ORIGINAL RESEARCH ARTICLE



Real-World Assessment of Interferon-β-1b and Interferon-β-1a Adherence Before and After the Introduction of the BETACONNECT[®] Autoinjector: A Retrospective Cohort Study

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Abstract

Background Both interferon beta-1b (IFN- β -1b) and interferon beta-1a (IFN- β -1a) are immunomodulators that require regular subcutaneous self-administration by patients with multiple sclerosis (MS). However, no electronic autoinjector is available for IFN- β -1a in the US.

Objective This retrospective cohort study investigated adherence to two subcutaneous disease-modifying therapies, IFN-β-1b and IFN-β-1a, during two periods (before and after the introduction of the BETACONNECT[®] autoinjector for IFN-β-1b). **Patients and Methods** Data were evaluated from the MarketScan database for adults in the US with an MS diagnosis and a medical claim for subcutaneous IFN-β-1b or IFN-β-1a, either before (October 2013–September 2015) or after the introduction of BETACONNECT (October 2016–September 2018). Patient populations were propensity-score matched by demographic and clinical characteristics. Persistence was recorded, and adherence was evaluated by medication possession ratio (MPR). **Results** The study included 196 IFN-β-1b and 365 IFN-β-1a people with MS (PwMS) (pre-BETACONNECT period), and 126 IFN-β-1a PwMS (post-BETACONNECT period). In the pre-BETACONNECT period, the proportion with at least 80% MPR was higher for IFN-β-1a (90%) than for IFN-β-1b (83%), but in the post-BETACONNECT period, median persistence (in days) was higher for IFN-β-1a (199) than for IFN-β-1b (152), while in post-BETACONNECT period persistence was higher for IFN-β-1a (229).

Conclusions Following the introduction of BETACONNECT, this exploratory study suggested that PwMS taking IFN- β -1b were more adherent compared with those taking IFN- β -1a, with higher persistence, and more than 90% reached 80% MPR, a threshold commonly used to define good adherence.

1 Introduction

Multiple sclerosis (MS) is a chronic, debilitating immunemediated condition, with complex underlying pathological processes affecting the central nervous system, typically

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requiring lifelong therapy [1, 2]. MS is considered to be incurable, and so therapies focus on management of disease symptoms, prevention of relapses, and slowing MS disease progression [2, 3]. Disease-modifying therapies (DMTs) such as immunomodulators can also change patients' underlying pathological immune responses, becoming first-line therapies for relapsing forms of MS [2, 4, 5]. Since their introduction, DMTs have resulted in significant improvements in patient outcomes and quality of life, preventing relapses, and slowing down the progression of MS [1]. Poor adherence to a DMT regimen is a major factor that may prevent the optimal management of MS. Lack of adherence can have serious consequences, such as increased risk of relapses, and can increase medical costs [6, 7]. Although maintaining adherence can be an issue for most chronic conditions, for people with MS (PwMS) adherence may

Key Points

Maintaining adherence is challenging for chronic conditions such as multiple sclerosis. For disease-modifying therapies requiring regular subcutaneous self-administration, autoinjector devices offer a safe, simple, modifiable, and reliable method of self-administration that may help overcome injection-related factors interfering with comfort and treatment adherence.

Single-arm trials and patient surveys have indicated that autoinjectors are helpful for treatment and improve adherence; however, real-world evidence on this topic is lacking.

In the current real-world study, we find that following the introduction of BETACONNECT[®], an autoinjector for interferon- β -1b, adherence to interferon- β -1b indexed by medication possession ratio, and persistence, were higher than for interferon- β -1a, another therapy requiring regular subcutaneous self-administration without an autoinjector.

be particularly challenging owing to the physical and psychological symptoms that characterize this disease, such as poor motor skills, fatigue, depression, or cognitive deficits [1]. Many DMTs for relapsing-remitting multiple sclerosis (RRMS) require regular subcutaneous self-administration, and patients may become tired of injecting or find selfinjections challenging because of loss of fine motor skills or if they experience forgetfulness along with MS disease progression [1]. As such, there have been efforts to improve subcutaneous self-administration of DMTs by developing autoinjectors, which have become increasingly sophisticated, and widely preferred by PwMS to their previous self-injection method [8, 9]. In part, this may be because the attributes of modern electronic autoinjectors can fulfil the desires of PwMS for easier and more comfortable subcutaneous selfadministration and reduce the incidence of injection-site reactions [1]. This may result in greater patient satisfaction and thus potentially increase medication adherence [9, 10].

The BETACONNECT[®] device is an electronic autoinjector for the injection of interferon beta-1b (IFN- β -1b; Betaseron[®]/Betaferon[®]), a DMT approved for use in patients with RRMS. It is fully electronic, with an ergonomic design to allow one-handed injection, with fully adjustable speed and depth of injection, optical and audible signals of injection completion, and dose reminder function [10]. The BETACONNECT also features a four-phase injection technology, comprising (i) automatic needle insertion; (ii) delivery of the medication; (iii) dwell time, when the needle remains in the skin momentarily, reducing the risk of an injection-site reaction; and (iv) automatic needle retraction [10]. Patient surveys of BETACONNECT have indicated that PwMS find the device helpful for their treatment, with high levels of satisfaction [9–11]. In addition, singlearm, prospective, observational cohort studies in Germany (BETAEVAL, ClinicalTrials.gov identifier NCT02121444) [12] and the United States (US) (BETAEVAL Global, NCT02247310) [13] demonstrated high levels of adherence among patients with RRMS treated with IFN-β-1b using BETACONNECT, with >80% injecting at least 80% of their prescribed doses throughout the whole 24-week study periods. However, owing to the lack of comparator groups and these relatively short study times, it is unclear what effect the introduction of the BETACONNECT device might have on patient adherence, particularly over longer periods.

The aim of the current study was to describe adherence rates in PwMS taking IFN-β-1b and a comparator, interferon beta-1a (IFN-β-1a; Rebif[®]), in the periods before and after the introduction of BETACONNECT. IFN-B-1a was chosen as a comparator to IFN-\beta-1b as both are immunomodulators in the interferon family used to treat RRMS and both require regular subcutaneous self-administration. However, no electronic autoinjector is currently available for IFN-β-1a in the US (though the RebiSmart electronic autoinjector for the delivery of IFN-β-1a is available in some other parts of the world). As such, it seems likely that differences in adherence between IFN-β-1b and IFN- β -1a in the period following the introduction of the BETA-CONNECT device could be driven by the introduction of BETACONNECT electronic autoinjector. Persistence was measured, and adherence was quantified using the indirect measurement method of medication possession ratio (MPR) for PwMS taking IFN-β-1b or IFN-β-1a in the period before the introduction of the BETACONNECT device and in the period following the introduction and uptake of BETACONNECT. The MPR refers to the period of time in which a patient had a recorded supply of the prescribed therapy in relation to the dispensing period of time, between treatment onset and discontinuation or the end of the study. Persistence refers to the continuity of therapy over the entire recommended treatment period. MPR and persistence have been investigated previously in retrospective and prospective cohort studies of adherence to DMTs in patients with RRMS [13–15].

No formal hypothesis testing of adherence was conducted as the current study was exploratory in nature. STROBE criteria (Strengthening the Reporting of Observational Studies in Epidemiology) for observational cohort studies [16] were followed in the reporting of this study.

2.1 Study Design, Setting, and Participants

This was a retrospective cohort study of adult PwMS (≥ 18 years of age) who received at least one prescription for subcutaneous IFN- β -1b or IFN- β -1a, using data from the US healthcare claims research database, IBM MarketScan. To be evaluated, patients must have had a recorded diagnosis of MS and a medical claim for IFN-β-1b or IFN-β-1a, either before the introduction of BETACONNECT (October 2013-September 2015) or after the approval and uptake of BETACONNECT (October 2016-September 2018). The BETACONNECT device was approved in the US in late 2015 and introduced to the US market in the final quarter of 2015. Based on available Bayer AG internal device distribution data, it is estimated that by September 2016, > 50% of IFN- β -1b users had received the BETACONNECT device. To allow for the implementation and uptake of the BETACONNECT device, the period from October 1, 2015 to August 31, 2016 was excluded from the analysis.

Four cohorts were defined: (i) PwMS taking IFN- β -1b over the 2 years before the introduction of BETACON-NECT; (ii) PwMS taking IFN- β -1a over the 2 years before the introduction of BETACONNECT; (iii) PwMS taking IFN- β -1b over the 2 years after the introduction and uptake of BETACONNECT; and (iv) PwMS taking IFN- β -1a over the 2 years after the introduction and uptake of BETACONNECT.

Participants must also have had at least one confirmed diagnosis of MS in the year before their first IFN- β -1a or IFN- β -1b prescription during the above time periods. Additional inclusion criteria were for PwMS to have a minimum of 1 year free of their respective DMT before the index date (date of first IFN- β -1b or IFN- β -1a prescription during the aforementioned periods), requiring continuous enrollment in IBM MarketScan during this time. Exclusion criteria were PwMS with any incomplete or implausible IFN- β -1b or IFN- β -1a claim during the index period (e.g., days of supply values missing or a value for days of supply that was ≤ 0), and only data from the first entry was used in the analysis for those who met the entry criteria more than once within the same time period.

2.2 Data Sources

IBM MarketScan was the data source for this study. The IBM MarketScan databases capture longitudinal, individuallevel administrative claims data from the US, and encompass the commercial claims and encounters (CCAE) and the Medicare supplemental and coordination of benefits (MDCR) databases. Patients in these databases are active employees, dependents, retirees, Consolidated Omnibus Budget Reconciliation Act (COBRA) recipients, and Medicare or Medicaid enrollees. Data are drawn from large employers, health plans, and public organizations in the US. At the time of analysis, data were available from January 1, 2002 to September 30, 2018, representing approximately 200 million patients.

2.3 Key Variables and Outcomes

Demographic and clinical information for each of the four cohorts, including age, sex, and comorbidity burden, was described for the study participants. Adherence rates were captured using the indirect measurement methods of MPR. A variable rather than a fixed MPR was calculated, and for this we used the time between the index date and the last fill of the relevant DMT (IFN-β-1b or IFN-β-1a) prescription before switching, discontinuation or end of data (end of study period or end of enrollment). In PwMS that discontinued or switched and restarted therapy, the date of the last fill of IFN-β-1b or IFN-β-1a before the first switch or long treatment gap was used. Thus, the MPR was calculated as the number of doses dispensed (sum of all the days' supply of IFN-β-1b or IFN-β-1a except last fill) divided by the dispensing period of time (number of days between the index date and the last fill date). The proportion of PwMS that discontinued after the first prescription of IFN-β-1b or IFN-β-1a was also reported, as in these cases MPR could not be defined. The proportion of PwMS with at least 80% MPR was reported, as the majority of studies investigating medication adherence use a threshold of 80% MPR to denote good adherence [17]. Persistence was defined as the continuity of DMT therapy, calculated as the number of days from starting a DMT to the occurrence of a first gap of >1.5 times the days of medication supply (minimum 30 days) from the previous prescription in the medication profile (discontinuation of DMT), or a switch to another DMT. National drug codes (NDCs) were used to define RRMS DMTs.

The Charlson/Deyo comorbidity index (CCI) was used to measure the comorbidity burden. The CCI is a weighted score derived from the sum of the scores for the following 17 comorbid conditions: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease—rheumatic disease, peptic ulcer disease, mild liver disease, diabetes without complications, diabetes with complications, paraplegia and hemiplegia, renal disease, cancer, moderate or severe liver disease, metastatic carcinoma, and AIDS/HIV [18–21]. A score of zero indicates that no comorbidities were found, and the higher the score, the higher the likelihood of death or higher resource use. International classification of disease (ICD) codes were used to define comorbidities and other conditions that may also influence adherence, such as depression and pregnancy.

2.4 Statistical Methods

Statistical analyses were exploratory only. The primary aim of the study was to estimate adherence separately in the four cohorts of PwMS: (i) IFN- β -1b/pre-BETACON-NECT period, (ii) IFN- β -1a/pre-BETACONNECT period, (iii) IFN- β -1b/post-BETACONNECT period, and (iv) IFN- β -1a/post-BETACONNECT period. The study did not aim to confirm or reject pre-defined hypotheses, and statistical analyses were of a descriptive nature. No formal statistical comparisons were conducted between DMTs (IFN- β -1a vs IFN- β -1b) or across the two time intervals (pre-BETACON-NECT vs post-BETACONNECT). All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and/or R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Population characteristics such as baseline demographics (i.e., age, sex) and clinical characteristics (i.e., depression) that may affect adherence and persistence as well as the CCI (and the 17 contributing comorbid conditions) were analyzed descriptively using the following statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e., mean, standard deviation, minimum, median, quartiles, and maximum). Measures of adherence and persistence were described for the cohorts of interest but no formal hypothesis testing was conducted.

It is possible that variables that influenced adherence and persistence could have varied systematically between different populations, leading to confounded estimates. Thus, within each time period, patient populations were propensity-score (PS) matched on demographic and clinical characteristics, as well as assessment time. The PS can be defined as a patient's probability of receiving IFN- β -1b given a set of known patient baseline characteristics. PS was calculated blinded to outcome by using multiple logistic regression on the following set of patient characteristics: age (numeric), sex (categorical), CCI score (numeric), depression (categorical), and index date quarter (categorical). For PS matching, the R package MatchIt was used (Comprehensive R Archive Network [CRAN]), performing a 1:2 'greedy nearest neighbor' matching with a caliper of 0.1. MatchIt implements the suggestions of Ho and colleagues for improving parametric statistical models, using a wide range of sophisticated matching methods to enable the selection of well-matched subsets [22]. Matched groups were considered as sufficiently balanced if the standardized mean difference was < 0.2. The final sample was 1:2 matched IFN-β-1b:IFN-β-1a.

In order to describe persistence in PwMS taking IFN- β -1a and IFN- β -1b over time, Kaplan–Meier estimates and Kaplan–Meier plots were used. The Efron method was used to handle ties in the survival analysis. Parameter estimates and 95% confidence intervals (CIs) of persistence were presented. MPR was described using descriptive statistics (mean, standard deviation [SD]), as well as categories (< 80%, \geq 80%). However, no *p* values were presented owing to a lack of interpretability.

Further details on the statistical methodology used are shown in the accompanying electronic supplementary material [ESM] 1.

3 Results

3.1 Baseline Demographic and Clinical Characteristics

Before matching, 199 IFN- β -1b and 598 IFN- β -1a PwMS were identified in the pre-BETACONNECT period, and 136 IFN- β -1b and 283 IFN- β -1a PwMS were identified in the post-BETACONNECT period. After 1:2 PS matching on key demographic and clinical variables, the final sample consisted of 196 IFN- β -1b and 365 IFN- β -1a PwMS in the pre-BETACONNECT period, and 126 IFN- β -1b and 223 IFN- β -1a PwMS in the post-BETACONNECT period, and 126 IFN- β -1b and 223 IFN- β -1a PwMS in the post-BETACONNECT period. Baseline demographic and clinical characteristics of the matched population are shown in Table 1 (see ESM 2 for baseline demographic and clinical characteristics of unmatched populations). PS-matched populations are presented in the remainder of the results.

3.2 Medication possession ratio (MPR)

MPR results are shown in Table 2 for all PS-matched PwMS with an MPR > 0%. In the pre-BETACONNECT period, this corresponded to 148 IFN- β -1b and 294 IFN- β -1a PwMS, and 106 IFN- β -1b and 191 IFN- β -1a PwMS in the post-BETACONNECT period. In the pre-BETA-CONNECT period, the proportion of PwMS with an MPR of at least 80% taking IFN- β -1b was 83% (95% CI 76–88) compared with 90% (95% CI 87–93) taking IFN- β -1a. This situation was reversed in the post-BETACON-NECT period: the proportion of PwMS with an MPR of at least 80% taking IFN- β -1b during this time was 92% (95% CI 85–95) compared with 86% (95% CI 81–91) taking IFN- β -1a. ESM 3 shows these results for unmatched populations. **Table 1** Baseline demographic and clinical characteristics for interferon- β -1b and interferon- β -1a patients in the pre- and post-BETACONNECT periods

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CCI Charlson Comorbidity Index, Q quarter

^aBefore the introduction of BETACONNECT (October 2013-September 2015)

^bAfter the approval/uptake of BETACONNECT (October 2016–September 2018)

^cBased on claims in the pre-index period (12 months before index date)

3.3 Persistence

Results for persistence in groups taking IFN- β -1a and IFN- β -1b over time are shown using Kaplan–Meier plots for the pre- and post-BETACONNECT periods (Figs. 1 and 2, respectively). ESM 4 and ESM 5 show these results for unmatched populations. Kaplan–Meier parameter estimates and 95% CIs of persistence are presented in Table 3. ESM 6 shows these results for unmatched populations.

4 Discussion

The aim of the study was to explore adherence to subcutaneous IFN- β -1b in the time periods before and after the introduction of the BETACONNECT device. We found that following the introduction of BETACONNECT, PwMS using IFN- β -1b showed numerically greater adherence and persistence to their regimen than PwMS taking another subcutaneous DMT (IFN- β -1a) that also requires regular

Table 2 Medication possession ratio (MPR) for interferon- β -1b or interferon- β -1a patients in the pre- and post-BETACONNECT periods

Parameter	Pre-BETACONNECT period ^a		Post-BETACONNECT period ^b	
	Interferon- β -1b ($n = 148$) ^c	Interferon- β -1a ($n = 294$) ^c	Interferon- β -1b ($n = 106$) ^c	Interferon- β -1a ($n = 191$) ^c
MPR, mean (SD)	0.92 (0.13)	0.94 (0.11)	0.93 (0.10)	0.94 (0.11)
MPR $\geq 80\%$, (<i>n</i>); % (95% CI)	$n = 123 \ (83\%) \ [76-88\%]$	$n = 266 \ (90\%) \ [87-93\%]$	$n = 97 \; (92\%) \; [85 - 95\%]$	n = 165 (86%) [81-91%]

CI confidence interval, MPR medication possession ratio, SD standard deviation

^aBefore the introduction of BETACONNECT (October 2013-September 2015)

^bAfter the approval/uptake of BETACONNECT (October 2016–September 2018)

^cNumber of patients with an MPR greater than 0%

subcutaneous self-administration (though without an electronic autoinjector), with > 90% exceeding the 80% MPR threshold that is used commonly to define good adherence. Adherence is defined by the World Health Organization (WHO) as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [23]. Although there is no 'gold standard' criterion by which to measure adherence [23], in the current study adherence was measured by MPR, in line with previous retrospective and prospective cohort studies of adherence to DMTs in patients with RRMS [13–15].

One limitation of the current study is that, whilst NDC codes were used to define IFN- β -1b and IFN- β -1a use, there

are no specific codes available to specifically identify PwMS using a BETACONNECT device in the IBM MarketScan database. As such, it is unknown how many of the PwMS prescribed IFN- β -1b in the post-BETACONNECT period were also actively using the BETACONNECT device. Thus, the effect of the BETACONNECT device on adherence may be underestimated. Notwithstanding this caveat, the adherence rates obtained in the current study compare favorably with those found in the literature, where discontinuation rates of > 50% within the first year have also been reported for DMTs in PwMS [14]. One more point to consider is that this study was conducted in the US, where no electronic autoinjector is currently available for the self-administration of subcutaneous IFN- β -1a. Availability of medical devices



Fig. 1 Kaplan–Meier plot for the pre-BETACONNECT period (before the introduction of the BETACONNECT device: October 2013–September 2015) for patients taking interferon- β -1b or interferon- β -1a



Fig. 2 Kaplan–Meier plot for the post-BETACONNECT period (after the introduction of the BETACONNECT device: October 2016–September 2018) for patients taking interferon- β -1b or interferon- β -1a

Parameter	Pre-BETACONNECT period ^a		Post-BETACONNECT period ^b	
	Interferon-β-1b	Interferon-β-1a	Interferon-β-1b	Interferon-β-1a
Persistence, % (95% CI) at				
180 days	48 (41–56)	53 (48–59)	66 (58–75)	57 (50-64)
360 days	28 (21-37)	38 (32–44)	45 (37–56)	36 (29-43)
540 days	17 (11–27)	24 (19–31)	37 (28–48)	22 (15-31)
Median persistence, days (95% CI)	152 (105–231)	199 (167–235)	327 (244-440)	229 (184–304)

CI confidence interval

^aBefore the introduction of BETACONNECT (October 2013–September 2015)

^bAfter the approval/uptake of BETACONNECT (October 2016–September 2018)

can differ from country to country, so it may not be appropriate to extrapolate the study results to some other geographical locations. Another potential limitation of this study to consider is whether the IBM MarketScan database was fully representative of the commercially insured or national US populations, as it is a convenience sample [24]. People without employer-based health insurance, either for themselves or their family members, may be underrepresented. In addition, though IBM MarketScan has good geographical coverage, proportionally more participants tend to reside in

Table 3 Persistence in taking interferon- β -1b or interferon- β -1a during the pre- and post-BETACONNECT periods

the Southern US states than accounted for in the general US population [24, 25]. Despite some potential limitations regarding the representativeness, the MarketScan database provides a reliable source of real-world data and has previously been used in published epidemiological analyses of incidence and prevalence [26, 27], safety [28], adherence [29], and healthcare utilization [24, 25]. Over 900 peerreviewed publications have incorporated MarketScan data, and the use of these data has increased greatly in the last decade [30].

5 Conclusion

Following the introduction of BETACONNECT, PwMS taking IFN- β -1b were more adherent compared with those taking IFN- β -1a requiring regular subcutaneous self-administration without an autoinjector, with higher persistence, and with > 90% of PwMS meeting at least 80% MPR, a threshold commonly used to define good adherence. For DMTs requiring regular subcutaneous self-administration, electronic autoinjector devices may offer a method of self-administration that can help improve treatment adherence. The current results may be informative for clinicians and healthcare professionals, who may consider such autoinjector devices when seeking to improve adherence to DMTs in PwMS.

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Declarations

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Conflicts of interest All authors are employees of Bayer AG.

Ethics approval This was a retrospective non-interventional study and all data collected were anonymized to preserve participant anonymity and confidentiality. Since this study is based on anonymized patient data, additional informed consent or institutional review board/ethical approval was not needed.

Consent to participate Since this study is based on anonymized patient data, additional informed consent or institutional review board/ethical approval was not needed.

Availability of data and material The raw data used for this analysis are not publicly available owing to the proprietorial nature of the data.

Code availability Not applicable.

Author contributions All authors contributed to the study conception and design, data collection, and analysis. All authors also participated in the interpretation of the results and contributed to the development of the manuscript. All authors read and approved the final manuscript.

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