The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis

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Background: Most disease-modifying therapies (DMTs) for multiple sclerosis (MS) are self-injectable medications that must be taken on an ongoing basis to reduce disease activity. Thus, adherence to therapy becomes an important challenge that must be addressed to maximize benefits of therapy. This study evaluated rates of adherence to prescribed treatment and explored factors affecting adherence amongst patients with relapsing-remitting MS.

Methods: This was an observational, multicenter, multinational, phase 4 study. Patients and physicians received paper questionnaires regarding adherence to DMTs approved at the time of the study, including intramuscular interferon beta-1a (IFNβ-1a), subcutaneous IFNβ-1a, IFNβ-1b, and glatiramer acetate. Quality of life and cognition data also were collected. Multivariate analysis was conducted to identify factors associated with adherence to long-term DMTs.

Results: Two thousand six hundred and forty-eight patients were studied, revealing an average treatment duration of 31 months. Seventy-five percent of patients ($n = 1923$) were adherent to therapy. The most common reasons for non-adherence were forgetting to administer the injection (50.2%) and other injection-related reasons (32.0%). Adherent patients reported better quality of life ($P < 0.05$) and fewer neuropsychological issues ($P < 0.001$) than non-adherent patients. Adherent patients had significantly shorter duration of disease ($P < 0.001$) and shorter duration of therapy ($P = 0.005$) than non-adherent patients. Women were more likely than men to adhere to treatment.

Conclusion: Identifying factors that affect adherence to prescribed treatments is the first step in improving adherence of patients with MS to therapy, thereby helping maximize the benefits of long-term DMTs.

Introduction

Adherence to therapy, defined by the World Health Organization (WHO) as the extent to which a person's behavior corresponds with agreed recommendations from a healthcare provider, is crucial for patients to obtain the full benefits of their treatment [1]. Patients with multiple sclerosis (MS) may be on therapy for decades and are likely to face challenges to their adherence at some point during the course of their treatment.

Disease-modifying therapies (DMTs) for MS, including intramuscular (i.m.) interferon beta-1a (IFNβ-1a) (Avonex®; Biogen Idec, Inc., Cambridge, MA, USA) and subcutaneous (s.c.) interferon IFNβ-1a (Rebif®; EMD Serono, Inc., Rockland, MA, USA); IFNβ-1b (Betaferon®/Betaseron®; Bayer Schering Pharma,

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Berlin, Germany); and glatiramer acetate (GA) (Copaxone®; Teva Neuroscience, Inc., Kansas City, MO, USA) represent the current mainstay of MS treatment. As DMTs are chronic therapies for MS, adherence is an important challenge that must be addressed to maximize benefits of therapy. Most studies that have evaluated adherence to therapy in patients with MS have focused on discontinuation of treatment. In community settings, reported discontinuation rates have ranged from 14% to 47% over 2–8 years or more [2–16]. However, patients may not always follow their prescribed treatment protocol.

Only a small number of studies have evaluated rates of adherence to prescribed treatment protocols or continuity of treatment in clinical practice [17,18]. The goals of this study were to evaluate rates of adherence to prescribed DMTs and to explore factors affecting adherence amongst patients with relapsing-remitting MS. In addition, this study evaluated quality of life and levels of cognition and depression in adherent and non-adherent patients.

Methods

Study design

This was an observational, multicenter, multinational, phase 4 study consisting of paper-based physician and patient questionnaires on adherence to therapy as well as a validated MS International Quality of Life (MusiQoL) questionnaire. In addition, patients in English-speaking countries were administered a brief neuropsychological questionnaire to assess cognition, the MS Neuropsychological Screening Questionnaire (MSNQ), which was only validated in English at the time of the study.

Patients were included in the study if they were at least 18 years of age at the time of enrollment, had a documented diagnosis of relapsing-remitting MS, and were on monotherapy with their current DMT for at least 6 months before enrollment. Patients were excluded from the study if they had progressive MS, were unable to complete any study component, had been involved in clinical or investigational drug studies within 6 months of enrollment, or had undergone treatment with immunosuppressive drugs or intravenous immunoglobulin in the last 12 months. DMTs used in this study were those that were commercially available at the time of the study: i.m. IFNβ-1a, s.c. IFNβ-1a, IFNβ-1b, and GA. Dosages were per country-specific requirements.

All participating investigators obtained local institutional review board/independent ethics committee approval before initiation of the study, and all patients provided written informed consent prior to enrollment.

Physician and patient questionnaires

At study initiation, participating physicians completed a practice-related questionnaire that collected information on site-specific details and patient treatment and management details concerning infrastructure, role of nurses, treatment paradigms, and education about MS, treatments, and factors that may affect adherence.

On each patient questionnaire, physicians or nurses completed the first 10 questions, covering issues including disease duration, degree of impairment, treatment and relapse history, and past and current therapy. Patients completed the remaining questions privately, covering demographics, current disease status, treatment, social support structure, education on MS and DMTs, views on medical management, adherence to current treatment, reasons for treatment lapses, views on their current DMT, and complications. Patients also completed the MusiQoL questionnaire if available in their country's language. The MusiQoL measures the presence and severity of MS symptoms and patient perception of disease and treatment [19]. In addition, patients in English-speaking countries filled out the MSNQ, which is a sensitive (0.83) and specific (0.97) predictor of neuropsychological impairment used to analyze the degree of a patient's cognitive impairment and depression [20].

Pre-specified analyses

The primary objective was to compare adherence rates across DMTs. Adherence was defined in this study as not missing a single DMT injection within 4 weeks before the study. Secondary objectives were to determine which factors were most influential on adherence, to compare MusiQoL and MSNQ data between adherent and non-adherent groups, to compare MusiQoL and MSNQ data amongst DMTs, and to compare practice-based factors on the physicians' questionnaire between adherent and non-adherent groups.

Statistical methods

Data were univariately analyzed to evaluate effects of various demographic, disease history, quality of life, and neuropsychological impairment factors on adherence. All analyses were conducted using two-sided tests with an α level of 0.05. Dichotomous and categorical data were analyzed using a chi-square test, normally distributed data were analyzed using an analysis of variance model, and non-normal data were analyzed using the Wilcoxon rank sum test. Analyses

of MusiQoL and MSNQ were also adjusted for demographic and baseline disease characteristics using an analysis of covariance (ANCOVA) and rank-based ANCOVA, respectively. Factors with an unadjusted association with adherence ($P \leq 0.10$) were considered for the multivariate analysis. Two complementary analyses – stepwise regression and all possible regressions – were performed to evaluate the effects of demographic characteristics, disease history, therapy factors, quality of life parameters, and neuropsychological impairment on treatment adherence. The results of both analyses were combined to identify variables associated with adherence. The following variables were selected for multivariate analysis: type of DMT, gender, education, frequency of visits to neurologist, satisfaction with therapy, duration of disease, treatment site, sources of support, ease of injection, and timing of discussions with neurologist about adherence.

Results

Patients

Two thousand six hundred and forty-eight patients were enrolled at 173 sites across 22 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Iran, Ireland, Israel, Italy, Mexico, the Netherlands, Portugal, Spain, Sweden, Switzerland, the United Kingdom, and Venezuela). Data were analyzed for 2566 of these patients. The remaining 82 patients had missing or conflicting adherence data, missing data on their current DMT, current DMT treatment of fewer than 6 months in duration, or age < 18 years and were therefore excluded from data analyses. Seven hundred and sixty-four (29.8%) patients received i.m. IFNβ-1a, 245 (9.5%) received s.c. IFNβ-1a 22 μg, 511 (19.9%) received s.c. IFNβ-1a 44 μg, 571 (22.3%) received IFNβ-1b, and 475 (18.5%) received GA. Patients were well matched by DMT; however, because of the observational nature of this cross-sectional study, some differences were seen in disease and treatment duration and on Patient-Determined Disease Steps (PDDS) [21], a reproducible measurement tool designed to clearly differentiate the functional stages of MS. The PDDS scale comprises seven different disease steps: 0 = normal; 1 = mild disability; 2 = moderate disability; 3 = intermittent use of a cane; 4 = cane-dependent; 5 = bilateral support; 6 = wheelchair confinement; U = unclassifiable [21]. Seventy-three percent of the patients studied were woman, with a median disease duration of 6 years and a median time on their current DMT of 31 months (Table 1).

Adherence rate

Overall, 75% of patients (n = 1923) were adherent to their prescribed treatment regimens (Fig. 1). The rate of adherence, defined as not missing a single dose, was significantly higher for patients receiving i.m. IFNβ-1a (applied 4 times per 4 weeks) than for patients receiving all other DMTs ($P < 0.01$). Patients treated with s.c. IFNβ-1a 22 μg (12 times per 4 weeks) were significantly more adherent than those treated with IFNβ-1b (14 times per 4 weeks) or GA (28 times per 4 weeks) ($P < 0.02$), and patients treated with s.c. IFNβ-1a 44 μg (12 times per 4 weeks) were significantly more adherent than patients treated with GA ($P = 0.023$). Patients receiving i.m. IFNβ-1a missed significantly fewer injections (0.2) in the preceding 4 weeks than patients receiving all other DMTs (s.c. IFNβ-1a 22 μg = 0.4; s.c. IFNβ-1a 44 μg = 0.6; IFNβ-1b = 0.6; GA = 1.1; all $P < 0.001$).

Reasons for non-adherence

The most common reason for non-adherence was forgetting to administer the injection, cited by 50.2% of non-adherent patients (Table 2). Injection-related reasons for non-adherence, including being tired of taking injections, pain at injection site, injection anxiety, skin reaction, did not feel need for every injection, and no one available to administer injection were reported by 32.0% of non-adherent patients. Additional non–injection-related reasons for non-adherence, reported by at least 10% of non-adherent patients, included fatigue, flu-like symptoms, headache, and other reasons.

Reasons for non-adherence varied across DMTs. Flu-like symptoms were the most common reason for non-adherence cited by patients on i.m. IFNβ-1a (28.9%), whilst flu-like symptoms were cited less often amongst patients treated with other DMTs (Table 2). Patients on s.c. IFNβ-1a 22 μg (67.3%), s.c. IFNβ-1a 44 μg (49.6%), IFNβ-1b (57.5%), and GA (57.8%) most commonly cited 'forgot to administer' as their reason for non-adherence. Injection-related reasons were more commonly cited by patients treated with s.c. IFNβ-1a 44 μg (38.1%) than patients in the other treatment groups. Other reasons were similar across treatment groups.

Adherence rate by disease and treatment duration

Both disease duration and treatment duration were determined to be univariate factors significantly associated with adherence. Adherent patients (n = 1913) had MS for a significantly shorter period of time (median 6.0 years) than non-adherent patients

Table 1 Patient characteristics

	Overall (N = 2566)	i.m. IFNβ-1a (n = 764)	s.c. IFNβ-1a 22 μg (n = 245)	s.c. IFNβ-1a 44 μg (n = 511)	IFNβ-1b (n = 571)	GA (n = 475)
Age, year, mean (SD)	39.7 (10.1)	39.6 (10.7)	39.7 (9.6)	38.8 (9.9)	40.5 (10.3)[a]	39.9 (9.2)
% Female	73.1	76.1[b]	70.6	70.6	70.1	75.6[c]
Relapses within last year, % of patients						
0	59.7	60.9	64.1	56.4[d]	57.5	61.6
1	26.5	27.4	25.3	27.0	27.6	24.1
≥2	13.8	11.7	10.6	16.7	15.0	14.4
PDDS, mean[e] (SD)	1.6 (1.6)	1.3 (1.6)	1.2 (1.4)	1.7 (1.6)[f]	1.8 (1.7)[g]	1.5 (1.6)[h]
Median disease duration, year (range)	6.0 (0–56)	6.0 (0–38)	6.0 (0–28)	6.0 (0–36)	7.0 (1–56)[i]	6.0 (1–30)[j]
Median time on current DMT, mos (range)	31.0 (6–192)	28.0 (6–192)	39.5 (6–126)[k]	30.0 (6–141)	36.0 (6–192)[l]	27.0 (6–156)

DMT, disease-modifying therapy; GA, glatiramer acetate; IFNβ, interferon beta; i.m., intramuscular; PDDS, Patient-Determined Disease Steps; s.c., subcutaneous; SD, standard deviation. [a]P = 0.008 vs. s.c. IFNβ-1a 44 μg; [b]P = 0.027 vs. s.c. IFNβ-1a 44 μg; P = 0.014 vs. IFNβ-1b; [c]P = 0.049 vs. IFNβ-1b; [d]P = 0.042 vs. i.m. IFNβ-1a; [e]Means of 1.2 to 1.8 represent mild to moderate disability; [f]P < 0.0001 vs. i.m. IFNβ-1a and s.c. IFNβ-1a 22 μg; P = 0.032 vs. GA; [g]P < 0.0001 vs. i.m. IFNβ-1a and s.c. IFNβ-1a 22 μg; P = 0.005 vs. GA; [h]P = 0.013 vs. i.m. IFNβ-1a; P = 0.006 vs. s.c. IFNβ-1a 22 μg; [i]P < 0.001 vs. i.m. IFNβ-1a and s.c. IFNβ-1a 44 μg; [j]P = 0.011 vs. i.m. IFNβ-1a; P = 0.006 vs. s.c. IFNβ-1a 44 μg; [k]$P \leq 0.001$ vs. i.m. IFNβ-1a, s.c. IFNβ-1a 44 μg, and GA; [l]P < 0.0001 vs. i.m. IFNβ-1a, s.c. IFNβ-1a 44 μg, and GA.

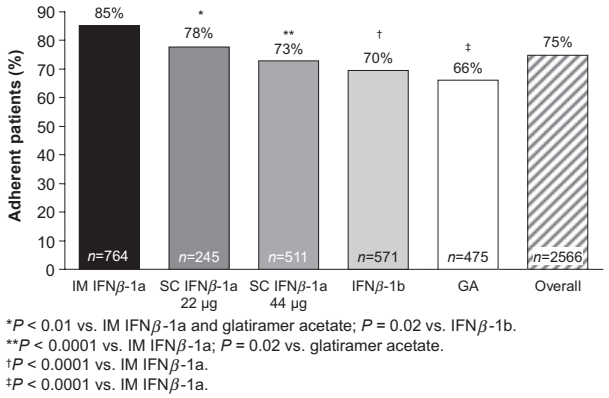

Figure 1 Overall adherence rate by disease-modifying therapy. i.m., intramuscular; IFNβ, interferon beta; GA, glatiramer acetate; s.c., subcutaneous.

(n = 640; median 7.0 years; P < 0.001); similarly, adherent patients were on their current DMT for a significantly shorter period of time (n = 1912; median 30.0 months) than non-adherent patients (n = 638; median 36.0 months; P = 0.005). Differences in adherence rates amongst DMTs were similar regardless of patients' disease duration and treatment duration, and no significant differences were found in the relationship between PDDS and adherence between adherent and non-adherent patients (data not shown).

Physician questionnaires

Physician estimates of adherence closely approximated the rates obtained by the patient questionnaire (75%). There were apparent trends but no significant differences between adherent and non-adherent patients in some aspects of the physicians' questionnaire. In particular, more adherent patients attended a dedicated MS center or clinic than private practice (P = 0.056) and were more likely to attend lower-volume than higher-volume practices (P = 0.057). Physicians of adherent patients reported spending slightly more time at diagnosis than physicians of non-adherent patients (P = 0.054), and nursing consultation was slightly more available to adherent than non-adherent patients (P = 0.057). More adherent than non-adherent patients were seen by physicians who often discuss adherence at treatment initiation (P = 0.005).

Multivariate analysis

A total of 15 variables significantly associated with adherence were entered into the multiple logistic regression model. Variables were grouped by demographic features, disease/therapy, and treatment/support features (Table 3). Women were more likely than men to adhere to treatment (P = 0.0572). Patients who earned advanced degrees were less likely to be adherent than were those who did not attend college or finish their degree (P = 0.0202). The duration of MS was related to treatment adherence, with a more protracted course predicting a lower likelihood of adherence (P = 0.0022). The choice of DMT also predicted treatment adherence. Other therapy-related factors that were independently associated with adherence were ease of injection (P = 0.0020) and overall patient satisfaction with therapy (P = 0.0007). Furthermore, patients who were treated at a dedicated MS center (P = 0.0066) were more likely to adhere to treatment. The odds of adherence increased by approximately 50% for patients whose neurologists discussed the

Table 2 Reasons for non-adherence: comparison across DMTs

Reason, % of patients[a]	Overall (N = 643)	i.m. IFNβ-1a (n = 114)	s.c. IFNβ-1a 22 μg (n = 55)	s.c. IFNβ-1a 44 μg (n = 139)	IFNβ-1b (n = 174)	GA (n = 161)
Forgot to administer	50.2	21.1	67.3	49.6	57.5	57.8
Tired of taking injections	20.4	16.7	21.8	23.7	19.0	21.1
Other	17.3	26.3	9.1	15.8	14.9	17.4
Fatigue	14.5	14.5	12.2	16.1	11.2	14.5
Flu-like symptoms	12.9	28.9	7.3	16.5	10.9	2.5
Pain at injection site	11.7	5.3	10.9	16.5	10.3	13.7
Headache	10.3	19.3	7.3	15.1	8.0	3.1
Inconvenient/difficult dosing schedule	9.5	10.5	7.3	10.1	10.3	8.1
Injection anxiety	9.5	14.0	12.7	9.4	4.6	10.6
Skin reaction	9.2	2.6	14.5	12.2	6.9	11.8
Weakness	7.5	14.0	3.6	7.2	6.9	5.0
Depression	5.8	7.0	3.6	10.1	4.0	3.7
Did not pick up medicine	4.5	7.0	3.6	4.3	2.9	5.0
Did not feel need for every injection	3.9	5.3	5.5	6.5	0.6	3.7
Nobody available to administer	3.4	4.4	0.0	4.3	2.3	4.3
Financial reasons	2.3	5.3	1.8	0.7	0.6	3.7
Not confident in treatment benefits	2.0	1.8	3.6	1.4	0.0	4.3
Pregnancy/planning for pregnancy	1.2	1.8	3.6	0.7	0.0	1.9
Summary of injection-related reasons[b]	32.0	33.3	30.9	38.1	25.9	32.9

DMT, disease-modifying therapy; GA, glatiramer acetate; i.m., intramuscular; IFNβ, interferon beta; s.c., subcutaneous. [a]Includes only non-adherent patients; patients may have cited more than one reason; [b]includes the following reasons: tired of taking injections, pain at injection site, injection anxiety, skin reaction, did not feel need for every injection, and no one available to administer. When counting injection-related reasons for non-adherence, each patient was counted only once.

importance of following treatment plans at the time treatment was initiated (P = 0.0057). In contrast, the likelihood of adherence was lower for patients who saw their neurologist less than once a year (P = 0.0047) and for patients whose neurologists waited to discuss adherence at follow-up visits (P = 0.0106). Excellent support from a spouse or partner was another variable that was independently associated with increased treatment adherence (P = 0.0157).

MS Quality of Life scale

Adherent patients reported having a better quality of life, with higher scores on average than non-adherent patients on all nine dimensions of the MusiQoL. In particular, adherent patients had significantly higher mean scores for physical well-being (P < 0.0001), symptoms (P = 0.0021), relationship with family (P < 0.0001), relationship with healthcare system (P = 0.0008), sentimental and sexual life dimensions (P = 0.0068), and activities of daily living (P = 0.0021) than non-adherent patients. Amongst all patients, significant differences amongst DMTs occurred in two dimensions of the MusiQoL: symptoms and relationship with friends. In symptoms, patients treated with GA scored significantly lower compared with patients treated with i.m. IFNβ-1a (P = 0.025), s.c. IFNβ-1a 22 μg (P = 0.022), and s.c. IFNβ-1a 44 μg (P = 0.013).

MS Neuropsychological Screening Questionnaire

Adherent patients (n = 301) had less neuropsychological impairment, with a significantly lower (i.e., better) median total MSNQ score (18.0) than non-adherent patients (n = 175; median = 22.0; P < 0.0001). Adherent patients had significantly lower scores on 14 of 15 questions on the MSNQ. There were no significant differences amongst DMTs overall or on any of the questions of the MSNQ.

Discussion

The goal of this study was to evaluate the degree to which patients comply with dosing schedules outlined by their neurologists.Therefore, for the purposes of this study, adherence was defined as not missing an injection within the 4-week period evaluated. Dosing schedules for the individual medications vary (from weekly dosing for i.m. IFNβ-1a to daily injections for GA). Therefore, the impact of missed doses on efficacy was not addressed in this study and is not known for this cohort.

Discontinuation of therapy has been shown to be more likely to occur early after initiation, within the first 6 months to 2 years [9,10,16], with the first 6 months reported to be the most critical [10]. This is possibly because of the side effects decreasing in intensity within the first 3 months after initiating therapy [22]. We therefore chose to focus on patients who had

Table 3 Independent predictors of adherence to long-term disease-modifying therapy in MS: results of a multivariate analysis

Variables	Odds ratio	95% CI	*P* Value
Demographics			
Gender, female	1.25	0.99, 1.56	0.0572
Completion of university education	0.77	0.62, 0.96	0.0202
Disease/therapy			
Disease duration	0.97	0.96, 0.99	0.0022
i.m. IFNβ-1a versus			
s.c. IFNβ-1a 22 μg	0.42	0.28, 0.64	< 0.0001
s.c. IFNβ-1a 44 μg	0.40	0.29, 0.55	< 0.0001
s.c. IFNβ-1b	0.38	0.27, 0.51	< 0.0001
s.c. glatiramer acetate	0.30	0.22, 0.41	< 0.0001
Ease of injection	1.47	1.15, 1.87	0.0020
Satisfaction with treatment	1.54	1.20, 1.98	0.0007
Treatment/support			
Treated at MS center	1.36	1.09, 1.71	0.0066
≤1 neurologist visit/year	0.66	0.50, 0.88	0.0047
Neurologist discussed adherence at treatment initiation	1.54	1.14, 2.10	0.0057
Neurologist discussed adherence at follow-up	0.68	0.50, 0.91	0.0106
Excellent family support	1.33	1.06, 1.67	0.0157

CI, confidence interval; i.m., intramuscular; IFNβ, interferon beta; MS, multiple sclerosis; s.c., subcutaneous.

been on therapy a minimum of 6 months, which allowed the opportunity to evaluate adherence in patients who continued on therapy past this critical period.

Most patients in this study took their DMT as prescribed, with 75% not missing an injection in the preceding 4 weeks. The level of disease activity was low, with most patients reporting no relapses in the previous year and only mild disability. As such, 25% of patients being non-adherent in a patient cohort with a mean exposure to their current DMT of 31 months is surprisingly high. This rate clearly underlines the need to address the issue of adherence frequently in the patient–physician interaction and independent of treatment duration.

Forgetting to administer the injection was the most common reason for non-adherence, cited by 50.2% of patients. Patients following a once-weekly protocol were more likely to adhere to treatment than patients following a once-daily protocol, and in general, adherence rates declined with increasing frequency of injection. Forgetting to administer injections may be related to complexity of treatment regimens, lower cognitive function or other neuropsychological problems in non-adherent patients. Neuropsychological problems, which may include cognitive difficulties or depression, were more common amongst non-adherent patients in this study than amongst adherent patients, although differences were not significant amongst DMT groups. Cognitive dysfunction is a common symptom of MS, found in 43–60% of patients [23,24]. Depression is also a common symptom of MS, and treatment of depression increases the likelihood of patients remaining on therapy [3,25]. Thus, treatment of neuropsychological factors may enhance adherence to therapy.

Injection-related reasons as a whole were the next most frequently cited reason for non-adherence (> 30%), despite a mean treatment duration of more than 2 years. This suggests that injection-related issues (e.g., anxiety because of fear of injection, injection-site pain, adverse skin reactions) do not diminish over time and eventually may have a substantial impact on patient motivation.

Adherent patients reported better quality of life than non-adherent patients. Patients have been shown to be more likely to remain on DMTs when they were seen at practices that were rated as more empathetic, with less formal relationships between healthcare practitioners and patients and more attention to patients' concerns and emotional states [5].

In addition, several factors independently related to increased adherence, included female gender, ease of administration, satisfaction with therapy, treatment at a dedicated MS center, and excellent family support. The type of therapy also was independently associated with improved adherence. These findings support the need to study the benefits of an individualized approach to improving treatment adherence that includes such components as patient education, realistic expectations about treatment efficacy, and improved communication between patients, family members, and the physician.

Discontinuation of DMTs has been shown to be significantly influenced by disease- and treatment-related factors such as adverse effects, efficacy, disability level, and prior treatments as well as by more internally driven factors such as self-efficacy, perceived pros and cons of treatment, therapeutic expectations, perceived support of healthcare practitioners, depression, and education level [2–6,8–12,14–16,18,26,27]. In the present study, adherent patients had shorter disease and treatment durations compared with non-adherent patients. However, amongst patients who continue with therapy, longer disease and/or treatment duration may increase risk of non-adherence to treatment protocols, simply by chance or by increased risk of encountering adherence-limiting factors such as decreases in quality of life or neurocognitive function. Stopping therapy has been shown to be more likely to occur early in therapy, within the first 6 months to 2 years [9,10,16]. Therefore, patients who continue on therapy over the long term may develop coping mechanisms to accommodate

factors that might otherwise decrease adherence, whilst patients who are unable to tolerate their therapy, experience worsening disease, or are otherwise unable to cope with their treatment regimen may be more likely to discontinue.

The patients in this study were a highly selective cohort, with a mean treatment duration of 31 months. As a result, the outcomes of this study may not represent issues affecting adherence amongst patients earlier in the course of their treatment. In addition, it is possible that patients with higher rates of non-adherence over the short time frame of this study may show a pattern of chronic non-adherence that may only be detected in a study with a longer duration. Nonetheless, within these constraints, this 4-week study provides insight into the common problems that influence adherence to treatment. Long-term studies may be useful to determine the influence of these common problems on adherence over longer time frames as well as to determine the effects of differing rates of adherence on clinical and MRI outcomes of therapy.

This study represents a retrospective evaluation of the adherence rate in patients with MS. Therefore, we decided to look at a pre-defined time frame of 4 weeks, which appeared reasonable to be remembered by patients with respect to their routine of drug administration. Furthermore, the definition of adherence in this study is rather rigid; however, given the short study interval of 4 weeks, we aimed to investigate a stringent criterion. Therefore, missing a single dose was considered the best definition. Given the large differences in the frequency of administration between all DMTs studied, it is perhaps not surprising that the injection of a drug given every day might be missed more frequently compared with other DMTs with a lower frequency of administration. However, it remains speculative to judge the impact of missing a single dose of GA versus a single dose of i.m. or s.c. IFNβ-1a, for example, within 4 weeks of treatment.

In summary, we believe that this is the largest study of adherence in patients with MS reported to date and one of the first to focus specifically on adherence to treatment protocols over time. The present findings confirm that treatment adherence is a relevant issue in MS and that factors related to therapy should be taken into consideration when choosing a therapy to facilitate adherence. The results of this study suggest that adherence to therapy may be enhanced by addressing common issues such as adverse events, complexity of treatment regimens, and cognitive factors. Discerning and addressing factors that increase the likelihood of patients remaining on therapy and adhering to treatment protocols may maximize the benefits they obtain from that therapy.

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Disclosure of conflict of interest

Dr Devonshire has received consulting fees from Bayer, Biogen Idec, Serono, and Teva Neuroscience. Dr Lapierre has served on advisory boards for Bayer, Biogen Idec, and Teva Neuroscience. Prof Macdonell has served on advisory boards for Biogen Idec, Novartis, Sanofi-Aventis, and Merck-Serono. Dr Ramo-Tello has received consulting fees from Bayer and Biogen Idec. Dr Patti has no significant relationships to disclose regarding the current study; however, he has received honoraria from Bayer-Schering, Dompè Biotec, Merck-Serono, and Sanofi-Aventis. Dr Fontoura has received speaking honoraria, grants, and travel support from Bayer-Schering, Biogen Idec, Merck-Serono, and Sanofi-Aventis; Dr Fontoura is currently an employee of F. Hoffmann-La Roche. Dr Suchet has received research support and speaker fees for meetings from Biogen Idec. Dr Hyde is an employee of Biogen Idec International GmbH. Mr Balla was an employee of Biogen Idec International GmbH at the time the study was conducted. Dr Kieseier has received honoraria for lecturing, travel expenses for attending meetings, and financial support for research from Bayer Health Care, Biogen Idec, Merck-Serono, Novartis, Sanofi-Aventis, and Teva Neuroscience. Dr Frohman has served on speakers bureaus for Biogen Idec, Serono, and Teva Neuroscience.

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Appendix

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