without an autoinjector.

The purpose of this 12-week European real-world observational study (EXCELLENT) conducted in patients

Figure 1 ExtaviJect® 30G autoinjector showing the thin 30-gauge needle.
Note: ExtaviJect® 30G autoinjector (Novartis Pharma AG, Basel, Switzerland).

with MS was to determine patient-reported compliance and satisfaction with treatment when using ExtaviJect 30G to self-administer interferon beta-1b subcutaneously. The study also captured the opinions of nurses who monitored patients using the device, as well as information about tolerability and health economic outcomes associated with use of the autoinjector.

Patients and methods

Patients aged 18–65 years and diagnosed with MS by McDonald criteria[19] were recruited between November 2010 and December 2011 from nine European countries (Belgium, Bulgaria, France, Germany, Greece, Italy, Poland, Portugal, and Romania). A total of 110 centers were included. Patients who were able to provide written informed consent and who had been prescribed interferon beta-1b using the ExtaviJect 30G autoinjector as part of their routine clinical care were eligible to participate in the study. This included patients who were previously receiving an injectable disease-modifying therapy (including interferon beta-1b) or who were treatment-naïve. The study was evaluated and approved by an ethics committee and/or national regulatory authority in all participating countries, depending upon local requirements. The study was conducted in accordance with national guidelines and the expected standards of Good Clinical Practice, including the principles of the Declaration of Helsinki. This was a single-cohort, multicenter, noninterventional, observational study with a follow-up period of 12 weeks. A noninterventional approach was used to obtain a representative, real-world study population. All patients self-administered interferon beta-1b at the dose prescribed by their physician using the ExtaviJect 30G autoinjector. Participants attended a baseline visit and a maximum of two follow-up visits at approximately 6 (±2) weeks and/or approximately 12 (±2) weeks. Follow-up visits were conducted when patients attended the physician's office as part of their routine clinical care and were therefore held in accordance with standard clinical practice in each country.

Treatment compliance was determined at weeks 6 and 12, and for the whole study. At weeks 6 and 12, the number of patient-reported missed injections during the 2 weeks before each visit was expressed as a percentage of the total number of injections prescribed in the same period (seven injections). For the whole study, the number of missed injections during the 2 weeks preceding both study visits was expressed as a percentage of the number of injections prescribed for those 4 weeks (14 injections). No missed injections were imputed at 12 weeks for patients who discontinued after 6 weeks.

Patients reporting at least 20% of missed injections were defined as noncompliant.[20] Patient and nurse evaluation of autoinjector use was assessed through questionnaires and rating scales at week 12. Patients completed the Multiple Sclerosis Treatment Concern Questionnaire and the Patient User Trial Questionnaire. Nurses completed the Trainer User Trial Questionnaire. All adverse events, including ISP or ISRs, were recorded. For ISP and ISRs, the severity levels reported by patients were collated for each type of reaction (itching/erythema, redness, swelling/inflammation, bruising, pain/stinging, and/or burning).

Patient satisfaction was assessed at the follow-up visits using the three scales of the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) assessment, covering: effectiveness (three questions); convenience (three questions); and global satisfaction (three questions). The scores in each domain of the TSQM-9 were calculated as recommended by the instrument's authors.[21,22] Health-related quality of life at baseline and at week 12 was analyzed using both the EuroQol-5 Dimension (EQ-5D) instrument[23] and the Patient-Reported Indices for MS (PRIMUS) questionnaire.[24,25] Assessment of generic health outcomes using the EQ-5D instrument included the descriptive system (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and the self-rating visual analog scale measure of current health-related quality of life. Validated translations of the TSQM-9 were obtained from Quintiles (Reading, UK). Validated translations of questionnaire EQ-5D were obtained from EuroQol (Rotterdam, Netherlands). Translations of PRIMUS were provided by the sponsor in French, German, and Italian, and use was therefore confined to France, Germany, and Italy. PRIMUS was validated linguistically by forward and reverse translation and by cognitive debriefing; only two of the three independent assessment scales in the validated PRIMUS questionnaire were used (covering activity limitations and health-related quality of life). Evaluation of health care resource utilization included the number of hospitalizations since the last visit and the number of contacts with nurses and other health professionals during the course of the study due to MS.

Statistical analysis

A sample size of 580 patients was calculated to be suitably powered to allow estimation of different occurrence rates (from 10% to 50%) with a maximum 95% confidence interval width of ±0.041 points (when $P=0.05$). All patients enrolled in the study were included in the analysis population. Data analysis was performed using the statistics software package SAS version 9.1 (SAS Institute Inc, Cary, NC, USA). For between-group comparisons, an α-value of 0.05 was set as the significance level for all statistical tests. To analyze the relationship between different variables, the appropriate bivariate analysis was performed. For normally distributed continuous variables, strata were compared by Student's t-test or analysis of variance models. Otherwise, continuous variables were analyzed using the nonparametric Mann–Whitney or Kruskal–Wallis test. For categorical variables, the differences between strata were analyzed using the Chi-square or Fisher's Exact test.

Results

Baseline demographic and clinical characteristics

Of 582 patients enrolled, 568 (97.6%) received at least one injection and attended the first follow-up visit at 6 weeks, and 542 (93.1%) attended the second follow-up visit at 12 weeks (Figure 2). A total of 15 patients (ten at 6 weeks, five at 12 weeks) discontinued treatment during the study; 12 following adverse events, one owing to a dislike of injections, one after receiving a change of therapy, and one after becoming pregnant.

Most patients (500 [85.9%]) had relapsing-remitting MS, the remainder either having secondary progressive MS or clinically isolated syndrome; baseline demographics and disease characteristics are summarized in Table 1. Mean (standard deviation [SD]) age was 40.1 (10.7) years and most patients (407 [69.9%]) were female. The mean (SD) time interval between diagnosis and the baseline visit
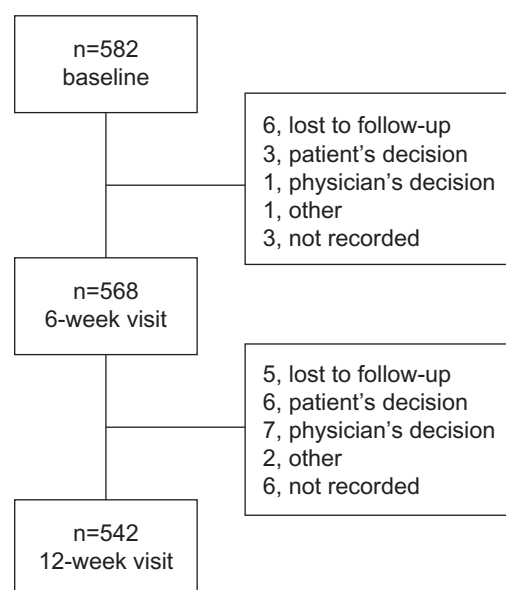

Figure 2 Patient flow.

Table 1 Baseline demographic and disease characteristics

Characteristic	n=582
Gender [n (%)]	
Men	175 (30.1)
Women	407 (69.9)
Age, years [mean (SD)]	40.1 (10.7)
Participants by country (n)	
Belgium	15
Bulgaria	33
France	24
Germany	153
Greece	5
Italy	98
Poland	98
Portugal	8
Romania	148
Time from first symptoms of MS, months [mean (SD)] (n=499)	78.5 (70.3)
Time from MS diagnosis, months [mean (SD)]	66.9 (67.0)
Subtype of MS [n (%)]	
Clinically isolated syndrome	18 (3.1)
Relapsing-remitting MS	500 (85.9)
Secondary progressive MS	64 (11.0)
Patients with relapses in the last 2 years [n (%)]	374 (64.3)
Relapses in the last 2 years [mean (SD)] (n=363)	1.8 (1.0)
No previous treatment for MS [n (%)] (n=579)	111 (19.2)
Previous medical treatment for MS [n (%)] (n=579)	468 (80.8)
Type of previous treatment [n (%)]a	
Extavia	327 (56.2)
Immune modulators (other than Extavia)	270 (46.4)
Monoclonal antibodies	7 (1.2)
Immunosuppressants	21 (3.6)
NSAIDs	57 (9.8)
Corticosteroids for acute relapses	270 (46.4)
Corticosteroids for other reasons	7 (1.2)
Other	23 (4.0)
Type of current treatment (at baseline visit) [n (%)]a	
Extavia	314 (54.0)
Immune modulators (other than Extavia)	39 (6.7)
Monoclonal antibodies	1 (0.2)
Immunosuppressants	3 (0.5)
NSAIDs	16 (2.7)
Corticosteroids for acute relapses	43 (7.4)
Corticosteroids for other reasons	1 (0.2)
Other	14 (2.4)
Reasons to switch to new autoinjector [n (%)]a	
To treat patient with Extavia	285 (49.0)
Availability of new autoinjector	264 (45.4)
Compliance problems	13 (2.2)
Patient not satisfied with treatment	30 (5.2)
Other reasons	24 (4.1)
Comorbidities at baseline visit (>20% frequency) [n (%)]	
Other neurologic disorder	140 (24.1)
Other inflammatory disorder	123 (21.1)
Other autoimmune disorder	122 (21.0)
Cardiovascular and/or metabolic disease	153 (26.3)
Osteoporosis	120 (20.6)

(Continued)

Table 1 (Continued)

Characteristic	n=582
Comorbidities related to MS at baseline visit (>20% frequency) [n (%)]	
Dysarthria	132 (22.7)
Sensory disorders	325 (55.8)
Ataxia	255 (43.8)
Spasticity	225 (38.7)
Nystagmus	159 (27.3)
Visual disorders	210 (36.1)
Bladder/urinary functional disorders	200 (34.4)
Cognitive dysfunction	151 (25.9)
Depression	156 (26.8)
Fatigue	281 (48.3)
Pain	164 (28.2)

Note: aMultiple response variable. Extavia® (Novartis Pharma AG, Basel, Switzerland).
Abbreviations: MS, multiple sclerosis; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.

was 66.9 (67.0) months. Most patients (374 [64.3%]) had experienced an MS relapse within the 2 years preceding the study, reporting a mean (SD) of 1.8 (1.0) relapses. Previous medical treatments for MS were reported at baseline for 468 patients (80.8%), and 111 (19.2%) patients were treatment-naïve (Table 1). A total of 314 (54.0%) patients were receiving Extavia at baseline.

Treatment compliance

For the entire study period, 548 of 568 (96.5%) patients were treatment compliant (they had received more than 80% of their prescribed injections). Respective compliance levels at 6 weeks and 12 weeks were 97.4% (553/568) and 99.1% (537/542).

Injection-related questionnaires/ rating scales

When asked to assess the practicability of the autoinjector, 93.6% (470/502) of patients considered it "easy" or "very easy" to use. The overall level of patient comfort with the autoinjector was also high (Figure 3A). Between 56% and 98% of patients agreed that the correct dose is easy to set and the device is easy to handle, that the needle is small, and they were neither afraid of it nor afraid of seeing it, that it did not take long to inject themselves, and that physician's recommendations could be followed accurately. Furthermore, no significant differences in patient comfort level were seen comparing patients who were treatment-naïve at baseline with those previously receiving treatment for MS.

Most nurses reported positive responses by patients relating to use of the autoinjector, with 59%–98% of nurses agreeing that patients prepared injections easily, quickly, and unaided, with the correct dose, felt comfortable injecting
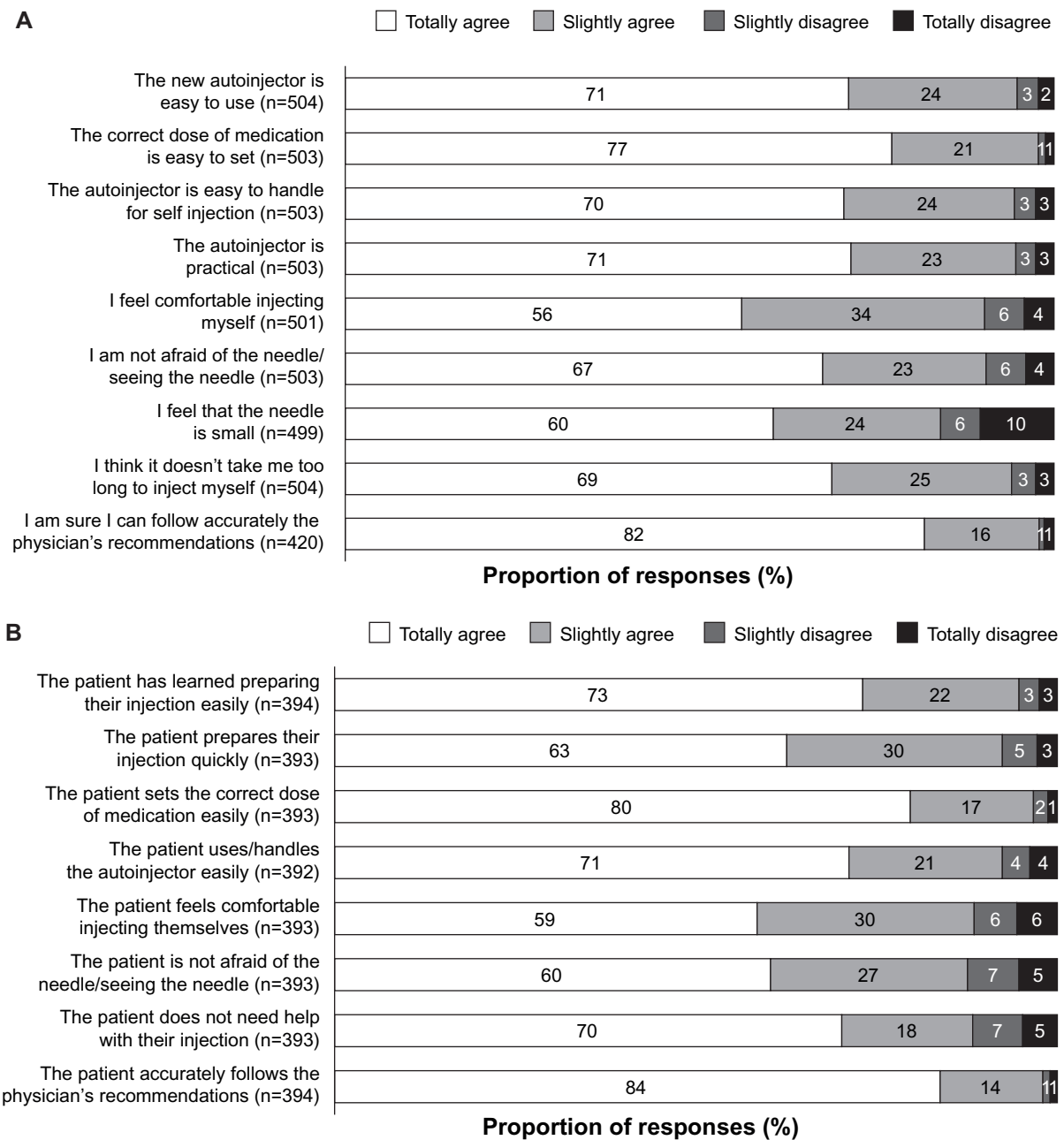
A

☐ Totally agree ▨ Slightly agree ▨ Slightly disagree ■ Totally disagree

The new autoinjector is
easy to use (n=504) — 71 | 24 | 3 2

The correct dose of medication
is easy to set (n=503) — 77 | 21 | 1 1

The autoinjector is easy to handle
for self injection (n=503) — 70 | 24 | 3 3

The autoinjector is
practical (n=503) — 71 | 23 | 3 3

I feel comfortable injecting
myself (n=501) — 56 | 34 | 6 4

I am not afraid of the needle/
seeing the needle (n=503) — 67 | 23 | 6 4

I feel that the needle
is small (n=499) — 60 | 24 | 6 10

I think it doesn't take me too
long to inject myself (n=504) — 69 | 25 | 3 3

I am sure I can follow accurately the
physician's recommendations (n=420) — 82 | 16 | 1 1

Proportion of responses (%)

B

☐ Totally agree ▨ Slightly agree ▨ Slightly disagree ■ Totally disagree

The patient has learned preparing
their injection easily (n=394) — 73 | 22 | 3 3

The patient prepares their
injection quickly (n=393) — 63 | 30 | 5 3

The patient sets the correct dose
of medication easily (n=393) — 80 | 17 | 2 1

The patient uses/handles
the autoinjector easily (n=392) — 71 | 21 | 4 4

The patient feels comfortable
injecting themselves (n=393) — 59 | 30 | 6 6

The patient is not afraid of the
needle/seeing the needle (n=393) — 60 | 27 | 7 5

The patient does not need help
with their injection (n=393) — 70 | 18 | 7 5

The patient accurately follows the
physician's recommendations (n=394) — 84 | 14 | 1 1

Proportion of responses (%)

Figure 3 Patient (**A**) and nurse (**B**) evaluations of the autoinjector.

themselves without fear of the needle, and accurately followed the physician's recommendations (Figure 3B). In agreement with patients' evaluation of using the autoinjector, no significant differences in nurses' assessments of their patients were seen when comparing patients who were treatment-naïve at baseline with those previously treated for MS.

Tolerability

In total, 227 of 582 (39%) patients experienced one or more adverse events, and 674 adverse events were recorded overall.

Most (493 [73.3%]) were mild in severity; the severity of one adverse event was not reported. General disorders and administration site reactions (597 [88.7%]) were those most frequently documented. Nine serious adverse events were reported among eight patients, the most common being MS relapse (n=4). Other serious adverse events were optic neuritis (n=2), right limb hypoesthesia, critical ischemia of the second and third fingers of the right hand, and renal failure.

Eighteen adverse events leading to treatment discontinuation occurred in 12 patients. Nine patients discontinued

treatment owing to tolerability concerns, the most common of which were fever (four events), ISP/ISRs (three events), and myalgia or pain in the limbs (three events). The reason for the remaining three discontinuations was given as "other"; these were an allergic reaction, Quincke's edema, and a rash.

During follow-up visits, at least one ISR or report of ISP was recorded by 304 of 568 patients (53.5%, Table 2), and in most of these 304 patients (185 [60.9%]), ISP/ISRs were experienced only occasionally (defined as occurring after one of three injections) and were mild in severity. Among the 568 patients who received at least one injection, 222 (39.1%) experienced erythema, 206 (36.3%) pain, 95 (16.7%) itching, 84 (14.8%) swelling, and 13 (2.3%) phlebitis. Of the 504 reported ISRs, 429 (85.1%) did not require treatment, 48 (9.5%) were treated with nonsteroidal anti-inflammatory drugs, six (1.2%) with corticosteroids, and 21 (4.2%) with other medications.

Patient satisfaction and health-related quality of life

Comparing TSQM-9 assessment scores in the whole patient population between weeks 6 and 12, there was a significant increase in score in the convenience domain (P=0.0009), and nonsignificant increases in effectiveness and global satisfaction scores (Table 3). Significant increases in convenience score during this period were also seen among patients previously receiving any treatment (P=0.0030) and among patients previously treated with Extavia (P<0.0001). Increases were seen in all other domains and subgroups between weeks 6 and 12, but were not significant.

Patient health-related quality of life, measured using the descriptive EQ-5D system (Table 4), found that, overall, the proportion reporting no problem in each of the five domains was numerically greater at week 12 than at baseline, and in four of the five domains more patients reported no more problems at week 12 than at baseline, despite a reduction in overall patient numbers. Of those patients who reported no health-related quality of life problems in each domain, a greater proportion was treatment-naïve than in those previously receiving treatment for MS. This difference was significant (P<0.01) at baseline in all domains except "anxiety/depression". At 12 weeks, the proportions of previously treated patients in all domains reporting no problems had increased from baseline, so only the domains "mobility" and "usual activities" continued to be significantly different compared with treatment-naïve patients (P<0.05).

Among patients previously receiving treatment for MS, there were no significant differences in any of the descriptive

Table 2 Summary of highest levels of injection site reactions and/or pain

Characteristic, n (%)	n=568
Reaction and/or pain at the injection site	
No	264 (46.5)
Yes	304 (53.5)
At 6 weeks only	69 (22.7)
At 12 weeks only	35 (11.5
At 6 weeks and at 12 weeks	200 (65.8)
Type of reaction and/or pain[a]	
Pain	206 (36.3)
Itching	95 (16.7)
Erythema	222 (39.1)
Swelling with inflammation	84 (14.8)
Phlebitis	13 (2.3)
Other	26 (4.6)
Frequency of reaction and/or pain, n=304	
Always (after each injection)	47 (15.5)
Often (after 2 of 3 injections)	72 (23.7)
Occasionally (after 1 of 3 injections)	185 (60.9)
Time to point of reaction and/or pain, n=304	
Immediately	130 (42.8)
After 30 minutes	65 (21.4)
After 60 minutes	31 (10.2)
>60 minutes	78 (25.7)
Use of medication for treatment of reaction and/or pain, n=504[b]	
No	429 (85.1)
Yes	75 (14.9)
Type of medication used, n=75	
NSAIDs	48 (64.0)
Corticosteroids	6 (8.0)
Other	21 (28.0)
Frequency of medication, n=75	
Always	22 (29.3)
Often	20 (26.7)
Occasionally	33 (44.0)
Highest reported injection site reaction and pain	
Itching/erythema, n=518	
None	303 (58.5)
Mild	143 (27.6)
Moderate	61 (11.8)
Severe	11 (2.1)
Redness, n=527	
None	184 (34.9)
Mild	190 (36.1)
Moderate	108 (20.5)
Severe	45 (8.5)
Swelling/inflammation, n=514	
None	328 (63.8)
Mild	107 (20.8)
Moderate	63 (12.3)
Severe	16 (3.1)
Bruising, n=517	
None	280 (54.2)
Mild	130 (25.1)
Moderate	78 (15.1)
Severe	29 (5.6)

(*Continued*)

Table 2 (*Continued*)

Characteristic, n (%)	n=568
Pain, stinging and/or burning, n=525	
None	217 (41.3)
Mild	160 (30.5)
Moderate	107 (20.4)
Severe	41 (7.8)

Notes: [a]Multiple response question; [b]number of reactions during the follow-up period.
Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

EQ-5D domains between those previously receiving Extavia and those previously receiving another therapy. Analysis of the relationship at week 12 between patient satisfaction with treatment (assessed for the three TSQM-9 domains) and health-related quality of life (assessed for the five descriptive EQ-5D domains) found that patients reporting no health-related quality of life problems awarded significantly higher scores ($P<0.0001$) in all TSQM-9 domains than those experiencing health-related quality of life problems.

There was a significant increase in mean (SD) visual analog score between baseline and 12 weeks (3.0 [15.0]; $P<0.0001$), representing an improvement in patient-reported health-related quality of life. There was no significant difference when comparing the change from baseline score at week 12 between treatment-naïve and previously treated patients, or when comparing patients previously treated with Extavia with those previously receiving a different therapy. Stratification of visual analog score by severity of ISP demonstrated that increases in ISP correlated significantly with reductions in visual analog score and therefore with health-related quality of life ($P<0.0001$). No significant changes between baseline and week 12 were seen in either of the PRIMUS assessment scales applied.

Health care utilization

Of the 568 patients who received at least one injection, 40 (7.0%) contacted an MS nurse by telephone once or more during the follow-up period. Of these individuals, ten (25.0%) called because of ISRs, eight (20.0%) because of difficulty using the autoinjector, six (15.0%) because of ISP, and 16 (40.0%) for other reasons. Visits to the MS nurse were made by 18 (3.2%) patients, of whom four (22.2%) visited because of ISRs, four (22.2%) because of ISP, two (11.1%) because of autoinjection difficulties, and eight (44.4%) for other reasons.

Physicians were contacted by telephone by nine (1.6%) patients, all for reasons other than ISRs, ISP, or difficulty using the autoinjector, and 26 (4.6%) patients visited

Table 3 Treatment Satisfaction Questionnaire for Medication-9 scores at weeks 6 and 12

	TSQM-9 score		P-value[a]
	6 weeks	12 weeks	
All patients, n=568			
Convenience	52.1 (15.6)	55.0 (16.1)	0.0009
	n=510	n=503	
Effectiveness	48.0 (18.3)	49.7 (18.6)	0.0708
	n=505	n=497	
Global satisfaction	45.9 (19.7)	47.3 (19.6)	0.4314
	n=508	n=502	
Treatment-naïve patients, n=111			
Convenience	52.7 (15.2)	55.9 (15.4)	0.1207
	n=100	n=99	
Effectiveness	49.1 (17.7)	51.1 (20.8)	0.0681
	n=98	n=96	
Global satisfaction	47.1 (18.6)	49.6 (20.4)	0.1255
	n=100	n=99	
Previously treated patients, n=468			
Convenience	52.0 (15.6)	54.8 (16.3)	0.0030
	n=409	n=404	
Effectiveness	47.6 (18.3)	49.3 (18.1)	0.1022
	n=406	n=401	
Global satisfaction	45.6 (19.9)	46.8 (19.4)	0.9185
	n=407	n=403	
Patients previously treated but not with Extavia, n=141			
Convenience	53.0 (17.3)	54.5 (20.1)	0.9141
	n=111	n=107	
Effectiveness	43.4 (19.7)	47.4 (18.9)	0.2124
	n=108	n=106	
Global satisfaction	40.1 (23.9)	42.6 (22.5)	0.6509
	n=109	n=107	
Patients previously treated with Extavia, n=327			
Convenience	51.6 (15.0)	54.9 (14.7)	<0.0001
	n=298	n=297	
Effectiveness	49.1 (17.6)	50.0 (17.7)	0.2175
	n=298	n=295	
Global satisfaction	47.6 (17.9)	48.3 (18.0)	0.8828
	n=298	n=296	

Notes: [a]Comparison of scores at 6 and 12 weeks. Data are presented as the mean (standard deviation). Extavia® (Novartis Pharma AG, Basel, Switzerland).
Abbreviation: TSQM-9, Treatment Satisfaction Questionnaire for Medication-9.

physicians for ISRs (three [11.5%]), ISP (one [3.8%]), or for other reasons (22 [84.6%]). Two patients (0.4%) visited an outpatient clinic and eight (1.4%) were hospitalized; mean hospitalization duration was 9.7 days.

Discussion

In this prospective, observational, real-world clinical study of patients with MS using the ExtaviJect 30G autoinjector for administration of interferon beta-1b, there was a high level of treatment compliance, and both patients and nurses regarded the device as quick and easy to use. Improvements in convenience scores and health-related quality of life

Table 4 Descriptive EuroQol-5 Dimension system scores at baseline and week 12

	Overall		Previously treated		Treatment-naïve		P-value[a]	
	Baseline, n (%)	12 weeks, n (%)	Baseline, n (%)	12 weeks, n (%)	Baseline, n (%)	12 weeks, n (%)	Baseline	12 weeks
Patients reporting no problems								
Mobility	314 (58.4)	324 (63.8)	232 (53.7)	251 (61.2)	82 (77.4)	73 (74.5)	<0.0001	0.0403
	n=538	n=508	n=432	n=410	n=106	n=98		
Self-care	462 (85.4)	436 (85.8)	360 (82.8)	344 (84.1)	102 (96.2)	92 (92.9)	0.0003	0.0751
	n=541	n=508	n=435	n=409	n=106	n=99		
Usual activities	325 (60.1)	329 (64.9)	246 (56.6)	255 (62.5)	79 (74.5)	74 (74.7)	0.0026	0.0441
	n=541	n=507	n=435	n=408	n=106	n=99		
Pain/discomfort	225 (41.7)	273 (53.7)	161 (37.1)	211 (51.6)	64 (60.4)	62 (62.6)	<0.0001	0.0899
	n=540	n=508	n=434	n=409	n=106	n=99		
Anxiety/depression	282 (52.1)	320 (63.0)	217 (49.9)	250 (61.1)	65 (61.3)	70 (70.7)	0.1117	0.1281
	n=541	n=508	n=435	n=409	n=106	n=99		

Note: [a]Previously treated versus treatment-naïve patients.

were recorded during the study, and relatively few patients contacted a physician or nurse, suggesting little associated burden on the health care system.

Self-injection can be uncomfortable and inconvenient for many patients; fear of needles is common, and patients can perceive injections to be one of the burdens of their disease rather than a means of managing it.[26] Autoinjectors may mitigate some of these issues by reducing the incidence of ISRs compared with manual self-injection,[14,18] potentially leading to improvements in compliance. In one study, use of an autoinjector for interferon beta-1b was the strongest predictor of therapy adherence over 2 years.[17] Treatment compliance is important because it is associated with better clinical and economic outcomes, including lower risks for MS relapse and MS-related hospitalization, and with lower MS-related medical costs.[27] In our study, more than 95% of patients were compliant overall and at each visit, a level of adherence that is even higher than that reported recently for another autoinjector (88%) in a 12-week study that used the same compliance criteria.[28]

Several studies show that administration of interferon formulations using an autoinjector can increase satisfaction and/or convenience in patients with MS.[12,13,15,29] Convenience and ease of use are recognized by patients as notable benefits of autoinjectors.[16,28] This is echoed in our study, where questionnaires completed by patients revealed that almost all found ExtaviJect 30G "easy" or "very easy" to use and, importantly, almost all agreed they felt confident that they were following their physician's recommendations. Additionally, almost all nurses in our study agreed that their patients were accurately following these recommendations. These findings of ease of use corroborate those of an earlier study[30] in which patients with MS were asked to compare the ExtaviJect 30G

autoinjector with the BetaJect® Comfort autoinjector (Bayer Schering Pharma AG). About 70% of patients said they would prefer to use the ExtaviJect 30G device, believing it to be easier to load and to handle.[30] Such considerations are very important among patients who are commonly affected by loss of manual dexterity and, as summarized in Figure 3A, more than 90% of patients agreed that the ExtaviJect 30G autoinjector was practical and easy to handle for self-injection, and that it was easy to set the correct dose.

The safety and tolerability of treatment with interferon beta-1b is long established among patients with MS.[7] Consistent with this, very few serious adverse events were recorded in our study, most of which were either disease-related (MS relapse) or may have been disease-related (optic neuritis and right limb hypoesthesia). Approximately half of patients reported ISRs or ISP of generally mild severity, and mostly requiring no treatment and not leading to discontinuation of therapy. Patients commonly experience ISRs or ISP when self-administering parenteral therapy.[8,11] About half of the patients in our 12-week study experienced ISP/ISRs during follow-up, with erythema, pain, and itching being the most common symptoms. However, this is a considerable improvement on that seen in a study that evaluated self-assessed ISP among patients receiving interferon beta-1b, where a similar proportion (51%) of patients reported ISRs, with pain, itching, or erythema after only 6 weeks.[11] Patients in the same study reported more pain-free injections when using a 29–30G needle compared with using a larger 25–27G needle,[11] and similar findings have been reported elsewhere,[12] so the needle gauge of ExtaviJect 30G may also be a factor determining this relatively low rate of ISP/ISR.

Improvements in the convenience of therapy were seen during our study, based on the TSQM-9 assessment, and

there was a general trend toward improvement in the effectiveness and general satisfaction domains of the instrument. Improvement across the study was also seen in health-related quality of life and in most of the descriptive scales of the EQ-5D assessment, with more patients reporting no problems at the end of the study than at enrollment. There may also be benefits for health care providers associated with the use of ExtaviJect 30G, given that fewer than 10% of patients contacted their physician or nurse during the study. The main reason for contacting a health care provider was an ISR or ISP, which might be expected in the context of parenteral therapy.

Our study has several limitations: treatment compliance was patient-reported, so has the potential for recall bias and therefore overestimation; a longer follow-up period may have improved the accuracy of the compliance assessment, although a period of 12 weeks has been reported elsewhere;[28] and it would have been interesting to include a TSQM-9 assessment at baseline because this may have revealed significant changes in all of the domains.

Building on these findings of the importance to patients of convenience and ease of use of autoinjectors, a new device (the ExtaviPro™ 30G, Novartis Pharma AG) is in development for subcutaneous administration of interferon beta-1b (Extavia). This new autoinjector has been ergonomically designed to sit comfortably in the hand to allow one-handed operation. It is hoped that this design could lead to improvements in convenience and support even higher rates of compliance among patients in future.

Conclusion

This prospective, observational study in a real-world setting indicates that use of the ExtaviJect 30G autoinjector to facilitate administration of interferon beta-1b (Extavia) results in a high level of compliance with therapy, accompanied by a high degree of patient satisfaction.

Acknowledgment

Disclosure

References

1. Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology*. 2006;67:1242–1249.
2. Durelli L, Verdun E, Barbero P, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). *Lancet*. 2002;359:1453–1460.
3. [No authors listed]. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. *Lancet*. 1998;352:1491–1497.
4. Panitch H, Miller A, Paty D, Weinshenker B. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology*. 2004;63:1788–1795.
5. [No authors listed]. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. *Neurology*. 1993;43:655–661.
6. Goodin DS, Ebers GC, Cutter G, et al. Cause of death in MS: long-term follow-up of a randomised cohort, 21 years after the start of the pivotal IFNbeta-1b study. *BMJ Open*. 2012;2:pii:e001972.
7. Reder AT, Ebers GC, Traboulsee A, et al. Cross-sectional study assessing long-term safety of interferon-beta-1b for relapsing-remitting MS. *Neurology*. 2010;74:1877–1885.
8. Giovannoni G, Southam E, Waubant E. Systematic review of disease-modifying therapies to assess unmet needs in multiple sclerosis: tolerability and adherence. *Mult Scler*. 2012;18:932–946.
9. Girouard N, Theoret G. Management strategies for improving the tolerability of interferons in the treatment of multiple sclerosis. *Can J Neurosci Nurs*. 2008;30:18–25.
10. Smith B, Carson S, Fu R, et al. Drug class review: Disease-modifying drugs for multiple sclerosis: Final Update 1 Report. Portland, OR: Oregon Health and Science University; 2010. Available from http://www.ncbi.nlm.nih.gov/books/NBK50570/. Accessed August 5, 2013.
11. Baum K, O'Leary C, Coret Ferrer F, et al. Comparison of injection site pain and injection site reactions in relapsing-remitting multiple sclerosis patients treated with interferon beta-1a or 1b. *Mult Scler*. 2007;13:1153–1160.
12. Jaber A, Bozzato GB, Vedrine L, et al. A novel needle for subcutaneous injection of interferon beta-1a: effect on pain in volunteers and satisfaction in patients with multiple sclerosis. *BMC Neurol*. 2008;8:38.
13. Wray S, Armstrong R, Herrman C, et al. Results from the single-use autoinjector for self-administration of subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis (MOSAIC) study. *Expert Opin Drug Deliv*. 2011;8:1543–1553.
14. Mikol D, Lopez-Bresnahan M, Taraskiewicz S, Chang P, Rangnow J. A randomized, multicentre, open-label, parallel-group trial of the tolerability of interferon beta-1a (Rebif) administered by autoinjection or manual injection in relapsing-remitting multiple sclerosis. *Mult Scler*. 2005;11:585–591.
15. Devonshire V, Arbizu T, Borre B, et al. Patient-rated suitability of a novel electronic device for self-injection of subcutaneous interferon beta-1a in relapsing multiple sclerosis: an international, single-arm, multicentre, Phase IIIb study. *BMC Neurol*. 2010;10:28.
16. Devonshire VA, Verdun di Cantogno E. Review of subcutaneous interferon beta-1a, delivered via the electronic self-injection device RebiSmart, for the treatment of multiple sclerosis. *Ther Deliv*. 2011;2: 1455–1465.
17. Pozzilli C, Schweikert B, Ecari U, Oentrich W. Supportive strategies to improve adherence to IFN beta-1b in multiple sclerosis – results of the betaPlus observational cohort study. *J Neurol Sci*. 2011;307:120–126.

18. Brochet B, Lemaire G, Beddiaf A. [Reduction of injection site reactions in multiple sclerosis (MS) patients newly started on interferon beta 1b therapy with two different devices.] *Revue Neurologique*. 2006;162:735–740. French.

19. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol*. 2005;58:840–846.

20. Harley CR, Frytak JR, Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. *Am J Manag Care*. 2003;9:S136–S143.

21. Atkinson MJ, Kumar R, Cappelleri JC, Hass SL. Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. *Value Health*. 2005;8 Suppl 1:S9–S24.

22. Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes*. 2004;2:12.

23. [No authors listed]. EuroQol – a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy*. 1990;16:199–208.

24. Doward LC, McKenna SP, Meads DM, Twiss J, Eckert BJ. The development of patient-reported outcome indices for multiple sclerosis (PRIMUS). *Mult Scler*. 2009;15:1092–1102.

25. McKenna SP, Doward LC, Twiss J, et al. International development of the patient-reported outcome indices for multiple sclerosis (PRIMUS). *Value Health*. 2010;13:946–951.

26. Cohen BA, Rieckmann P. Emerging oral therapies for multiple sclerosis. *Int J Clin Pract*. 2007;61:1922–1930.

27. Tan H, Cai Q, Agarwal S, Stephenson JJ, Kamat S. Impact of adherence to disease-modifying therapies on clinical and economic outcomes among patients with multiple sclerosis. *Adv Ther*. 2011;28:51–61.

28. Lugaresi A, Florio C, Brescia-Morra V, et al. Patient adherence to and tolerability of self-administered interferon beta-1a using an electronic autoinjection device: a multicentre, open-label, phase IV study. *BMC Neurol*. 2012;12:7.

29. Cramer JA, Cuffel BJ, Divan V, Al-Sabbagh A, Glassman M. Patient satisfaction with an injection device for multiple sclerosis treatment. *Acta Neurol Scand*. 2006;113:156–162.

30. Kozubski W. Autoinjector improves injection-related tolerability issues in patients with multiple sclerosis. Exploring the new Extaviject 30G system for the injection of interferon beta-1b. *Eur Neurol Rev*. 2010;5:77–81.