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Adherence to Disease-Modifying Therapies in Spanish Patients with Relapsing Multiple Sclerosis: Two-Year Interim Results of the Global Adherence Project

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Introduction

Multiple sclerosis (MS) is a chronic and debilitating disease that can partly be controlled with long-term use of disease-modifying therapy (DMT). The DMTs on the market on initiation of the Global Adherence Project (GAP) were intramuscular (IM) interferon-β (IFNβ)-1a (Avonex®), subcutaneous (SC) IFNβ-1a 22 μg (Rebif®-22), SC IFNβ-1a 44 μg (Rebif® 44), IFNβ-1b (Betaferon®), and glatiramer acetate (Copaxone®). The WHO defines treatment adherence as compliance (that is, taking the medication according to the prescribed dosing regimen) and persistence with dosing (taking the medication throughout the entire indicated treatment period), and affirms that lack of adherence contributes to reduced efficacy in the treatment of chronic diseases [1]. Between 19 and 39% of patients with MS stop treatment with IFNβ within 3 years [2, 3]. Moreover, it has been reported that between 10 and 20% of patients who stop treatment do so in the first 6 months [3, 4].

In clinical trials, the patients undergo close follow-up and regular examinations and are encouraged to continue treatment, while the healthcare professionals are monitored by the sponsor. In observational studies, in contrast, monitoring of adherence is variable and may be influenced by several factors to which patients in clinical
trials are not exposed, thus allowing a more faithful evaluation of clinical practice [5–7].

Patients are often wary of starting DMT because of the side effects and chronic administration regimens with frequent injections [6]. It has been observed that DMT might not be effective in those patients with a poor level of adherence in the long term [2]. According to different authors, the main factors that contribute to whether the patient is adherent are related to perceived lack of efficacy, lack of information or too complex information, false hopes of improvement in the disease, problems administering treatment (such as fear of needles or self-injections) and sociocultural factors [8, 9].

Few studies have compared adherence among DMTs currently available for MS [6, 10]. The international GAP study, an observational, multicenter, phase IV, post-marketing, retrospective, cross-sectional study, included 2,648 patients with relapsing-remitting MS (RRMS) in 22 countries [5]. A global adherence rate of 75% was found, with forgetting to inject the factor that most contributed to lack of adherence (50.2%).

In Spain and Portugal, a 5-year follow-up study is being conducted to assess long-term adherence and the factors that influence adherence in patients who were previously enrolled in the GAP study [5]. In this article, we report the results of the first 2 years of the study in Spain.

**Patients and Methods**

This is an observational, multicenter, phase IV, post-marketing, retrospective, cross-sectional study of patients with RRMS who attend annual visits for 5 years. The secondary objectives in Spain included assessment of patient satisfaction and physician satisfaction with the new presentation of IM IFN-β-1a and the health-related quality of life – these data will be published separately.

Non-adherence was defined as missing an injection or dose modification in the 4 weeks prior to completing the survey. The patients signed an informed consent both at the start of the study and for follow-up, and the ethics committees approved the initial study in 18 centers and the follow-up study in 15.

The study included adult patients with RRMS in treatment for at least 6 months prior to inclusion in the study with one of the DMTs available at the start of the study (in accordance with the prescribing information and the judgment of the MS Assessment Committee in each Spanish autonomous region, if applicable).

Each center aimed to include the same number of patients in each of the treatment groups. For each treatment group, it was planned to include at least 3 patients and at most 6. The maximum number of patients included per center was therefore 30. Patients were included consecutively as they attended their regular follow-up appointment and gave their consent to participate in the study.

The questionnaire data were compared with the medical records by monitoring visits conducted by an independent company. Patients and neurologists filled out the questionnaires independently and without any interaction in a single annual visit. The Neurologist Questionnaire comprised 13 questions that included information on details of the place of work (infrastructure, roles of nurses and/or other professions involved), questions on the information provided to the patients about treatment (mechanism of action, adverse reactions, administration method) and questions about the relevance of adherence and factors that might influence it. The patient questionnaire collected information on the point of view of the patients about the care received (healthcare staff involved, value of the different visits and education that was given during these visits), personal view of the current MS therapy and its complications, adherence to drugs for treating MS in the last 4 weeks and sources of support that might influence patient adherence. In each patient questionnaire, the healthcare worker completed the first 10 questions about disease duration, degree of disability, treatment, and history of relapses and treatment.

**Statistical Analysis**

A descriptive analysis was undertaken, along with a correlation analysis of the variables or factors that influence adherence. Continuous data were described using appropriate statistics: mean and standard deviation, or median and range. Possible group differences were analyzed by means of a parametric test (ANOVA) and a non-parametric one (Kruskal-Wallis test); categorical data were presented by frequency distribution and percentage for each group of DMT.

Adherence rates were estimated and compared between IM IFN-β-1a and the other DMTs. The analyses were done using two-tailed tests with a type-I error (α-type error) of 0.05.

Frequencies and percentages for ‘good treatment adherence’ versus ‘lack of treatment adherence’ variable were analyzed, and possible differences between treatment environments were investigated using the χ² test or the Fisher exact test.

Factors potentially related to treatment adherence were analyzed using a log-rank test. The dependent variable (adherence) was analyzed according to treatment satisfaction, effectiveness of current treatment, ease of treatment administration, treatment tolerability, effect on delaying disease progression and improvement in MS symptoms, in addition to sociodemographic variables.

**Results**

The Spanish part of the GAP study included 254 patients at the baseline visit, 142 after 1 year of follow-up (visit 1) and 131 after 2 years of follow-up (visit 2). The baseline demographic characteristics are presented in Table 1. Significant differences were only found in the glatiramer-acetate-treated group (lower mean age, shorter treatment duration and shorter disease duration), in the SC IFN-β-1a 44-μg-treated group (shorter treatment duration) and the IFN-β-1b-treated group (greater disease dura-
prescribing information and the judgment of the MS Assessment at least 6 months prior to inclusion in the study with one of the modification in the 4 weeks prior to completing the survey. The rately.

health-related quality of life – these data will be published separately.

might not be effective in those patients with a poor level of injection adherence [6]. It has been observed that DMT treatment is not exposed, thus allowing a more faithful eval-
tion). The median time on current therapy was 28.0 months and the median disease duration was 2.3 years (table 1).

### Patient Questionnaire

#### Adherence Rate

The overall adherence rate was 85.4% at baseline and 82.4% after 2 years (fig. 1). At the baseline visit, after almost 3 years on treatment, patients receiving IM IFNβ-1a were significantly more adherent (96.4%) than those receiving SC IFNβ-1a 22 μg (79.1%; p = 0.0064), SC IFNβ-1a 44 μg (79.6%; p = 0.0064) and glatiramer acetate (82.7%; p = 0.0184) (fig. 2). The reasons for lack of adherence at baseline are summarized in table 2. The overall adherence rate at visit 1 was 86.6% and patients receiving IM IFNβ-1a were significantly more adherent than those receiving SC IFNβ-1a 22 μg (93.9 vs. 66.7%; p = 0.0251). At visit 2, the overall adherence rate was 82.4%; this was greater for IM IFNβ-1a (87.5%) versus the remaining DMTs (SC IFNβ-1a 22 μg: 80%; SC IFNβ-1a 44 μg (77.8%); IFNβ-1b (85.2%) and glatiramer acetate (80%). After 2 years, 30.3% of all patients continued with the same treatment as at baseline; 43% continued with IM IFNβ-1a, a significantly higher percentage (p = 0.0103) than with the other DMTs (fig. 3).

### Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>IM IFNβ-1a (n = 56)</th>
<th>IFNβ-1a 22 μg (n = 43)</th>
<th>IFNβ-1a 44 μg (n = 54)</th>
<th>IFNβ-1b (n = 49)</th>
<th>GA (n = 529)</th>
<th>Overall (n = 254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD, years</td>
<td>38.8 ± 10.1</td>
<td>37.2 ± 9.0</td>
<td>38.4 ± 10.6</td>
<td>40.1 ± 11.0</td>
<td>35.1 ± 8.2a</td>
<td>37.9 ± 9.9</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>78.2</td>
<td>62.8</td>
<td>68.5</td>
<td>67.3</td>
<td>73.1</td>
<td>70.4</td>
</tr>
<tr>
<td>Mean number of relapses in prior year, % patients</td>
<td>0.0</td>
<td>0.0</td>
<td>5.4</td>
<td>0.0</td>
<td>0.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Median (range)</td>
<td>Current treatment duration</td>
<td>40.5 (6–108)</td>
<td>40.0 (6–120)</td>
<td>24.0 (6–60)b</td>
<td>45.0 (6–124)</td>
<td>15.0 (6–42)c</td>
</tr>
<tr>
<td>Disease duration</td>
<td>8.0 (1–33)</td>
<td>7.0 (1–17)</td>
<td>5.0 (1–34)</td>
<td>7.0 (1–37)d</td>
<td>6.0 (1–16)e</td>
<td>6.0 (0–37)</td>
</tr>
</tbody>
</table>

GA = Glatiramer acetate; IFN = interferon; IM = intramuscular.

#### Table 2. Reasons for lack of adherence at baseline: treatment comparison

<table>
<thead>
<tr>
<th>Reason, % patients</th>
<th>IM IFNβ-1a (n = 56)</th>
<th>IFNβ-1a 22 μg (n = 43)</th>
<th>IFNβ-1a 44 μg (n = 54)</th>
<th>IFNβ-1b (n = 49)</th>
<th>GA (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forgotten</td>
<td>0</td>
<td>16.3</td>
<td>11.1</td>
<td>12.2</td>
<td>13.5</td>
</tr>
<tr>
<td>Injection-related reasons</td>
<td>3.6</td>
<td>4.7</td>
<td>7.4</td>
<td>4.1</td>
<td>11.6</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Weakness</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>0</td>
<td>1.9</td>
<td>2.0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Medication not collected</td>
<td>0</td>
<td>0</td>
<td>3.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Did not feel the need to inject</td>
<td>0</td>
<td>2.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No help for administration</td>
<td>1.8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not confident about the treatment benefits</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.9</td>
</tr>
</tbody>
</table>

GA = Glatiramer acetate; IFN = interferon; IM = intramuscular.
**Fig. 1.** Overall adherence rate at baseline and visits 1 and 2.

**Fig. 2.** Adherence rates by treatment at baseline and visits 1 and 2. GA = Glatiramer acetate; IM = intramuscular; IFN = interferon. \( ^a \) \( p = 0.0064 \) vs. IM IFN\( \beta \)-1a; \( ^b \) \( p = 0.0251 \) vs. IM IFN\( \beta \)-1a; \( ^c \) \( p = 0.0064 \) vs. IM IFN\( \beta \)-1a; \( ^d \) \( p = 0.0184 \) vs. IM IFN\( \beta \)-1a.

**Fig. 3.** Percentage of patients who continued with the same treatment at 2 years. \( ^a \) \( p = 0.0103 \) versus other treatments (abbreviations as in fig. 2).
Factors Related to Lack of Adherence

Treatment-Related Factors. At baseline, the most common reason cited for lack of adherence was forgetting to inject (70.3%), followed by injection-related reactions (43.2%) which encompassed the following aspects: tired of self-injection, skin reactions, needle phobia, injection-site pain, not feeling the need to inject and nobody available to administer the injections. At years 1 and 2, the most common reason for lack of adherence was injection-related factors (89.5 and 72%, respectively), followed by forgetting to dose (42.1 and 32%, respectively). After 2 years of treatment, among the injection-related reasons, being tired of injecting (28%) stands out.

Fig. 4. Considerations highlighted by the patients at visit 2.
The considerations with the highest score for the patients at 2 years when the MS treatment is chosen, on a scale of 0–5 were: medication delays disease progression (4.61), medication reduces relapses (4.5), how the medication works (4.3) and the independence afforded by the treatment (4.1) (fig. 4).

Factors Related to the Healthcare Provider. The neurologists and nurses of adherent patients saw the patients more often and more regularly both at the baseline visit (89.1 and 25.7%) and at 2 years (99 and 31%), respectively.

Treatment decisions on the type of DMT that the patient was to receive was an activity shared between the neurologist and the patient; however, at the start of the study, the neurologists’ decision had greater weight (in 13% of the cases, the patient did not take any decision about treatment), whereas in the second year, the decision was shared equally.

Sociocultural Factors. At the baseline visit, 36% of the patients worked full-time and 16% were retired or receiving assistance for MS. At 2 years, 32.2% of the patients were working full-time and 16% were retired or receiving assistance for MS at the baseline visit. Most patients were living with their spouse/partner or family (parents or children) both at the baseline visit and at 2 years.

The main sources of patient support at the start and after 2 years of the study were, respectively: family (87 and 85.8%), spouse/partner (84.8 and 83.6%), physician

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**Fig. 5.** Considerations highlighted by the neurologist at visit 2 (abbreviations as in fig. 2).
Among the support staff for the neurologist in clinical practice at the baseline visit and at 2 years, of note were the nurses (83.3 and 85.7%), neuropsychologist (44.4 and 71.4%), the physiotherapeutist (27.8 and 50.0%), and the collaborating physician (50.0 and 42.9%).

### Discussion

The international GAP study [5] is being extended in Spain for 5 years, and an interim analysis has been performed at 2 years. At 2 years, an inflexion point in adherence was observed, with a decrease across all treatments. The adherence rate has remained high among all DMTs for the first 2 years of the study, and was significantly higher with IM IFNβ-1a compared to other DMTs after a median of more than 3 years of treatment. The number of patients who continued with the same treatment after 2 years was significantly higher with IM IFNβ-1a versus the other DMTs.

The results of the baseline visit of the GAP study in Spain are consistent with the results from the international study [5], with an overall adherence rate more than 10% higher (75% in the international GAP study [5] vs. 85.4% in the Spanish GAP study). The distribution of the adherence rates in all treatments is also greater in the Spanish GAP study. At the baseline visit, among factors inherent to the medication, forgetting to inject was the most common in both studies. Differences were found between the healthcare-provider-related and sociocultural factors. At the baseline visit, unlike the international GAP study [5], no significant differences were found regarding sex and level of education of the patients. The involvement of the nurse in the follow-up of the patients showed no changes between the baseline visit and visit 2, remaining steady at 12% (table 3). In contrast, after 2 years, an increase in multidisciplinary follow-up of the patients in the form of incorporation of neuropsychologists and physiotherapeutists was detected compared to the baseline visit. In view of the decrease in overall adherence rate at visit 2, it might be necessary to review the role of nursing staff in follow-up. Of note is the neurologists’ perception of adherence, which is almost 3 points lower than the real patient adherence. This perceived adherence is only higher in the case of IM IFNβ-1a and SC IFNβ-1a 44 μg, suggesting that the neurologists overestimate real adherence in their patients with these treatments and dedicate them less time. After 2 years of follow-up, the partner, family members and religious beliefs continue to play an important role.

### Table 3. Time dedicated to the consultation with an MS patient at baseline and visits 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis of the disease</th>
<th>Start of treatment</th>
<th>Routine follow-up visits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurologist</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline visit</td>
<td>49.17%</td>
<td>35.83%</td>
<td>21.67%</td>
</tr>
<tr>
<td>Visit 2</td>
<td>50.71%</td>
<td>35.36%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Nurse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline visit</td>
<td>30.59%</td>
<td>49.12%</td>
<td>12.85%</td>
</tr>
<tr>
<td>Visit 2</td>
<td>12.65%</td>
<td>30.71%</td>
<td>12.14%</td>
</tr>
</tbody>
</table>

and nurse (80.6 and 77.4%), friends (69.6 and 69.2%), other healthcare workers (50.2 and 54.8%), and religious beliefs (49.4 and 48.4%).

**Neurologist Questionnaire**

**Adherence Rate**

The estimated overall adherence according to the neurologist at baseline and visit 2 was 87.3 and 79.7% (SC IFNβ-1a: 93.9 and 90.9%; SC IFNβ-1a 22 μg: 88.5 and 81.7%; SC IFNβ-1a 44 μg: 85.0 and 80.0%; IFNβ-1b: 82.8 and 75.4%, and glatiramer acetate: 86.5 and 71.1%, respectively).

**Factors Related to Lack of Adherence**

**Treatment-Related Factors.** After 2 years of treatment, among the reasons related to lack of adherence, the neurologists highlighted the development of new relapses (66.8%) (fig. 5).

For the neurologist, the 5 attributes that were most important for discussing with the patient when offering treatment for MS at the baseline visit and visit 2 were effectiveness at preventing relapses (94.4 and 92.9%, respectively) and disease progression (77.8 and 92.9%, respectively), factors related to adverse effects of treatment (88.9 and 92.9%, respectively), frequency of administration (44.4 and 42.9%, respectively), administration skill (44.4 and 50.0%, respectively) and disease activity according to magnetic resonance imaging (44.4 and 42.9%, respectively).

**Factors Related to the Healthcare Provider.** At the baseline visit and visit 2, the time dedicated by the neurologist to diagnosis of the disease, starting treatment, and routine follow-up visits was similar, whereas the nurse dedicated more time to the patients at the baseline visit compared to follow-up visits (table 3).

Two-Year Adherence to MS Therapy: The GAP Study

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One of the limitations of this study is the way adherence is measured. Observational studies usually have to rely on measures susceptible to bias such as patient recall of missed doses in the past 4 weeks, as is the case in the present study. Given that patients with MS can experience progressive cognitive decline [11], recall could be influenced by memory decline. In English-speaking countries of the international GAP study [5], the MS Neuropsychological Screening Questionnaire was administered to patients; unfortunately, these data were not available in our subpopulation. It is not clear how a decline in cognitive function would affect recall of adherence, that is, whether patients with cognitive decline are more likely to overestimate or underestimate adherence. We do note, however, a greater apparent difference in the neurologist’s assessment of adherence (87.3% at baseline vs. 79.7% after 2 years) as compared to the patient assessment (85.4 vs. 82.4%). Cognitive decline may also have a direct influence on adherence [12].

Another of the limitations of this study is the loss to follow-up (48.4%) either due to personal decision of the neurologist (in 1 center) or due to the decision of the centers themselves (in 2 centers). This resulted in a loss of statistical power making a β-type error possible. The groups were fairly homogeneous at baseline. Certain significant differences were only found in the glatiramer acetate group, the SC IFNβ-1a 44 μg group and the IFNβ-1b group. These differences can be explained by the shorter time on the market of glatiramer acetate and SC IFNβ-1a 44 μg, and the longer time on the market in the case of IFNβ-1b. However, at the different visits, adjustments between groups were not made for baseline values, essentially because of the obvious decrease in sample size. Other factors that might complicate analysis of the study include the lack of randomization, differences in treatment duration and withdrawals or changes in treatment, which are typical occurrences in observational studies.

The present study has shown that the therapeutic option may directly affect adherence of an MS patient to DMT.

The most common reasons for lack of adherence were forgotten doses and injection-related factors, with such factors predominating during follow-up (particularly getting tired of injection), probably due to the treatment duration and chronic nature of the disease.

Frequency of drug administration, side effects of the medication and the patients’ perception of treatment efficacy were treatment-related factors found to affect lack of adherence. These factors should be considered when making therapeutic choices. Healthcare staff should deal with these factors that influence adherence, maintaining fluid dialogue with the patient and monitoring aspects related to the safety of the drug. Although these are dynamic factors, if they are managed effectively, there would be greater emphasis on patient education and long-term adherence would be enhanced.

The results of the Spanish GAP study, along with the studies conducted until present [6, 10], confirm the need to be aware of the importance of adherence to MS therapy with DMTs. The use of questionnaires enabled assessment of the views of the neurologists and patients on factors that may influence adherence. This shows that in general, adherence in Spain is higher than in other countries and remains high after 2 years of follow-up, remaining above the international baseline level despite a decrease of 3%.

Follow-up of the GAP study in Spain has enabled us to verify the importance of certain health and sociocultural factors described previously, as well as aspects of quality of life and patient and neurologist satisfaction, which will be published separately. In Spain, of particular note is the support of the partner, family and healthcare staff (neurologist, nursing staff) as factors that have a positive influence on treatment adherence. After 2 years of follow-up, multidisciplinary staff such as neuropsychologists and physiotherapists played an increasing role in the care of patients with MS. Neurologists were also found to remain involved in patient follow-up. We believe that these factors contribute positively to the high adherence to DMTs seen in this country. The positive correlation of IM IFNβ-1a with adherence is due, we believe, to the lower frequency of injection compared to other DMTs. We wish to highlight that in 2 years of follow-up, forgetting to inject went from being the principal reason for poor adherence to second place (after injection-related factors), with a 38.3% decrease. We therefore believe that the greater awareness among healthcare staff and patients in the study is having a positive effect on remembering to inject the medication.

To date, as far as we are aware, this is the only observational study of adherence to DMTs that is being conducted in MS patients in Spain. Observational studies with long-term follow-up have the added value of being able to compare the results of clinical trials with daily clinical practice and analyze aspects relating to effectiveness, which are not studied in clinical trials. This has prompted us to draw up adherence questionnaires which will be published separately. We consider it necessary to develop tools that help healthcare staff assess adherence to DMTs in order to anticipate any problems that patients might have with specific therapeutic regimens and DMTs in general. This would help optimize the outcomes of

References

Appendix 1
current DMTs. These questionnaires would also provide healthcare staff with the most appropriate measures for improving follow-up of therapy in MS patients, particularly in those at high risk of lack of adherence and in those with longer disease and treatment durations, in whom adherence has been found to be poorer.

In conclusion, in the Spanish GAP study, the overall rate of adherence remained high over the 2 years of follow-up reported here, and higher than the baseline adherence recorded in the international GAP study [5]. It was highest with IM IFNβ-1a; this difference was significant at the baseline visit (after nearly 3 years on therapy) compared with other DMTs. It would be appropriate to strengthen the role of nursing staff in the follow-up of patients receiving DMTs. Treatment adherence is also improved if both patients and healthcare providers are aware of its importance.

Appendix 1

GAP Investigators
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